Tampere University

JUSSI POHJONEN

# Gut Connection in IgA Nephropathy

Tampere University Dissertations 944

Tampere University Dissertations 944

JUSSI POHJONEN

# Gut Connection in IgA Nephropathy

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 16 February 2024, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Department of Internal Medicine
Finland

| | | |
|---|---|---|
| *Responsible supervisor and Custos* | Professor Katri Kaukinen<br>Tampere University<br>Finland | |
| *Supervisors* | Docent<br>Satu Mäkelä<br>Tampere University<br>Finland | Professor Emeritus<br>Jukka Mustonen<br>Tampere University<br>Finland |
| *Pre-examiners* | MD, PhD Kati Kaartinen<br>University of Helsinki<br>Finland | MD, PhD Jukka Koffert<br>University of Turku<br>Finland |
| *Opponent* | Professor Patrik Finne<br>University of Helsinki<br>Finland | |



Cover design: Roihu Inc.

ISBN 978-952-03-3260-0 (print)
ISBN 978-952-03-3261-7 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-3261-7

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

*"Iskä, mites se sun väitöskirja etenee?"*

To Eeva, Ellen, Linnea and Loviisa.

# ACKNOWLEDGEMENTS

This study was carried out at the Faculty of Medicine and Health Technology, Tampere University, at the Celiac Disease Research Center, Tampere University and at the Department of Internal Medicine, Tampere University Hospital. Financial support was received in the form of grants from the Finnish Kidney and Liver Association, the Finnish Celiac Disease Society, the Mary and Georg C. Ehrnrooth Foundation, the Department of Internal Medicine of Tampere University Hospital and the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital.

I owe my warmest and most sincere gratitude to my supervisors Professor Katri Kaukinen, Docent Satu Mäkelä and Professor Emeritus Jukka Mustonen. You are all colleagues with vast knowledge, not only in your respective fields of study, but in medicine in general. You inspire and encourage. This journey has been an honour. Thank you for offering me to your guidance.

Katri, since day one, you had a clear of view where the study should go. Whenever I was in doubt, you showed the way with firm guidance. You trusted and provided no ready-made answers. You never questioned my slow progress with the project.

Satu, you are an excellent manager and researcher, in addition to being excellent company. During the study project I completed my specialization in nephrology under your guidance. You have always been available for discussions whatever the matter has been and provided guidance in clinical and scientific issues.

Jukka, I thank you for kindling my inspiration for science. In a lecture back in 2014, you presented the research you had conducted throughout your career. The studies of the intestines of IgA nephropathy patients were inspiring. Around that time you were starting research projects with Katri. The time was right and my long-lasting vision of conducting research was to come true. Since then, we have had multiple conversations around different topics. I admire your energy in trying to fix the ills you meet in healthcare and in society.

I am very grateful to all three of you, Docent Jaakko Antonen, Docent Hannu Päivä and Sami Mustajoki, PhD for providing the facilities to conduct this study and your encouraging attitude. Sami, I especially thank you for the continuous gentle push to ensure the progress of this project. I also warmly thank you, Professor Heikki

Saha, as my educator in nephrology and medicine and as a role model in collegiality and academic.

Tina Katto, I thank you for your help with all the administrative work, especially with the second part of this project. A modern research plan would have never materialized without your guidance. Atte Kukkurainen, thank you for your crucial role in taking the biological samples and all the organizing with the timetables and the study patients to ensure that this all came true. We made it right before Covid-19. A close one, would someone say. Heidi Kontro at the Celiac Disease Research Center, thank you for all your practical support these years. And all the researchers and colleagues at CeliRes, thank you for taking me as a nephrological "outlier" into your community.

I am sincerely thankful to my co-authors for your valuable contribution. Thank you, Heini, for statistical analyses and patience in clarifying the world of statistics. Martti, a superb senior role model, thank you for so much shared wisdom and humour in daily life. Professor Katri Lindfors and Professor Ilkka Pörsti, thank you both for your sincere help and advice whenever it was needed. Not to forget the time you spent with tables and figures, Ilkka. Virginia Mattila, thank you for all the careful revision of the English language, which enhanced the message of this project. Thank you all.

If anyone, it is you, Rakel, to whom I show thankfulness today. Without you, this project would never have materialized. Your determination led to the first two articles. This characteristic of yours has not fade since then, quite the opposite. I hope we can collaborate on even more exciting projects in the future.

I thank you, Docent Pia Oksanen and Docent Jenni Koskela, the members of the follow-up group. Pia, you made an important contribution to Study I and made sure I would take care of the theoretical courses when the project proceeded. Jenni, we have worked together since our specializations in internal medicine. Thank you for being a friend and part of the biggest project of my career.

I am grateful to you Kati Kaartinen, PhD and Jukka Koffert, PhD the pre-examiners, for your time and effort in reviewing the manuscript. Your valuable comments, the conversations we had and the corrections recommended helped improve the final result. And Professor Patrik Finne, thank you for kindly agreeing to be my opponent at the forthcoming public defence.

Thank you, mother and father, Hanna-Leena and Matti, for your unconditional love, encouragement and help throughout my life. You set the bar, yet you never told there was one and how high it was set. I keep on jumping. Father, I wish you too could be here with us today. Minna and Kaisa, I had the good fortune to be born

your little brother. Not to forget your children, the oldest of whom I feel like my little brothers. During the latter half of my life so far, you, Terttu, Hannu, Eero and your family, and Juhani, have provided me with another loving and encouraging family. I feel proud indeed to celebrate together with you today.

LOS boys and all you colleagues in Tampere and Pori, both doctors and nurses, friends and relatives not yet mentioned by name. I have been privileged to know many brilliant and funny people, so allow me to put it briefly: Thank you for all the joy, help and wisdom you have brought to my life.

Ellen, our firstborn, thank you for asking me the key question a few years ago. I doubt that my interest to persevere with the never-ending research project would have carried on. Linnea, our middlemost, thank you for your straight and honest feedback whenever this project took too much time from our family. And Loviisa, the baby of the team, I hope you remember that your childhood was not work around the clock. All three of you, you are the pride and joy of my life. I love you. I wish and pray for the good of you all.

Finally, I owe my deepest gratitude to the love of my life, my wife Eeva. I apologize for not being able to conduct this project following my original plan of you not noticing what is going on. You sure did, especially during the last year. Thank you for making time and space for this project. Without you by my side, there would not have been any dissertation to be presented. Thank you, my love.

Kissanmaa, December 2023

Jussi Pohjonen

# ABSTRACT

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and was identified over half a century ago. Appearance of transient gross haematuria during episodes of mucosal infections is the classical clinical presentation of IgAN. The research of the role of the gut in IgAN goes back as far as the 1980s. The emergence of corticosteroid therapies with promising efficacy for the survival of the kidneys of IgAN patients in the 1990s probably delayed study activity around the so-called gut-kidney axis for nearly two decades. Yet interest in this connection has resurfaced in international IgAN research in recent years.

The dissertation project focused on connections between diseases and processes of the intestine and kidney diseases. The prevalence of inflammatory bowel disease (IBD) was first evaluated among patients referred to kidney biopsy due to clinical indications. The focus was soon targeted to IgAN and phenomena in the intestines of biopsy-verified IgAN patients. The prevalence of coeliac disease (CeD) and IBD among IgAN patients was elucidated. Thereafter, presence of gastrointestinal symptoms and serum levels of indirect biomarkers of intestinal damage were studied in IgAN patients with no known diseases of the intestine. The dissertation consists of four sub-studies.

Study I investigated the prevalence and phenotypes of IBD in patients referred to kidney biopsy on a clinical basis from 2000 to 2012 at Tampere University Hospital (TAUH). Altogether 35 out of the 819 kidney-biopsied patients had IBD (4.3%). Crohn's disease (CrD) and ulcerative colitis (UC) were equally common. The prevalence of IBD was 13.3% in patients diagnosed with tubulointerstitial nephritis and 4.6% in patients diagnosed with IgAN. In general population, prevalence of diagnosed IBD in 2008 was 0.6%. IBD was not associated with any increased risk of end-stage kidney disease during a median follow-up of nearly five years.

Study II evaluated the prevalence of diagnosed CeD, the prevalence of coeliac autoimmunity detected by serum levels of transglutaminase 2 targeted antibodies and the prevalence of IBD in 629 patients diagnosed with IgAN at TAUH from 1976 to 2012. The prevalence of CeD and coeliac autoimmunity decreased among IgAN patients from 5.6% in the 1980s to 1.4% by the beginning of the 21st century,

whereas the prevalence of IBD increased from 2.0% to 4.4% over the same period of time.

Study III surveyed health-related quality of life and gastrointestinal (GI) symptoms experienced by 104 IgAN patients living in the TAUH catchment area in 2019. Conventionally, GI symptoms have been acknowledged to present in end-stage kidney disease. The questionnaires used were the self-administered, structured, well-validated Gastrointestinal Symptom Rating Scale (GSRS) and the Psychological General Well-Being Index. The results were compared with those of healthy people. IgAN patients reported more GI symptoms than did healthy people. The GSRS total score of the IgAN patients was about the same as in earlier studies on dialysis patients. Specifically, female patients and patients with preserved kidney function experienced an excess of GI symptoms. Health-related quality of life was likewise lower in IgAN patients than in healthy individuals.

Study IV used as its subjects 85 volunteer IgAN patients who had participated in Study III. Subclinical CeD was excluded with negative serum coeliac autoantibody tests from all participants and IBD with negative faecal calprotectin test from 57 volunteer patients. Thereafter, serum levels of three indirect biomarkers of intestinal damage were measured in all 85 patients. Test results were compared with those of healthy people and patients suffering from dyspepsia. Serum levels of a protein released into the circulation from enterocytes upon cell damage, intestinal fatty-acid binding protein, were higher in IgAN patients than in healthy people. Serum levels of soluble cluster of differentiation molecule 14, a biomarker likely representing increased intestinal permeability, did not differ between IgAN patients and healthy controls, but were lower in dyspepsia controls. Serum levels of another possible biomarker of intestinal permeability, lipopolysaccharide-binding protein, showed no difference between the groups. In none of the three biomarkers did the serum levels correlate with the GI symptoms measured by GSRS score.

In conclusion, IBD is present in a notable percentage of patients with clinical signs of a kidney disease. IBD should be kept in mind, especially when the kidney biopsy histology shows either tubulointerstitial nephritis or IgAN. The prevalence of IBD and especially that of Crohn's disease is increasing in IgAN. Conversely, the prevalence of CeD in conjunction with IgAN is decreasing. IgAN patients and especially female IgAN patients experience more GI complaints than do healthy people. IgAN patients experience GI symptoms even without kidney failure. The finding of elevated serum levels of an indirect biomarker of intestinal damage among IgAN patients gives ground for further studies to explore gut phenomena in IgAN in more detail.

# TIIVISTELMÄ

IgA-nefropatia (IgAN) on maailman yleisin primäärinen munuaiskerästen tulehduksellinen sairaus, glomerulonefriitti. Limakalvojen infektion yhteydessä ilmaantuva ohittuva näkyvä verivirtsaisuus on taudin klassinen ilmentymä. IgAN tunnistettiin jo reilu puoli vuosisataa sitten. Suoliston ja IgAN:n yhteyden tutkimus käynnistyi jo 1980-luvulla. Glukokortikoidihoidon mahdollisesti munuaistaudin ennustetta parantavan vaikutuksen osoittaminen IgAN-potilailla 1990-luvulla todennäköisesti johti vähentyneeseen tutkimusaktiivisuuteen suoliston ja IgAN:n yhteyksien selvittämiseksi lähes kahdeksi vuosikymmeneksi. Viime vuosina yhteys on noussut uudelleen kansainvälisen IgAN-tutkimuksen ytimeen.

Väitöskirjaprojekti keskittyi suoliston sairauksien ja ilmiöiden sekä munuaissairauksien yhteyksiin. Ensin selvitettiin tulehduksellisten suolistosairauksien (inflammatory bowel disease, IBD) esiintyvyyttä munuaisen koepalan ottoon kliinisin syin ohjatuilla potilailla. Mielenkiinto kohdentui pian IgA-nefropatiaan ja munuaisen koepalalla varmennettujen IgAN-potilaiden suoliston ilmentymiin. Keliakian ja IBD:n esiintyvyys IgAN-potilailla selvitettiin neljän vuosikymmenen ajalta. Seuraavaksi kartoitettiin potilaiden kokemia suoliston oireita sekä mitattiin suolen vauriota epäsuorasti kuvaavien, verenkierrosta määritettävissä olevien merkkiaineiden pitoisuudet sellaisilta IgAN-potilailta, joilla ei ollut todettua suoliston sairautta. Väitöskirja koostuu neljästä osatutkimuksesta.

Osatyössä I tutkittiin IBD:n esiintyvyyttä ja taudinkuvia potilailla, joilta oli otettu munuaisbiopsia kliinisin perustein vuosien 2000 ja 2012 välillä Tampereen yliopistollisessa sairaalassa (Tays). Kaikkiaan 819 munuaisbiopsiaan ohjatusta potilaasta 35:llä (4,3 %) oli IBD. Crohnin tauti ja haavainen paksusuolentulehdus olivat aineistossa yhtä yleiset. IBD:n vallitsevuus oli 13,3 % potilailla, joilla todettiin tubulointerstitiaalinen nefriitti ja 4,6 % niillä, joilla todettiin IgAN. Diagnosoidun IBD:n vallitsevuus väestössä vuonna 2008 oli 0,6 %. IBD ei yhdistynyt loppuvaiheen munuaistaudin riskiin lähes viiden vuoden seurannassa.

Osatyössä II arvioitiin diagnosoidun keliakian, seerumista mitattavalla vasta-ainetutkimuksella todetun keliakiaimmuniteetin ja IBD:n vallitsevuutta 629 IgAN-diagnoosin Taysissa vuosien 1976 ja 2012 välillä saaneen potilaan joukossa. Keliakian ja keliakiaimmuniteetin yhteen laskettu vallitsevuus laski 1980-luvun 5,6 prosentista

1,4 prosenttiin 2000-luvulle tultaessa, kun taas IBD:n vallitsevuus kasvoi samana ajanjaksona 2,0 prosentista 4,4 prosenttiin.

Osatyössä III kartoitettiin terveyteen liittyvää elämänlaatua ja koettuja suoliston oireita 104 IgAN-potilaalla, jotka asuivat Taysin piirissä syksyllä 2019. Perinteisesti suolen oireiden on katsottu esiintyvän vasta loppuvaiheen munuaistautia sairastavilla potilailla. Käytetyt kyselyt olivat henkilön itsensä täyttämät, rakenteiset ja laajalti validoidut Psychological Well-Being Index ja Gastrointestinal Symptom Rating Scale (GSRS). Vastauksia verrattiin terveiden henkilöiden vastauksiin. IgAN:aa sairastavat kokivat terveitä henkilöitä enemmän suolioireita. Erityisesti oireita kokivat naiset ja ne potilaat, joilla munuaisten toiminta oli säilynyt hyvänä. Terveyteen liittyvä elämänlaatu oli huonompaa IgAN-potilailla terveisiin verrattuna.

Osatyössä IV mitattiin 85 osatyössä III mukana olleen vapaaehtoisen IgAN-potilaan kolmen epäsuorasti suolen vauriota mittaavan merkkiaineen pitoisuudet seerumista. Oireeton keliakia poissuljettiin seerumista mitattavin keliakian vasta-ainetestein sekä 57 potilaalta IBD ulosteen kalprotektiinin määrityksellä. Merkkiaineiden pitoisuuksia verrattiin terveisiin henkilöihin sekä henkilöihin, joilla oli todettu dyspepsia. Ohutsuolen soluista soluvaurion yhteydessä vapautuvan rasvahappoa sitovan proteiinin pitoisuus seerumissa oli korkeampi IgAN-potilailla kuin terveillä henkilöillä. Oletetusti suoliston lisääntynyttä läpäisevyyttä kuvaavien liukoisen CD14-molekyylin (cluster of differentiation, CD) ja lipopolysakkaridia sitovan proteiinin tasot seerumista mitattuina eivät eronneet IgAN-potilaiden ja terveiden verrokkien välillä, mutta sCD14 oli dyspepsia-potilailla muita ryhmiä matalampi. Yhdenkään tutkitun merkkiaineen pitoisuudet eivät korreloineet GSRS-kyselyn pisteisiin.

Yhteenvetona voidaan todeta, että IBD:a esiintyi merkittävällä osalla sellaisista potilaista, joilla oli munuaissairauteen viittaavia oireita. Eritoten IBD tulisi muistaa silloin, jos munuaisen koepalassa todetaan tubulointerstitiaalinen nefriitti tai IgAN. IBD:n ja eritoten Crohnin taudin vallitsevuus IgAN:n yhteydessä lisääntyi seuranta-aikana. Sen sijaan keliakian ja keliakia-autoimmuniteetin vallitsevuudet laskivat vuosikymmenten saatossa. IgAN-potilaat ja heistä eritoten naiset kokivat terveitä henkilöitä enemmän suolisto-oireita. Potilailla oli suoliston oireita hyvänä säilyneestä munuaistoiminnasta huolimatta. Havainto suoliston vauriota epäsuorasti mittaavan merkkiaineen kohonneista tasoista IgAN-potilaiden seerumissa kannustaa jatkossa tutkimaan IgAN:n yhteydessä havaittavia suoliston ilmentymiä tarkemmin.

# CONTENTS

## *List of Figures*



## *List of Tables*

# ABBREVIATIONS

| | |
|---|---|
| 5-ASA | 5-aminosalicylic acid |
| $^{51}$Cr-EDTA | Radioactive chromium complexed with ethylene diamine tetracetic acid |
| AGA | Anti-gliadin antibody |
| APRIL | A proliferation-inducing ligand |
| BMI | Body mass index |
| C3 | Complement component 3 |
| CD | Cluster of differentiation molecule |
| CeD | Coeliac disease |
| CeliRes | Celiac Disease Research Center, Tampere University |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CrD | Crohn's disease |
| DH | Dermatitis herpetiformis |
| eGFR | Estimated glomerular filtration rate |
| EIM | Extraintestinal manifestation |
| ELISA | Enzyme-linked immunosorbent assay |
| EmA | Endomysial antibody |
| ESKD | End-stage kidney disease |
| Gd-IgA1 | Galactose-deficient immunoglobulin A1 |
| GFD | Gluten-free diet |
| GFR | Glomerular filtration rate |
| GI | Gastrointestinal |
| GN | Glomerulonephritis |
| GSRS | Gastrointestinal Symptom Rating Scale |
| GWAS | Genome-wide association study |
| HLA | Human leukocyte antigen |
| IBD | Inflammatory bowel disease |
| IBS | Irritable bowel syndrome |

| | |
|---|---|
| I-FABP | Intestinal fatty-acid binding protein |
| IgA | Immunoglobulin A |
| IgAN | Immunoglobulin A nephropathy |
| IL | Interleukin |
| IQR | Interquartile range |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LBP | Lipopolysaccharide-binding protein |
| LPS | Lipopolysaccharide |
| MEST | Mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S) and interstitial fibrosis/tubular atrophy (T) |
| PGWB | Psychological General Well-Being Index |
| sCD14 | Soluble cluster of differentiation molecule 14 |
| SD | Standard deviation |
| TAUH | Tampere University Hospital |
| TG2 | Transglutaminase 2 |
| TG2Ab | Transglutaminase 2 antibody |
| TIN | Tubulointerstitial nephritis |
| UC | Ulcerative colitis |

# ORIGINAL PUBLICATIONS

This thesis is based on the following original publications which are referred to in the text by their Roman numerals.

Publication I Pohjonen J., Nurmi R., Metso M., Oksanen P., Huhtala H., Pörsti I., Mustonen J., Kaukinen K. and Mäkelä S. (2019). Inflammatory bowel disease in patients undergoing renal biopsies. *Clinical Kidney Journal*, 12(5):645-651. doi:10.1093/ckj/sfz004

Publication II Nurmi R., Pohjonen J., Metso M., Pörsti I., Niemelä O., Huhtala H., Mustonen J., Kaukinen K. and Mäkelä S. (2021). Prevalence of inflammatory bowel disease and celiac disease in patients with IgA nephropathy over time. *Nephron*, 145(1):78-84. doi:10.1159/000511555

Publication III Pohjonen J.T., Kaukinen K.M., Metso M.J., Nurmi R.K.K., Huhtala H.S.A., Pörsti I.H., Mustonen J.T. and Mäkelä S.M. (2022). Presence of gastrointestinal symptoms in IgA nephropathy: a cross-sectional study. *BMC Nephrology*, 23:395. doi:10.1186/s12882-022-03019-8

Publication IV Pohjonen J., Kaukinen K., Huhtala H., Pörsti I., Lindfors K., Mustonen J. and Mäkelä S. Indirect markers of intestinal damage in IgA nephropathy. Submitted.

# AUTHOR'S CONTRIBUTIONS

The author contributed to the planning of the study design in collaboration with the research group. He prepared the statement for application to the Ethics Committee of Tampere University Hospital for Studies III and IV. He was mainly responsible for collection and editing of the data, except for Study II, for which the data were collected and edited with fellow researcher Rakel Nurmi. The author analysed the data with the help of a statistician and the co-authors (I, III and IV). The data of Study II were analysed by Rakel Nurmi and a statistician. The author was responsible for the evaluation of the results with the assistance of his supervisors and co-authors. The author wrote the first drafts and was the first author in original publications I, III and IV. He was also responsible for editing and submitting the final versions of the original publications I, III and IV. He participated in the writing process of original publication II as the second author.

# 1 INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis world-wide and defined as an autoimmune disease (Knoppova et al., 2016; Rodrigues et al., 2017). The pathogenesis of IgAN is assumed to follow four crucial steps, starting from the production of the pathognomonic IgA-molecule (Suzuki H. et al., 2011). Where exactly this IgA-molecule originates, is still unknown. Most likely it originates in the mucosal tissues, especially those in the gut (Sanchez-Russo et al., 2022). The gut-kidney axis has accordingly been a hot topic in the field of IgAN research in recent years (Coppo, 2015; Monteiro & Berthelot, 2021). However, the impetus for gastrointestinal study in IgAN came back in the 1980s and 1990s (Coppo et al., 1986, 1992; Pasternack et al., 1990; Rantala et al., 1999; Rostoker et al., 1993). Despite a long history and now quickly accumulating knowledge about gastrointestinal phenomena in IgAN, many questions remain unanswered.

# 2 REVIEW OF THE LITERATURE

## 2.1 Chronic kidney disease

Nephrons are the approximately one million microscopic structures in each kidney (Latin *ren*, Greek *nephros*), filtering blood to produce urine. A nephron consists of a renal corpuscle (*glomerulus*) connected to a complex tubular system. Glomeruli are tufts of specialized microscopic arterioles located in the outer layer (cortex) of the kidney. The glomerulus is attached to the mesangium, which is established by the mesangial cells and mesangial matrix. Both the glomerulus and the mesangium are enclosed in a pouch-like extension of the tubule, the Bowman capsule. The major part of a glomerular artery is located toward the urinary space, being covered by the glomerular basement membrane and specialized cells, podocytes. This portion of the arterial wall represents the filtration area (Feehally et al., 2019). The filtration barrier entails a complex interplay between different types of cells, together forming a sieve for blood purification (Haraldsson & Jeansson, 2009). The glomerular filtration rate (GFR) cannot be measured directly in humans (Feehally et al., 2019).

Urinalysis is a mandatory diagnostic tool for evaluating kidney diseases. Presence of erythrocytes (haematuria) and/or albumin (proteinuria) are hints of a glomerular disease. Haemoglobin is detected by a dipstick test. Automated analysis of urine sediment confirms the presence of erythrocytes. The albumin dipstick test has a detection limit between 0.25-0.3 g/l. As the dipstick test provides only a semiquantitative measurement, other methods are needed for accurate quantification of albuminuria. The albumin-to-creatinine ratio measured in a random urine sample is a practical alternative. The twenty-four-hour protein excretion is considered the reference method to quantify proteinuria. Importantly, it quantifies urine total proteins and not only albumin. Tubular or monoclonal proteins can be recognized and quantified with specific tests (Feehally et al., 2019).

Urinary findings have traditionally been named according to the presence of proteinuria and haematuria; e.g. haematuria with varying degrees of proteinuria is the hallmark of the nephritic sediment, whereas nephrotic range proteinuria refers to proteinuria exceeding 3.5 grams per day (Feehally et al., 2019; Wirta et al., 2008). Percutaneous kidney biopsy is sometimes needed to set a specific diagnosis, to

evaluate disease activity and to provide information for the decisions regarding treatment (see in more detail Chapter 2.2.2). Generally accepted indications for kidney biopsy are acute and progressive kidney injury, unexplained chronic kidney disease (CKD) and persistent proteinuria greater than 1 g/24 h (Feehally et al., 2019).

Estimation of GFR is necessary for the detection, evaluation, and management of kidney disease. GFR is the product of the average filtration rate of each nephron, multiplied by the number of nephrons in both kidneys. GFR can be estimated (eGFR) using serum levels of endogenous filtration markers, which are substances generated in the body at a relatively constant rate and eliminated largely by glomerular filtration. GFR can also be assessed from clearance measurements of exogenous solutes that are mainly eliminated by glomerular filtration. The classic method for GFR measurement is the urinary clearance of inulin, which is the reference against which other clearance methods are evaluated (Feehally et al., 2019).

The most widely used endogenous filtration marker is creatinine, which is an end-product of muscle catabolism and thus varies according e.g. to muscle mass and diet. The advantages of creatinine are its ease of measurement, low cost and the widespread availability of assays (Feehally et al., 2019). GFR can be estimated from serum creatinine by equations such as the widely used Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation, which includes age, ethnicity and sex in conjunction with serum creatinine (Levey et al., 2009). The CKD-EPI (2021) equation has subsequently been updated to estimate GFR regardless of ethnicity (Inker et al., 2021). The normal level for GFR is approximately 130 ml/min/1.73m$^2$ for men and 120 ml/min/1.73m$^2$ for women, yet declining approximately 0.75 ml/min/year after 40 years of age (Feehally et al., 2019).

GFR less than 60 ml/min/1.73m$^2$ for three months or longer is the main criterion for CKD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). GFR decline correlates with decline in other functions of the kidney (Feehally et al., 2019). Examples of such functions are regulation of acid, fluid and salt balance, removal of the waste products of metabolism, vitamin D metabolism and production of erythropoietin (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). Deficiency in handling these functions is the phenotype of CKD. CKD arises from multiple heterogenous diseases and environmental factors which vary globally. Diabetes and hypertension are the main causes of CKD in all high- and middle-income countries (Webster et al., 2017).

End-stage kidney disease (ESKD) is the final and the most advanced form of CKD, requiring kidney replacement therapy by dialysis and/or kidney transplantation (Kastarinen et al., 2010). CKD and ESKD are associated with

systemic inflammation and acquired immunodeficiency, which promote cardiovascular disease, body wasting and infections as leading causes of death (Anders et al., 2013). Mortality rises as eGFR diminishes and increasing albuminuria is also an independent risk factor for both all-cause mortality and cardiovascular mortality (Matsushita, 2010). The global prevalence of CKD is steadily increasing and the number of people receiving kidney replacement therapy has been predicted to rise to over five million by 2030 (Coresh, 2017). Importantly, CKD is largely preventable and treatable (Bikbov et al., 2020; Helve et al., 2018).

The Finnish Registry for Kidney Diseases has collected data on almost all kidney replacement therapy patients in Finland since 1964. The registry has produced an annual report for over 30 years. At the end of 2021, there were 1,903 dialysis patients and 3,394 kidney transplantation patients in Finland, yielding a prevalence of 955 per million inhabitants for kidney replacement therapy. The incidence of kidney replacement therapy was 82 per million inhabitants in 2021 and the most common CKD diagnosis of patients entering therapy was type 2 diabetes mellitus-associated nephropathy, as it had been for the previous 20 years. Glomerulonephritis (GN) and type 1 diabetes mellitus-associated nephropathy were the second most common diagnoses (Finnish Registry for Kidney Diseases: Report 2021). GN are inflammatory diseases of the glomeruli, of which IgA nephropathy (IgAN) is the most common worldwide (Kaartinen et al., 2019).

## 2.2 IgA nephropathy

### 2.2.1 Clinical presentation

Patients with IgAN may present with various clinical pictures, from asymptomatic invisible (microscopic) haematuria to rapidly progressive glomerulonephritis (Lv et al., 2013b). The relative frequency of the presentations depends in part upon screening practices and the population being evaluated.

The characteristic presentation is transient gross (visible, macroscopic) haematuria at the time of an infectious episode, most commonly an infection of the upper respiratory tract (Berthoux et al., 2008; Suzuki Y, et al., 2021). From one fourth to one third of biopsy-verified IgAN patients have a history of macroscopic haematuria (Le et al., 2014; Suzuki Y et al., 2021). Macroscopic haematuria in IgAN is extremely rare after the age of 40 (Knoppova et al., 2016).

The two most common clinical presentations are asymptomatic microscopic haematuria, with or without proteinuria, and slowly progressive kidney disease (Pettersson et al., 1984; Rodrigues et al., 2017). Other typical phenomena are proteinuria and hypertension (Knoppova et al., 2016). Nephrotic syndrome and rapidly progressive glomerulonephritis are rare manifestations of IgAN (Cattran et al., 2009; Wyatt & Julian, 2013).

Coinciding diseases are a common finding in IgAN, gastrointestinal (GI) and liver disorders being the most common ones (Makdassy et al., 1984; Montenegro & Monteiro, 1999; Mustonen, 1984; Saha et al., 2018; Tissandié et al., 2011; Tota et al., 2023). Concomitant extrarenal diseases seem not to influence the course or prognosis of IgAN (Mustonen et al., 1985). IgA vasculitis (formerly known as Henoch-Schönlein syndrome) possibly represents the same disease with cutaneous, GI and articular involvement (Pillebout, 2021; Suzuki H et al., 2018). The term secondary IgAN has occasionally been used to characterize cases in which IgAN presents with another disease involving changes in immunoglobulin A (IgA) immune regulation, e.g. alcoholic liver cirrhosis (Pouria & Barratt, 2008). The term primary IgAN is sometimes used in cases in which no other condition known to be associated with glomerular IgA deposition is present (Berthoux et al., 2008; Cassol et al., 2020). Yet there is no generally accepted definition for secondary IgAN and no histologic features differentiate primary from secondary IgAN (Cassol et al., 2020; Saha et al., 2018).

### 2.2.2 Diagnosis

Kidney biopsy is the gold standard for the diagnostic evaluation of kidney diseases (Rovin et al., 2021). This is a percutaneous procedure performed under local anaesthesia and ultrasound guidance with a disposable automated spring-loaded biopsy needle (Feehally et al., 2019). The target is the cortical kidney tissue, to get glomeruli on a sample. A kidney biopsy specimen is routinely divided into three pieces, yielding a fresh sample for subsequent freezing for immunofluorescence microscopy, a formalin preserved sample for light microscopy and a glutaraldehyde preserved sample for electron microscopy (Feehally et al., 2019). The samples are evaluated by a nephropathologist.

IgAN should be suspected in any patient presenting either with an episode or episodes of gross haematuria (especially if accompanied by a mucosal infection), with persistent microscopic haematuria (with or without proteinuria) or with slowly

progressive kidney failure in the absence of other etiology (Petrou et al., 2023). The diagnosis of IgAN can only be confirmed with a kidney biopsy (Berthoux et al., 2008). However, in many countries, including Finland, kidney biopsies are not routinely taken from all patients with a clinical picture indicative of IgAN, if establishing the diagnosis would not alter the course of treatment for an individual patient (Feehally et al., 2019; McQuarrie et al., 2009; Wirta et al., 2008).

Diagnosis of IgAN is based on immunohistology (Feehally & Cameron, 2011). The presence of glomerular IgA deposits can be demonstrated by immunofluorescence microscopy of frozen tissue sections or by immunoperoxidase staining of paraffin embedded tissue sections (Roberts, 2014). The diagnostic hallmark is the predominance of IgA deposits in the glomerular mesangium, either alone or with immunoglobulin G, immunoglobulin M, or both (Mustonen et al., 1985; Wyatt & Julian, 2013). Complement component 3 (C3) is frequently (in > 90% of biopsy samples) co-deposited as a sign of the involvement of the alternative pathway of the complement system (Mustonen et al., 1985; Roberts, 2014). Light microscopy findings usually include mesangial hypercellularity and increased mesangial matrix (Knoppova et al., 2016). Features of chronicity such as glomerulosclerosis, tubulointerstitial inflammation and fibrosis are present in advanced disease (Haas, 1997). Electron microscopy typically reveals electron-dense deposits consistent with immune complexes in the mesangium, but deposits may also occur in the subendothelial and subepithelial spaces (Knoppova et al., 2016).

The Oxford classification published in 2009 was created to improve interobserver replicability of the kidney biopsy findings of IgAN (Roberts, 2014). In the original classification four pathologic features independently associated with kidney outcomes were evaluated (Cattran et al., 2009; Roberts et al., 2009). These were mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy and interstitial fibrosis (T), forming the alternative name of the classification, the MEST score. The prognostic value of crescents has been subsequently confirmed and recommended to be added to the MEST score as C for crescents (Haas et al., 2017; Katafuchi et al., 2011; Lv et al., 2013a). Starting from 2017, biopsy reporting should include the Oxford classification as a MEST-C score (Trimarchi et al., 2017). It is notable that immunostaining is not included in the Oxford classification (Bellur et al., 2011). The importance of the Oxford classification has been understood in recent years as enabling to better predict the risk of progression of IgAN (Coppo, 2019; Rovin et al., 2021).

### 2.2.3 Epidemiology

IgAN was described in 1968 by two French pathologists, Jean Berger and Nicole Hinglais (Berger & Hinglais, 1968). It was previously also called Berger's disease and sometimes IgA glomerulonephritis (Berthoux et al., 2008; Kaartinen et al., 2019).

Prevalence of IgAN varies geographically, being more common in eastern parts of the world, the prevalence being lowest in Africa (Kiryluk et al., 2012; Kiryluk & Novak, 2014). IgAN is found in about 20% of all kidney biopsies performed in Europe (Almroth et al., 2006). Incidence of biopsy-proven IgAN in European and Australian studies varies between 0.8 to 10.5 per 100,000 (Wirta et al., 2008). In a systematic review the incidence was at least 2.5 per 100,000 in adults (McGrogan et al., 2011).

Biopsy registry data underestimate IgAN incidence as patients with mild disease are not biopsied, and in countries lacking screening programmes the disease may not be detected (Rodrigues et al., 2017). By contrast, in Japan, for example, about 75% of IgAN patients are identified through screening programmes started in childhood (Suzuki H, 2019; Suzuki Y et al., 2021). Interestingly, latent mesangial IgA deposits were found in 16% of Japanese kidney allografts and in one fifth of those mesangial C3 depositions and mild mesangial proliferation were also present, probably as a sign of subclinical IgAN (Suzuki K et al., 2003). Also, a Finnish autopsy study showed mesangial IgA deposition to be much more common compared to the prevalence of IgAN itself. The authors concluded that the population prevalence of IgAN might be as high as 1.3%, if all cases found with mesangial IgA together with morphological or clinical findings suggestive of kidney disease were regarded as IgAN (Varis et al., 1993). In a more recent study, incidental IgA deposits were present in up to 24.5% of deceased donor kidneys at the first post-transplantation biopsy (Gaber et al., 2020).

The onset of IgAN has traditionally been in the second and third decades of life (Berthoux et al., 2008). The disease also affects children, even those as young as four years of age (Knoppova et al., 2016). Interestingly, age at onset has risen over time and may be attributable in part to decreased screening policies (Berthoux et al., 2008; Gutiérrez et al., 2018). Among Europeans IgAN affects men more often than women, the male-to-female ratio being 2-3:1 (Knoop et al., 2013, 2017; Mustonen et al., 1985; Radford et al., 1997). IgAN has been shown to shorten life expectancy; by as much as ten years in a single-centre study from the United States and by six years according to a Swedish nationwide register study (Hastings et al., 2018; Jarrick et al., 2019; Knoop et al., 2013).

### 2.2.4 Pathogenesis

IgAN is defined as an autoimmune disease (Knoppova et al., 2016; Petrou et al., 2023). Mesangial IgA deposition is an early event that subsequently leads to glomerular inflammation and sclerosis, interstitial damage, and eventually ESKD in a substantial proportion of affected individuals (Roos et al., 2006). The deposited IgA molecule is of the subtype IgA1 (Hiki et al., 2001). The pathognomonic finding of the IgA1 molecule in IgAN is an abnormal *O*-glycosylation of the hinge region of the molecule (Hiki et al., 2001; Smith et al., 2006). This so-called galactose-deficient IgA1 molecule (Gd-IgA1) acts as an autoantigen (Suzuki H et al., 2009). Other types of IgA molecules have also been found in kidney biopsies from IgAN patients, secretory IgA as an example in 15% of cases (Oortwijn et al, 2006b; Oortwijn et al., 2007). It is not clear whether all patients with kidney findings interpreted as IgAN share a common disease process (Boyd et al., 2012; Floege & Feehally, 2016; Saha et al., 2018). For example, the *N*-glycosylation was also found to be modified in patients with alcoholic liver cirrhosis and the IgA found in cirrhosis was not able to induce mesangial cell proliferation (Tissandié et al., 2011). It has been debated whether the glomerular IgA found in assumed secondary forms of IgAN is of the same type as in primary IgAN (Cassol et al., 2020; Lee M et al., 2021; Suzuki H et al., 2018; Tang et al., 2023; Wang M et al., 2020).

The concept of a four-hit model puts together the four most crucial steps in the pathogenetic process; formation of Gd-IgA1, synthesis of antibodies directed against Gd-IgA1, binding of Gd-IgA1 molecule by antibodies to form immune complexes and accumulation of the complexes into the glomerular mesangium initiating glomerular injury (Suzuki H et al., 2011). A cascade of multiple inflammatory cytokines and cells follows from the mesangial deposition of immune complexes, leading e.g. to increased matrix formation, podocytopathy, tubulointerstitial injury and ultimately kidney failure (Chan L.Y.Y. et al., 2005; Lai, 2012; Trimarchi & Coppo, 2019). Also, metabolic factors like hypertriglyseridaemia, hyperuricaemia and elevated plasma insulin levels have been shown to contribute to the development of kidney injury and progression of IgAN (Kaartinen et al., 2007; Myllymäki et al., 2005; Syrjänen et al., 2000).

The production of Gd-IgA1 is a complex process consisting first of all factors crucial in the class switching of B cells into IgA-secreting B cells like the B cell activation factor and the proliferation-inducing ligand (APRIL), but also of the altered expression of glycosyltransferases in IgA1-producing B cells, which in turn are affected by various cytokines, especially interleukins (IL) 4 and 6, but also by the

APRIL independently (Gale et al., 2017; Makita et al., 2020; Qin et al., 2005, 2008; Sallustio et al., 2020; Suzuki H et al., 2008, 2014; Yamada et al., 2017). Higher plasma APRIL levels were associated with elevated circulating levels of Gd-IgA1, higher amount of proteinuria and lower eGFR in IgAN patients (Zhai et al., 2016). Elevated Gd-IgA1 levels were in turn independently associated with a greater risk of deterioration in kidney function (Zhao et al., 2012). Elevated circulating Gd-IgA1 levels have been found in asymptomatic relatives of IgAN patients, but high serum levels of Gd-IgA1 alone are not sufficient to produce IgAN (Gharavi et al., 2008; Kiryluk & Novak, 2014).

The exact place of origin of Gd-IgA1 is unclear (Buck et al., 2008; Harper et al., 1994; Sanchez-Russo et al., 2022). Mucosal plasma cells displaced to bone marrow as the source of Gd-IgA1 is one option among others, though such is the case in healthy people too (Harper et al., 1996). Most likely Gd-IgA1 originates from mucosal tissues (Sanchez-Russo et al., 2022). This conclusion is further supported by the depleting therapy of circulating B-cells having no effect on either serum Gd-IgA1 levels or autoantibody levels to Gd-IgA1 (Lafayette et al., 2017).

Circulating immune complexes consist of Gd-IgA1 bound by autoantibodies directed against the galactose residues in the hinge region of the molecules (Berthoux et al., 2012; Suzuki H et al., 2009; Tomana et al., 1997, 1999). The Gd-IgA1-specific antibodies are of both immunoglobulin A and G isotypes (Huang et al., 2016; Yanagawa et al., 2014). Immunoglobulin G specific for Gd-IgA1 has been found in kidney biopsy specimens – even among IgAN patients with negative immunofluorescence microscopy on immunoglobulin G (Rizk et al, 2019b). Immune deposits were shown to clear within weeks in a kidney from a donor with subclinical IgAN after transplantation into a recipient with a non-IgAN kidney disease (Knoppova et al., 2016). Failure in serum immune complex clearance may play a role in the mesangial deposition of IgA (Grossetête et al., 1998).

The cluster of differentiation molecule (CD) 71 (also known as transferrin receptor) acts as a major IgA receptor on mesangial cells in IgAN (Haddad et al., 2003; Moura et al., 2001). Mesangial expression of CD71 is not specific for IgAN, yet it is not expressed in healthy glomeruli (Haddad et al., 2003). Molecular size and glycosylation of IgA1 favours the interaction with CD71 and ensuing glomerular deposition (Moura et al., 2004; Oortwijn et al., 2006a). CD71-dependent mesangial cell proliferation auto-amplifies itself, leading to further mesangial deposition of IgA and further mesangial proliferation (Moura et al., 2001, 2005; Novak et al., 2005). The circulating immune complexes stimulate proliferation of mesangial cells *in vitro*,

even more so when harvested from an IgAN patient's serum during an episode of macroscopic haematuria (Novak et al., 2005).

Other types of IgA receptors are also involved in IgAN (Kaneko et al., 2012; Molyneux et al., 2017; Novak et al., 2002). For example CD89 is crucial in the pathogenesis of IgAN (Grossetête et al., 1998; Launay et al., 2000). Soluble CD89 participates in the formation of circulating IgA1 complexes, which are trapped by CD71 on mesangial cells (Berthelot et al., 2012; Lechner et al., 2016). In a mouse model, deposition of IgA1 involved a direct binding of soluble CD89 to CD71 and the soluble CD89-CD71 interaction induced mesangial expression of transglutaminase 2 (TG2), which in turn upregulated CD71 expression, creating a pathogenic amplification loop (Berthelot et al., 2012). In an experimental model, inhibition of TG2 reduced the development of fibrosis and scarring, thus also preventing a decline in kidney function (Johnson et al., 2007).

The complement system is critical in the pathogenesis of IgAN (Medjeral-Thomas et al., 2017; Tortajada et al., 2019). Without the activation of the complement, no glomerular inflammation would occur, and the more intense the activation in terms of mesangial deposition of C3 is, the worse is the prognosis of IgAN (Kim et al., 2012; Nam et al., 2020; Park S et al., 2020; Zhu et al., 2015). Immune complexes can activate complement via the alternative or the lectin pathway of the complement system (Maillard et al., 2015; Zhang W & Lachmann, 1994). IgA does not activate the classical pathway (Woof & Ken, 2006). Activation of the lectin pathway is associated with more severe disease (Espinosa et al., 2014; Rizk et al., 2019a; Roos et al., 2006). Complement activation probably occurs both systemically in circulating immune complexes and locally in glomeruli (Czerkinsky et al., 1986; Knoppova et al., 2016; Rizk et al., 2019a). Complement factor H is a complement control protein and a key regulator of the alternative pathway, playing an important role in the progression of IgAN (Atkinson & Goodship, 2007; Medjeral-Thomas et al., 2017). A genome-wide association study (GWAS) identified protective alleles against IgAN in complement factor H and complement factor H-related genes plus the genotype provenly affected the phenotype of IgAN (Gharavi et al., 2011; Jullien et al., 2018; Zhu et al., 2015).

An Italian study reported higher risk of IgAN among first-degree than second-degree relatives (Schena et al., 2002). GWAS in IgAN patients with different ancestries have shown associations with genes at the human leukocyte antigen (HLA) locus of the genome (Feehally et al., 2010; Gharavi et al., 2011; Kiryluk et al., 2012; Li M et al., 2020; Yu X.Q. et al., 2012). The geographical distribution of IgAN may be linked to genetically driven functional modifications in the mucosal immune

system and an interplay with the gut microbiome may be an important disease modifier of IgAN (Floege & Feehally, 2016; Kiryluk & Novak, 2014). Nevertheless, the genetic loci discovered to date explain less than 10% of the risk for IgAN (Kiryluk & Novak, 2014; Lafayette & Kelepouris, 2018). Ultimately, the pathogenesis of IgAN is a combination of genetic and environmental factors (Feehally et al., 2010; Gharavi et al., 2011). Environmental factors are presented in more detail in Chapter 2.5.5.

### 2.2.5 Risk of progression

IgAN is generally asymptomatic and follows a slowly progressive course with approximately 25 to 30% of patients suffering kidney failure within 20 to 25 years from presentation (KDIGO Glomerular Diseases Work Group, 2021). The risk of progressive disease forms the basis for decision-making regarding treatment (Medjeral-Thomas et al., 2017). Individuals at highest risk of progression are those with decreased GFR, more severe proteinuria and persistent hypertension (Barbour & Reich, 2012; Bartosik et al., 2001).

Patients with normal kidney function, microscopic haematuria and minimal proteinuria (< 0.5 g/day) at the time of diagnosis are believed to have excellent long-term prognoses (Gutieŕrez et al., 2012). Also, macroscopic haematuria is a favourable prognostic sign (Le et al., 2014; Mustonen et al., 1985). Persistent microscopic haematuria was, however, found to be independently associated with the risk of progression in a Chinese study (Yu G et al., 2020). The prognosis is particularly poor in crescentic IgAN (Boyd et al., 2012). The kidney survival rate was only 50% at one year and 30% at five years among Chinese patients with crescents in more than 50% of the glomeruli (Lv et al., 2013b). Crescents are more common among individuals with Asian ethnicity (Barbour et al., 2019; Yu G et al., 2020).

The amount of proteinuria at the time of kidney biopsy predicts the future risk of progressive kidney disease, as the risk of composite kidney outcome (50% reduction in eGFR or ESKD) can vary from about 10% at 10 years for those with proteinuria < 1 g/day to as high as 60% for those with proteinuria exceeding 3 g/day (Barbour et al., 2016; Radford et al., 1997). Importantly, when treated to partial remission in means of proteinuria (< 1 g/day), the disease course demonstrably follows that of patients with naturally similar amounts of proteinuria (Reich et al., 2007). Accordingly, an ongoing proteinuria exceeding 1 g/day is the most important clinical risk factor for ESKD in IgAN, and the lesser the amount of proteinuria the

better the prognosis is (Barbour et al., 2015; Le et al., 2012). Also, duration of proteinuria remission affects the risk of future kidney failure (Canney et al., 2021). Blood pressure over 140/90 mmHg at presentation has a strong association with increased risk of decline in kidney function (Berthoux et al., 2011). Yet again, blood pressure over time is a better predictor of prognosis than that measured at the time of diagnosis (Bartosik et al., 2001; Reich et al., 2007).

The risk of disease progression can be assessed individually by combining the clinical parameters and the kidney biopsy histology (Barbour et al., 2016; Cattran et al., 2009; Coppo, 2019; D'Amico, 2000; Haas et al., 2017; Roberts et al., 2009). The MEST score combined with clinical data at biopsy predicted the risk of progressive disease better than the clinical data at biopsy alone; e.g. presence of mesangial hypercellularity decreased the likelihood of kidney survival to < 80% at five years compared to 90% in patients with similar clinical parameters at biopsy but without mesangial hypercellularity (Barbour et al., 2016). On the other hand, the prognosis was good in patients with a benign histology despite proteinuria between 1 and 1.5 g/day (Barbour et al., 2016). The importance of histology in baseline kidney biopsy for predicting the progression risk has since been corroborated (Barbour et al., 2019; Coppo, 2019; Coppo et al., 2020). For decades, there has been a lack of a patient-specific risk stratification tool, but the situation changed recently with the development of the International IgA Nephropathy Prediction Tool (Barbour et al., 2019, Zhang J et al., 2020). An updated Prediction Tool was created to be used one to two years after biopsy, whereas the original Prediction Tool should only be used at the time of biopsy (Barbour et al., 2022).

Grading of complement deposition together with the Oxford classification could improve risk prediction (Park S et al., 2020). Mesangial deposition of the complement component 4d is a marker of activation of the lectin pathway of complement and associated with more severe disease (Espinosa et al., 2009, 2014; Segarra et al., 2018).

Various biomarkers have been studied with regard to either diagnosing IgAN or to evaluating the risk of kidney failure (Krochmal et al., 2017; Moresco et al., 2015; Neuhaus et al., 2018; Suzuki H et al., 2019; Yanagawa et al., 2014). The urinary biomarkers studied have been, for example, IgA and immunoglobulin G containing immune complexes (Matousovic et al., 2006), soluble CD71 (Delanghe et al., 2013), TG2 and CD89 (Moresco et al., 2016), Gd-IgA1 (Suzuki H et al., 2016), and calprotectin (Neuhaus et al., 2018). A combination of multiple urine peptides probably predicts the risk of rapid kidney disease progression better than clinical parameters alone (Rudnicki et al., 2021). Higher serum levels of Gd-IgA1 at the time

of diagnosis have been shown to be associated with the rate of decline in kidney function (Maixnerova et al., 2019). Circulating levels of the complement components could serve as markers of disease activity (Medjeral-Thomas et al., 2018).

The risk of kidney failure also varies according to the treating centre (Geddes et al., 2003; Radford et al., 1997). One obvious explanation for this is the difference in the phase of IgAN in which it is detected (Ibels & Györy, 1994; Roberts et al., 2009; Szeto et al., 2001). In Helsinki the risk of ESKD was less than 10% in 10 years among those diagnosed with IgAN between 1980 and 1995 (Geddes et al., 2003). The impact of sex has been somewhat controversial, but male sex seems to carry a higher risk for more rapid decline in kidney function (Cattran et al., 2008; Neugarten et al., 2000).

### 2.2.6 Treatment

To date, there is no cure for IgAN and no specific treatment targeting its pathogenesis (Coppo, 2017). Even clinical remission is possible, but that is the case in less than one third of patients with biopsy-verified disease (Knoop et al., 2017). Also, reversibility in the histological findings was seen in a substantial proportion of Japanese patients in a single-centre study, yet no significant improvement in kidney function was observed (Hotta et al., 2002). All patients diagnosed with IgAN should be assessed for secondary causes (KDIGO Glomerular Diseases Work Group, 2021).

So-called supportive care including dietary advices and lifestyle modifications forms the basis of treatment of IgAN (Floege et al., 2021). As in all glomerular diseases, target blood pressure is set at low normal (< 120 mmHg) (Coppo, 2019; KDIGO Glomerular Diseases Work Group, 2021). As the time to progression to ESKD in IgAN is usually long, so-called surrogate end points are used as predictors of the efficacy of treatment. Reduction in proteinuria is regarded as the most suitable surrogate end-point in IgAN studies (Inker et al., 2016, Thompson et al., 2019). Inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin II type I receptor blockers forms the backbone of antiproteinuric antihypertensive medication and has been proven to improve kidney survival among IgAN patients with proteinuria (Li P.K.T. et al., 2006; Praga et al., 2003). In addition to lowering blood pressure, proteinuria should be reduced to < 1 g daily (Lv et al., 2017; Magistroni et al., 2015).

Persistent proteinuria exceeding 1 g/day for over three to six months, despite optimized supportive care, has traditionally justified the use of immunosuppressive therapy (Coppo, 2019). Yet persistent proteinuria can equally be a marker of progressive glomerular damage or scarring. Thus, based on the amount of proteinuria only it would be difficult to predict who is likely to benefit from immunosuppressive therapy (Medjeral-Thomas et al., 2017). If only the clinical information at biopsy is utilized in decision-making, as many as every third patient could be disqualified from the immunosuppressive therapy they would most likely benefit from (Barbour et al., 2016, 2019). Thus, an individual patient's risk of progressive kidney disease should be assessed with the International IgA Nephropathy Prediction Tool (Barbour et al., 2020; KDIGO Glomerular Diseases Work Group, 2021).

Corticosteroids demonstrably reduce proteinuria in IgAN (Lv et al., 2017, 2022; Manno et al., 2009; Mustonen et al., 1983; Pozzi et al., 1999; Zhou et al., 2011). A common problem with any immunosuppressive treatment is its toxicity (Coppo, 2013; Lv et al., 2017; Rauen et al., 2015). A Cochrane review published in 2020 concluded that corticosteroids may prevent kidney failure, but regarded the risks of serious infections as uncertain (Natale et al., 2020). The Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study published in 2022 is the largest completed treatment trial in IgAN to date, showing benefit from corticosteroid treatment. However, it has major limitations due to the geographically limited study population (mostly Chinese) and the changes in the treatment paradigm of IgAN after study enrollment (Campbell, 2022; Lv et al., 2022). The role of corticosteroids in the long-run has also been challenged (Cheung & Barratt, 2020). The extended follow-up of another big treatment study, the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial, reported no benefit from the early aggressive therapy during a ten-year follow-up (Rauen et al., 2020). The most recent international treatment guideline simply recommends grading the patients on the basis of the amount of proteinuria after the three-month period of optimized supportive care to either low-risk or high-risk (proteinuria > 0.75-1 g/day) patients, and to generally treat the high-risk patients with immunosuppressive therapy, namely corticosteroids (KDIGO Glomerular Diseases Work Group, 2021). A reduced corticosteroid regimen with a cautious policy on risk factors from corticosteroid therapy is advisable, including the use of antibiotic prophylaxis for pneumocystis pneumonia (Lv et al., 2022).

Immunosuppressive monotherapy other than corticosteroids has been studied with small patient samples (Natale et al., 2020). Treatment of variant forms of IgAN,

such as nephrotic syndrome or rapidly progressive glomerulonephritis, follow their own guidelines (KDIGO Glomerular Diseases Work Group, 2021). If histological findings revealing severe and irreversible damage are found, the focus should be on optimized supportive care instead of immunosuppression (Coppo, 2019). Multiple studies from Japan have reported improved kidney survival following tonsillectomy alone or with pulsed glucocorticoids (Coppo, 2013). Nevertheless, the most recent KDIGO guideline does not recommend tonsillectomy as a treatment for IgAN in Caucasian patients (KDIGO Glomerular Diseases Work Group, 2021).

IgAN recurs histologically in a substantial proportion of patients after kidney transplantation (Ponticelli et al., 2001; Wang A.Y.M. et al., 2001). Despite histological recurrence, the 10-year graft survival did not differ from that of patients who had received a transplant due to other kidney diseases (Ponticelli et al., 2001). Also, a 15-year European follow-up study showed a favourable long-term graft survival for IgAN patients, as the 15-year risk of death-adjusted graft failure was 1.17 (95% CI 1.05-1.31) compared to autosomal polycystic kidney disease (Pippias et al., 2016). In a retrospective study, the use of corticosteroids was shown to be associated with a reduced risk of kidney transplant loss from recurrent IgAN (Clayton et al., 2011). Altogether, the modern immunosuppressive therapy regimen seems to achieve better posttransplant kidney survival (Moroni et al., 2013).

Despite optimal modern treatment, 2.3% of Chinese IgAN patients reached ESKD each year at the beginning of the 21st century (Li X et al., 2014). Alternative treatment options are thus urgently needed. As the first therapy targeted at the supposed pathogenetic process of IgAN, enteric budesonide is proposed to act locally on the mucosal lymphoid tissue in the distal ileum and proximal colon (Smerud et al., 2011). Enteric budesonide additional to optimized supportive care lowered the amount of albuminuria and stabilized eGFR during a nine-month treatment (Fellström et al., 2017). Many studies targeting different steps in the pathogenesis of IgAN are ongoing, yet no ground-breaking results have been published to date (Floege et al., 2021). Although not targeted at the pathogenetic process of IgAN, inhibitors of sodium-glucose cotransporter-2 have been found promising in lowering the amount of proteinuria in IgAN (Barratt & Floege, 2021; Wheeler et al., 2021).

## 2.3 Inflammatory bowel disease

### 2.3.1 Clinical presentation

Inflammatory bowel disease (IBD) comprises three closely related disease entities: ulcerative colitis (UC), Crohn's disease (CrD) and the form of colitis with no definite histological or other evidence to favour either CrD or UC, called IBD unclassified (Satsangi, 2006). The first recognized phenotypes of IBD were severe, causing a transmural bowel inflammation, bloody diarrhoea, fever and frequently also death (Malik, 2015). Diarrhoea in IBD is often nocturnal and postprandial (Baumgart & Sandborn, 2007). Nowadays a majority of affected individuals progress to relapsing and chronic disease, which is incurable but in which mortality is fairly low (Jussila et al., 2014; Kaplan, 2015; Xavier & Podolsky, 2007).

IBD predominantly affects the GI tract, but is associated with many extraintestinal manifestations (EIMs); chronic inflammatory diseases affecting other organ systems (Rothfuss et al., 2006). A minority of patients may present with an EIM before the diagnosis of IBD (Fumery et al., 2018). EIMs frequently affect the joints, the hepatobiliary system, skin and eyes, but seldom the kidneys (Lakatos et al., 2003). Eye complications and primary sclerosing cholangitis are more frequent in UC, and joint and skin complications in CrD (Lakatos et al., 2003). EIMs are more common among females than males (Lakatos et al., 2003). The pathogenesis of EIMs is multifactorial, including genetic and environmental factors (Lakatos et al., 2003, Rogler et al., 2021).

A number of EIMs run independently of the course of the intestinal disease (Bernstein et al., 2001). The risk of EIMs is higher in extensive intestinal disease (Fumery et al., 2018; Lakatos et al., 2003). EIMs seem to be more frequent in patients with longer disease duration (Lakatos et al., 2003; Vavricka et al., 2015). The prevalence of EIMs is difficult to define as no uniform definition of an EIM exists (Bernstein et al., 2001; Lakatos et al., 2003; Rogler et al., 2021). The overall risk of EIMs in UC has been estimated to be as high as 17% (Fumery et al., 2018). In CrD an even higher prevalence of EIMs (36.6%) has been reported (Lakatos et al., 2003). According to a Swiss study, multiple EIMs may be present in about 8% of patients suffering from IBD (Vavricka et al., 2015).

### 2.3.2 Diagnosis and epidemiology

IBD typically onsets during the second and third decades of life (Xavier & Podolsky, 2007). In Finland, the point prevalence among patients aged 35 to 54 years was nearly 1% in 2008 when at the same time the nationwide point prevalence was 0.6% (Jussila et al., 2013). The incidence of UC in particular had increased to one of the highest reported in the world and the increase was regarded as a true increase in disease frequency (Jussila et al., 2012). The most recent data show a further increase in IBD prevalence in Finland, the current nationwide prevalence being 1%. The increase has been most notable among the elderly, aged over 70 (Kontola et al., 2023).

A considerable increase in IBD prevalence is a general phenomenon in Westernized countries, but newly industrialized countries show a similar trend (Hein et al., 2014; Kaplan & Ng, 2017). There is also a North-South gradient worldwide in the geographical prevalence of IBD, higher incidence rates being found in Northern countries, and also a gradient within certain countries Finland being one of them (Jussila et al., 2013; Kontola et al., 2023; Shivananda et al., 1996).

The prevalence of UC is about 3-fold compared to that of CrD in Finland (Jussila et al., 2012; Kontola et al., 2023; Manninen et al., 2010). Interestingly, in most of the populations studied, the incidence of UC is higher than and often precedes by one decade that of CrD (Ananthakrishnan, 2015). In Finland, the prevalence of UC is higher among men, but no sex-based difference is seen in CrD (Jussila et al., 2012, 2013; Kontola et al., 2023).

Ileocolonoscopy with intubation of the ileum and biopsies from both affected and unaffected areas of the mucous membrane are needed to confirm the diagnosis of IBD, but its main drawbacks are invasiveness and expense (Langhorst et al., 2016). If the terminal ileum is normal, further evaluation of the proximal GI tract is not needed unless there are symptoms or findings suggesting a diagnosis of CrD rather than of UC (Rubin et al., 2019). CrD is diagnosed on the basis of clinical, endoscopic, histologic and radiographic criteria (Henriksen et al., 2007; Lichtenstein et al., 2018).

Calprotectin is a calcium-binding protein found in abundance in neutrophils, but also in monocytes and macrophages (Lehmann et al., 2015). Faecal calprotectin is a highly sensitive biomarker to detect inflammation in the GI tract (Abraham & Kane, 2012). Faecal calprotectin cannot distinguish CrD from UC nor from infectious aetiology, but is good in differentiating IBD from irritable bowel syndrome (IBS) (Abraham & Kane, 2012). The concentration of calprotectin in the stool is proportional to the intensity of the neutrophilic infiltrate in the mucosa (Røseth et al., 1999). Faecal calprotectin can be utilized to differentiate patients with mucosal

healing from those with endoscopic inflammation (Langhorst et al., 2016). On the one hand, faecal calprotectin may be deceptively elevated in patients with other GI diseases and with some medications, like commonly used proton pump inhibitors and non-steroidal anti-inflammatory drugs (Lundgren et al., 2019). On the other hand, calprotectin may be low in ileal CrD despite extensive ulcers (Mizoguchi et al., 2021). IBD is possible in patients with faecal calprotectin below the test detection level of 50 μg/g and a clinically relevant CrD cannot be ruled out with a cut-off level of 100 μg/g (Mattila et al., 2022).

### 2.3.3 Pathogenesis

The evolution of IBD clearly follows the advancement of society (Kaplan, 2015). The role of environmental factors is supported by studies showing a relatively low concordance rate in identical twins and the way the incidence of UC increases in second-generation immigrants from Asia to Europe (Bernstein & Shanahan, 2008; Carr & Mayberry, 1999). The dietary factors increasing the risk for IBD are consumption of meat and sucrose, whereas consumption of fruits, vegetables and fibres is regarded as a protective factor (Piovani et al., 2019). Current smoking is a risk-factor for CrD whereas it has been shown to protect against UC in non-Jewish whites (Mahid et al., 2006; Piovani et al., 2019).

Convincing evidence from a variety of studies has shown the presence of gut dysbiosis in IBD patients, suggesting a causative role for microbiome in gut inflammation (Cerf-Bensussan & Gaboriau-Routhiau, 2010). In addition to the environmental factors, the pathogenesis of IBD involves genetic factors and immune response cells (Lee S.H. et al., 2018; Xavier & Podolsky, 2005). Interestingly, as many as 70% of the genetic risk loci are shared with other immune-mediated diseases like type 1 diabetes, coeliac disease (CeD) and many rheumatoid diseases (Zhernakova et al., 2009). Much of the genetic risk lies in how the host interprets the microbial environment (Ananthakrishnan, 2015; Baumgart & Carding, 2007; Jostins et al., 2012, Xavier & Podolsky, 2007). The genetic loci implicated in IBD show several crucial pathways for intestinal homeostasis, including e.g. intestinal barrier function, microbial defence and regulation of adaptive immunity (Khor et al., 2011). Even though UC and CrD have many similarities, they are separate entities with different immunopathogenesis (Park J.H. et al., 2017).

### 2.3.4 Special aspects of ulcerative colitis

UC was first described in a case report as early as in 1875 (Wilks & Moxon, 1875; Kirsner, 2001). Key features of UC include diffuse mucosal inflammation with extensive superficial mucosal, non-transmural ulceration that extends proximally from the rectum and is restricted to the colon (Baumgart & Sandborn, 2007; Xavier & Podolsky, 2007). Depending on the anatomic extent of involvement, patients can be classified as having proctitis, left-sided colitis or pancolitis (Baumgart & Sandborn, 2007). The disease naturally extends, but left-sided colitis is the most frequent location both at the time of diagnosis and during follow-up (Fumery et al., 2018). Histopathological features include the presence of neutrophils within the lamina propria and the crypts, where they form micro-abscesses (Xavier & Podolsky, 2007).

The majority of patients suffering from UC have a mild to moderate disease course, being most active at diagnosis and then with varying periods of remission or mild activity (Fumery et al., 2018; Solberg et al., 2009). The most severe forms are fulminant colitis and eventually toxic megacolon (Baumgart & Sandborn, 2007). Aggressive medical therapy, including intravenous corticosteroids is the first line treatment of the severe forms, but prompt surgical intervention is also often needed (Berg et al., 2002). In contrast to emergent colectomy, elective proctocolectomy is performed in case of lack of response to outpatient medical therapies or the management of colonic cancer (Kaplan et al., 2012). The colectomy rate has been declining since the beginning of the 21st century, especially as concerns elective surgery (Kaplan et al., 2012). In a Norwegian study, the colectomy rate was 9.8% during the first 10 years from diagnosis (diagnosis placed between 1990 and 1994), and one half of colectomies were performed during the first two years (Solberg et al., 2009).

Management of UC should consist of an assessment of an individual patient's risk of poor outcomes and initiation of effective and well-tolerated medical therapies (Rubin et al., 2019). The treatment targets are clinical remission, mucosal healing, normal health-related quality of life, and avoidance of surgery and colonic cancer (Rubin et al., 2019; Turner et al., 2021). The basis of the medical treatment of UC is 5-aminosalicylic acid (5-ASA) preparations; rectally in mild activity of proctitis or left-sided colitis and orally or combined according to increasing activity and extent of the disease – both in induction and in maintenance of remission (Fumery et al., 2018). In more active and extensive disease forms, the induction therapy may involve systemic corticosteroids, immunomodulatory medication, small molecules such as

inhibitors of the Janus kinase enzyme and biological treatments, like tumour necrosis factor inhibitors and anti-integrins. Systemic corticosteroids should be avoided in maintenance therapy (Rubin et al., 2019). New therapies for UC are expected (Sandborn et al., 2021).

### 2.3.5 Special aspects of Crohn's disease

The clinical picture of CrD was described at the beginning of the 20th century, well before the article by Dr Burrill Crohn et al. in 1932 (Crohn et al., 1932; Kirsner, 2001). In addition to the cardinal GI symptoms, fatigue is a prevalent symptom in CrD (Lichtenstein et al., 2018). The extent of CrD can be divided into four; colonic, ileocolonic, terminal ileum and upper GI-tract involvement (Lichtenstein et al., 2018). Perianal disease may present in conjunction with any of these four forms. As a sole manifestation perianal disease is rare (less than 5%) (Ingle & Loftus, 2007). Only a minority of patients will experience a change in disease location over time (Lichtenstein et al., 2018). The histopathological features of CrD are characterized by aggregation of macrophages, sometimes forming non-caseating granulomas. Intestinal inflammation in CrD is typically transmural (Xavier & Podolsky, 2007).

The disease course in early CrD is relapsing and remitting with intermittent symptoms of abdominal pain and diarrhoea, whereas in the late form of CrD, complications of chronic inflammation are frequently included; such as stricture, fistula and abscess development (Peyrin-Biroulet et al., 2010; Sandborn, 2008). Behaviour of CrD is divided into three categories according to the Vienna classification: inflammatory, stricturing and penetrating disease (Gasche et al., 2000). The penetrating form was present in nearly one half of the over 2000 CrD patients in a French single-centre study (Cosnes et al., 2002). CrD can be described as a progressive, destructive disease which in most patients leads to irreversible structural damage of the bowel with frequent need for surgical operations (Peyrin-Biroulet et al., 2010; Sandborn, 2008). Over long periods of observation, only 20 to 30% of CrD patients will have a non-progressive or indolent course (Lichtenstein et al., 2018).

The treatment paradigm in CrD has in recent years shifted from symptom control towards the reduction of long-term sequelae (Pariente et al., 2015; Turner et al., 2021). The role of transmural inflammation and the need for appropriate imaging modalities to assess GI tract damage is understood in the development of scoring systems to evaluate disease progression and efficacy of treatment (Pariente et al., 2015). Smoking cessation is strongly recommended in CrD (Lichtenstein et al.,

2018). Traditionally, CrD has also been treated with 5-ASA preparations, but these have subsequently been proven ineffective in CrD (Sandborn, 2008). Thiopurines are effective and should be considered as the first-line steroid-sparing agents. Biological therapies, like tumour necrosis factor inhibitors, anti-integrins and interleukin 12/23-inhibitors are recommended in thiopurine resistant disease (Lichtenstein et al., 2018). New treatment options for CrD, like inhibitors of Janus kinase enzyme and interleukin 23-inhibitors are anticipated (Ferrante et al., 2022; Loftus et al., 2023). In select cases even dual biological treatment can be considered, but more data on the efficacy and safety of such therapy are needed (Eronen et al., 2022).

## 2.4 Coeliac disease

### 2.4.1 Clinical presentation

The first clinical description of CeD was presented by Samuel Gee in 1888 (Gee 1888, Bottaro et al., 1999). In the 1940s the link between exposure to wheat and CeD was established (Dicke, 1950). The so-called classical phenotype is a severe disease with malabsorption, diarrhoea, weight loss and growth retardation in children (Ludvigsson et al., 2013). Nowadays, CeD is defined as a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals (Ludvigsson et al., 2013).

Symptomatic CeD is characterized by GI, but in more than half of the cases also extraintestinal manifestations – with or without GI symptoms (Jericho et al., 2017; Leffler et al., 2015). Extraintestinal manifestations may affect almost any organ (Laurikka et al., 2018). Some of the manifestations are regarded as direct consequences of autoimmunity, such as the cutaneous form called dermatitis herpetiformis (DH), whereas other are indirectly related to inflammation or malabsorption such as anaemia and delayed puberty (Leffler et al., 2015). However, even anaemia is most likely not just a matter of malabsorption in conjunction with CeD, as it can present even before the development of enteropathy (Repo et al., 2017).

DH occurs in up to 10% of CeD patients in Western countries, but the incidence is decreasing (Reunala et al., 2021). The decrease in DH incidence is most likely due to the increased recognition of subclinical CeD since the 1990s, when serological

screening for CeD became widely available (Salmi et al., 2011). Three-fourths of patients with DH have villous atrophy in the small bowel, and the rest have coeliac-type minor enteropathy (Reunala et al., 2021). Given the occurrence of extraintestinal manifestations, CeD should be regarded as a systemic disease (Korponay-Szabó et al., 2004).

Almost one third of adult CeD patients have a concomitant disease, type 1 diabetes being the most common (Bottaro et al., 1999; Collin et al., 1994). Serological screening has shown the risk of CeD to be as high as 10% in many autoimmune diseases; e.g. type 1 diabetes, Sjögren's syndrome and multiple autoimmune syndromes (Collin et al., 2002a; Kaukinen et al., 2010). Of note, prevalence of CeD can also be as high as 5 to 10% in Down's syndrome (Kaukinen et al., 2010). Any form of GN is more common (odds ratio 1.70, adjusted for diabetes) among CeD patients compared to general population; likewise the risk of dialysis (odds ratio 2.24) (Ludvigsson et al., 2006).

### 2.4.2 Diagnosis and epidemiology

CeD is known today to affect people worldwide (Lindfors et al., 2019). The prevalence of diagnosed CeD in Finland is at least 0.7% (Ilus et al., 2014). According to screening studies, the assumed prevalence of CeD in Finland had increased to as high as 2% at the beginning of the 21st century, being higher than the European mean prevalence of about 1% (Lohi et al., 2007; Mustalahti et al., 2010). Nevertheless, in Finland, too, the disease is widely underrecognized (Mustalahti et al., 2010). CeD is about twice as common among women as among men (Collin et al., 1994; Virta et al., 2009). The disease can occur at any age (Lohi et al., 2007; Mäki et al., 2003; Vilppula et al., 2009).

The diagnostic pathway of CeD usually starts from serological screening (Ludvigsson et al., 2014). Screening may be initiated because the individual has any of the broad symptoms associated with CeD, has a disease associated with CeD or is a first-degree relative of a CeD patient (Kahaly et al., 2018; Lindfors et al., 2019; Viljamaa et al., 2005). Active case finding is recommended rather than population-based mass screening (Bibbins-Domingo et al., 2017). In select patients with high-risk genetics, re-screening could be useful (Paavola et al., 2022).

Serological detection depends on the presence of specific endomysial antibodies (EmA) and transglutaminase 2 antibodies (TG2Ab), referred to as coeliac autoantibodies (Ludvigsson et al., 2014). Interestingly, coeliac autoantibodies have

been found deposited in the small intestinal mucosa before being detectable in the circulation (Korponay-Szabó et al., 2004). EmAs and TG2Abs have excellent sensitivity (90-100%) and close to 100% specificity for CeD (Lindfors et al., 2019). Temporary elevations in antibody tests are seen e.g. in conjunction with infectious diseases without CeD (Ferrara et al., 2009). Traditionally, a positive antibody test would have led to a diagnostic small intestinal biopsy (Ludvigsson et al., 2014).

In 2012, a European guideline allowed diagnosis of CeD to be set in symptomatic children and adolescents with high titres of TG2Ab (> 10 times the upper limit of normal) and positive EmA without a duodenal biopsy (Husby et al., 2012). Since 2018, the same criteria have applied to Finnish patients, also adults, despite the presence or absence of GI symptoms (Celiac Disease: Current Care Guidelines, 2018). If these conditions are not met, the diagnosis is confirmed by a small bowel biopsy from duodenum when the patient is on a gluten-containing diet (Ludvigsson et al., 2014). A duodenal biopsy should also be considered in seronegative patients showing signs of malabsorption (Ludvigsson et al., 2014). To establish a definite diagnosis of CeD, a histological finding of duodenal villous atrophy is required. Other typical findings are crypt hyperplasia and increased infiltration of intraepithelial lymphocytes (Ludvigsson et al., 2014). Yet villous atrophy is not just a peculiarity of CeD as it may be caused by various other pathologies, including autoimmune enteropathy, angiotensin blockers (especially olmesartan), *Helicobacter pylori* infection and human immunodeficiency virus infection (Lindfors et al., 2019, Ludvigsson et al., 2014).

### 2.4.3 Pathogenesis

The term gluten refers in general to various water insoluble seed proteins (prolamins) found in wheat (gliadins and glutenins). Other prolamins with similar immunogenic properties are also found in rye (secalins) and barley (hordeins). Gluten is poorly digested in the human intestine and gluten peptides cross intact into the submucosa of the small intestine (Lindfors et al., 2019). Intact gliadin or peptides complexed with IgA are transported from the apical to the basolateral side of intestinal epithelial cells via CD71 (Lebreton et al., 2012; Mantis et al., 2011). TG2 deamidates gluten peptides, generating an epitope that binds efficiently to HLA (Molberg et al., 1998). The modified HLA-bound gluten peptide is subsequently recognized by gluten-specific T-cells in the intestinal lamina propria. This results in T-cell activation, secretion of a legion of proinflammatory cytokines, production of gliadin- and TG2-

targeted autoantibodies, all followed by extensive tissue remodeling (Korponay-Szabó et al., 2004; Lindfors et al., 2019). Expression of CD71 is increased in epithelial cells in CeD, leading to progressive accumulation of toxic gliadin peptides in subepithelial areas and tissue damage (Matysiak-Budnik et al., 2008).

Gut microbiome is thought to play an important role in the pathogenesis of CeD (Cenit et al., 2015). Altered gene expression of toll-like receptors, destined to recognize different bacterial molecular patterns and located in the intestinal epithelial cells and the lamina propria were found in Finnish paediatric CeD patients (Kalliomäki et al., 2012). Also, a high prevalence of CeD among first-degree relatives of patients with CeD and a great concordance rate in monozygotic twins indicate a strong genetic component in CeD (Ludvigsson et al., 2014; Paavola et al., 2021). CeD is strongly associated with the HLA DQ2 and DQ8 haplotypes. More than 90% of patients share the HLA DQ2 haplotype, and most of the remainder carry the DQ8 haplotype (Kaukinen et al., 2002; Louka & Sollid, 2003). These two haplotypes also predispose to various other autoimmune conditions (Collin et al., 2002b). As DQ2 is a common HLA-type, there are also non-HLA associated risk factors for CeD (Dubois et al., 2010).

### 2.4.4 Treatment

A lifelong and strict gluten-free diet (GFD) is the mainstay of safe and effective treatment of CeD (Adriaanse et al., 2016). GFD usually refers to a diet free from wheat, rye and barley (Ludvigsson et al., 2013). The goal of the treatment is to relieve symptoms, achieve mucosal healing, avoid complications of CeD and promote a good quality of life (Viljamaa et al., 2005). Patients should be encouraged to eat naturally occurring gluten-free foods and alternative sources of carbohydrates (oat, corn, rice, potatoes etc.). It is important that the patients learn not only to avoid gluten but also to have sufficient intake of nutrients, vitamins, fibre and calcium (Ludvigsson et al., 2014). Long-term regular follow-up of patients is recommended in order to maintain good adherence to the diet (Lindfors et al., 2019; Tye-Din et al., 2022). As maintaining a strict GFD is difficult in practice, novel therapies are being studied (Lähdeaho et al., 2019).

## 2.5 The gut-kidney axis

### 2.5.1 Intestinal barrier and immunoglobulin A

The intestinal mucosa plays a decisive role as the site for the absorption of nutrients, but at the same time it is a crucial barrier against exogenous antigens and pathogens (Ramezani & Raj, 2014). The intestinal barrier includes surface mucus, interconnected epithelial cells and a well-evolved immune system, immunoglobulin A as a crucial part of it (Camilleri, 2019; Johansson et al., 2014). The mucosal immune system must be able on the one hand to defend against pathogenic incursions, but on the other hand to curtail the inflammatory responses to maintain a hyporesponsive state to commensal bacteria (Khor et al., 2011).

IgA influences the composition of the intestinal microbiome and promotes transport of antigens across the intestinal epithelium to gut-associated lymphoid tissue, which contains large numbers of IgA-producing cells (Kang et al., 2002; Mantis et al., 2011). Peyer's patches are regarded as the most significant immunological components of the gut-associated lymphoid tissue and they are most numerous in the terminal ileum (Barratt et al., 2020; Van Kruiningen et al., 2002).

IgA is the most abundantly produced immunoglobulin (about 65 mg/kg/day) in humans (Montenegro & Monteiro, 1999). IgA mediates multiple functions through interactions with specific receptors, which are expressed on a diverse range of cell types (Woof & Ken, 2006). There are two subclasses of human IgA; IgA1 and IgA2 (Woof & Ken, 2006). The majority of IgA is produced on mucosal surfaces, in which case both of the two subclasses are almost exclusively in a polymeric form (Zhang J et al., 2007). Mucosal IgA production is induced both by T-cell-dependent and independent mechanisms, in the latter case primarily stimulated by various interleukins and other cytokines (Coppo, 2018). The ratio of plasma cells secreting the two IgA subclasses changes throughout the GI tract, those secreting IgA1 being more abundant in the small intestine (Barratt et al., 2020).

Mucosal polymeric IgA is transported across the epithelial barrier into external secretions (Zhang J et al., 2007). Transport of polymeric IgA is mediated by the polymeric receptor (Zhang J et al., 2007). Once bound, the receptor-IgA complex is internalized and secreted at the luminal side of an epithelial cell. Secreted this way, polymeric IgA retains a portion of the polymeric receptor, forming secretory IgA that serves as the first line of defence against micro-organisms (Corthésy, 2007; Kerr, 1990; Zhang J et al., 2007).

In serum, IgA is mostly (up to 90%) in monomeric form, which is mainly produced by bone marrow plasma cells (Papista et al., 2011). Only little of the polymeric IgA reaches the circulation (Papista et al., 2011). IgA is the second most abundant immunoglobulin isotype in serum, after immunoglobulin G (Kerr, 1990). The role of monomeric IgA is essential in controlling the immune system by preventing the development of autoimmunity and inflammation (Jacob et al., 2008).

### 2.5.2 Indirect measurement of intestinal barrier damage

Intestinal inflammation leads to increased intestinal permeability with an elevated risk of bacterial translocation and endotoxemia (Rojo et al., 2007). Lipopolysaccharides (LPS) are the main component of the outer membrane of the cell wall of Gram-negative bacteria (Raetz & Whitfield, 2002). The term endotoxin refers to the hydrophobic anchor of LPS, lipid A, but is typically used synonymously with LPS (Raetz & Whitfield, 2002; Rojo et al., 2007). Once in the circulation, endotoxins form complexes with the lipopolysaccharide-binding protein (LBP), leading to activation of the immune system (Rojo et al., 2007). Endotoxins are very difficult to measure from blood samples, due in part to their short half-lives (1-3 hours) and low levels in the circulation (Hurley, 1995; Rojo et al., 2007). By contrast, the LPS recognition proteins LBP and soluble CD14 (sCD14), have long half-lives (24-48 hours), are measurable from blood samples and reflect long-term exposure to endotoxins (Rojo et al., 2007).

LBP and sCD14 play decisive roles in promoting innate immunity to Gram-negative bacteria, both by enhancing inflammation at local sites, and at the same time by preventing potentially detrimental systemic responses to endotoxins (Kitchens 2005). Elevated serum levels of LBP have been found in IBD patients, correlating with disease activity (Lakatos et al., 2011; Pasternak et al., 2010; Rojo et al., 2007). Results with serum sCD14 have been somewhat inconsistent in IBD (Lakatos et al., 2011; Pasternak et al., 2010; Rojo et al., 2007).

Intestinal fatty-acid binding proteins (I-FABP) are small cytosolic proteins present in enterocytes, mainly in the jejunum (Derikx et al., 2009). In the event of enterocyte damage I-FABP are released into the circulation and thus elevated serum levels are found, for example, in untreated CeD (Adriaanse et al., 2013; Derikx et al., 2009). Serum levels of I-FABP have been shown to correlate with the degree of villous atrophy and coeliac autoantibody levels (Adriaanse et al., 2013; Vreugdenhil

et al., 2011). Also, serum I-FABP levels were shown to increase during a short gluten challenge in CeD patients (Adriaanse et al., 2016).

Although intestinal permeability can be assessed on tissue samples (*in vitro*), it has most commonly been measured indirectly by the urinary excretion of orally ingested probes (*in vivo*) that enter the bloodstream by crossing the intestinal epithelium via the paracellular pathway (Camilleri, 2019). Radioactive chromium complexed with ethylene diamine tetracetic acid ($^{51}$Cr-EDTA) as a probe molecule and two-sugar assays (e.g. cellulose and mannitol) are the traditionally most often used study methods (Seikrit et al., 2023). It should be noted that, for example, bacterial breakdown of sugars may lead to false-negative results with sugar probe tests (Camilleri, 2019; Rostoker et al., 1993). A multi-sugar analysis has been shown to provide an accurate and site-specific analysis of intestinal permeability (Van Wijck et al., 2013).

### 2.5.3 Intestinal barrier and gut microbiome in chronic kidney disease

Structural and functional alterations of the intestinal barrier are seen in ESKD, including increased intestinal permeability (Magnusson et al., 1991; Vaziri et al., 2016). Uremia has been shown to deplete the key proteins of intestinal epithelial tight junctions throughout the GI tract in rats (Vaziri et al., 2012b, 2013b). Incubation of tight junction-forming human enterocytes ex vivo in the pre-dialysis plasma from ESKD patients led to marked reduction in the number of the tight junction proteins compared with incubation in the post-dialysis plasma (Vaziri et al., 2012a).

Disruption of intestinal barrier in CKD allows translocation of endotoxins and bacterial metabolites into circulation, which is claimed to contribute to systemic inflammation and further progression of CKD and cardiovascular disease (McIntyre et al., 2011; Ramezani & Raj, 2014). Gut bacterial translocation has also been shown to occur in ESKD, probably in conjunction with systemic inflammation (Wang F et al., 2012). Systemic inflammation in turn is associated with elevated mortality among CKD and ESKD patients (McIntyre et al., 2011; Zimmermann et al., 1999). Systemic inflammation present in ESKD is multifactorial (Bossola et al., 2009).

The composition of the gut microbiome has been shown to differ between healthy people and patients in ESKD (Vaziri et al., 2013a). There are multiple factors potentially affecting the composition of the gut microbiome in ESKD, including dietary restrictions, use of phosphate-binding agents, use of antibiotics, uremia itself

etc. (Anders et al., 2013; Vaziri et al., 2013a, 2016). Proliferation of dysbiotic intestinal bacteria in uremic milieu, and the ensuing production of uremic toxins capable of entering the circulation is a well-known phenomenon (Anders et al., 2013; Lau et al., 2015; Ramezani & Raj, 2014). To substantiate this, the plasma levels of two well-known uremic solutes, *p*-cresol sulphate and indoxyl sulphate, did not differ between dialysis patients who had previously undergone colectomy and healthy controls, as opposed to dialysis patients with intact colons (Aronov et al., 2011). Therapies to reduce colonic uremic retention molecules have been studied, but none have passed into clinical use (Evenepoel et al., 2009).

### 2.5.4 Gastrointestinal symptoms in chronic kidney disease

GI symptoms occur in approximately 70% of patients with kidney failure (Shirazian 2010). GI problems present in CKD and ESKD are diverse and tend to increase with progressive kidney failure (Costa-Moreira et al., 2020). Some kidney diseases have clear organic reasons for GI symptoms, like pain associated with cysts and liver problems in polycystic kidney disease (Hogan & Norby, 2010; Mikolajczyk et al., 2017). GI symptoms are common especially among patients with ESKD (Cano et al., 2007; Strid et al., 2002). Symptoms may be associated with uremia itself, but also with many drugs, dietary changes or lifestyle restrictions as a result of the illness or the dialysis treatment (Cano et al., 2007). Increased prevalence of GI symptoms has also been seen well before ESKD, yet symptoms probably become more prevalent below eGFR 45 ml/min (Zhang X et al., 2015).

Constipation is common among patients treated with peritoneal dialysis or haemodialysis, but also in those with advanced CKD that has not yet progressed to dialysis (Kosmadakis et al., 2018; Sumida et al., 2020; Yasuda et al., 2002). Abdominal pain and IBS are more common among dialysis patients than among people with preserved kidney function (Cano et al., 2007). A systematic review including over 5,000 dialysis patients found constipation, indigestion, abdominal pain and reflux to be the most prevalent GI symptoms (Zuvela et al., 2018). Constipation is more common among haemodialysis patients than among patients in peritoneal dialysis, whereas patients in peritoneal dialysis suffer more from reflux and eating dysfunction (Dong et al., 2014; Strid et al., 2002). GI symptoms correlate negatively with quality of life in CKD patients (Ekberg et al., 2007; Ponticelli et al., 2010; Strid et al., 2002).

Presence of GI symptoms has also been evaluated also among kidney transplant recipients and shown to be prevalent (Ekberg et al., 2007; Kleinman et al., 2006;

Ponticelli et al., 2010). Even though GI symptoms are common among transplant recipients, patients seldom report their symptoms to doctors (Ponticelli et al., 2010). One of the three key components in particular in the modern immunosuppression regime, mycophenolate mofetil, has GI side-effects that may necessitate dose reductions and thus even lead to increased risk of rejection (Kleinman et al., 2006; Shehata et al., 2009).

### 2.5.5 Intestinal mucosa in IgA nephropathy

An hypothesis of an exaggerated IgA antibody response to various antigenic stimuli leading to increased production of IgA-containing immune complexes and their deposition in glomerular mesangium was presented back in the 1980s (Coppo et al., 1992; Pasternack et al., 1986). For example, serum antibody response to a previously common enteric pathogen, *Helicobacter pylori*, was found to be exaggerated in IgAN patients (Barratt et al., 1999). Also, serum antibodies to dietary antigens like gluten have been found to be elevated in patients with IgAN (Nagy et al., 1988). Under normal circumstances, ingested dietary proteins would not activate immunological mechanisms (Coppo et al., 1992).

Oral vaccinations have also been shown to lead to enhanced antibody response in IgAN (Leinikki et al., 1987) as have various vaccines injected subcutaneously (Endoh et al., 1984; Fortune et al., 1992; Pasternack et al., 1986). Regardless of the route of immunization, the antigen-specific IgA responses were seen predominantly in polymeric forms, but in both IgAN patients and controls (Eijgenraam et al., 2008). Recently, both IgAN patients and patients with other GN were shown to have increased levels of circulating intestinal-activated B lymphocytes compared with healthy controls (Sallustio et al., 2020). The finding was interpreted to support the pathogenic role of hyperresponsive intestinal mucosa in IgAN, resulting in abnormal production of Gd-IgA1.

It has been speculated that a mucosal infection could prime naïve B cells to class-switch to IgA-secreting plasma cells (Boyd et al., 2012). The majority of B cells in the intestinal immune system undergo class-switch in Peyer's patches and the adjacent lamina propria (Barratt et al., 2020; Lycke & Bemark, 2012). Hence, the idea in treating IgAN patients with enteric budesonide is that the target area of the medicine, the terminal ileum, is the region of the GI tract with the highest density of Peyer's patches (Barratt et al., 2020).

Intestinal permeability evaluated with $^{51}$Cr-EDTA was found elevated in IgAN patients with preserved kidney function and the increased permeability was associated with increased proteinuria and haematuria. During a four-year follow-up the deterioration of kidney function was greater in IgAN patients with increased intestinal permeability (Kovács et al., 1996). The same method showed an increased intestinal permeability also to exist in other primary GN (Rostoker et al., 1993). Conversely, another small study using mannitol and cellobiose found no signs of increased intestinal permeability in 18 patients with IgAN, of whom almost all had active urinary sediment in means of haematuria (Layward et al., 1990). As stated in Chapter 2.5.2, methodological differences could explain the discrepancy found. Only recently did German researchers find an elevated small intestinal permeability among patients with variable glomerular diseases, including IgAN, and concluded that elevated intestinal permeability was not specific to IgAN (Seikrit et al., 2023). However, this was a single-centre study, in which fifteen out of the eighteen control patients were receiving immunosuppressive therapy.

Hyperresponsitivity in IgAN could favour abnormal responses to gut microbiome, lead to increased antigen absorption and activation of the immune system, followed by subclinical intestinal inflammation (Coppo, 2015). Increased numbers of intestinal intraepithelial inflammatory cells have been reported in many studies on IgAN patients (Honkanen et al., 2005; Rantala et al., 1999; Rostoker et al., 2001). The findings have correlated with the amount of proteinuria and haematuria (Honkanen et al.; 2005, Rostoker et al., 2001). Increased numbers of inflammatory cells were also found in the duodenal biopsies of IgAN patients with elevated antigliadin antibody levels, without verified CeD (Almroth et al., 2006). Thus, an ongoing subclinical small intestinal inflammation and stress with microscopically normal epithelial architecture has been speculated to be present in IgAN (Rantala et al., 1999).

Finally, in a mouse model of vasculitis, intestinal T lymphocytes were found to be mobilized from the gut to the kidneys (Krebs et al., 2016). Interestingly, a subtype of T lymphocytes (γδ T cells) mostly found at mucosal epithelial surfaces was found in kidney biopsies of patients suffering from progressive IgAN (Falk et al., 1995). Both diminished and elevated levels of γδ T cells have been found in the duodenal mucosa of patients with IgAN (Olive et al., 1997; Rantala et al., 1999). Comparison of these contrasting results is difficult because the two studies used different methods. Convincingly, genetically manipulated mice which developed a spontaneous T cell-mediated intestinal inflammation had serum IgA levels up to 30-

to 40-fold higher than wild type mice and increased glomerular depositions of IgA and C3 (Wang et al., 2004).

### 2.5.6 Inflammatory bowel disease and kidneys

Kidney and urinary complications have been reported to occur in up to 23% of IBD patients, but a majority of these are urological problems (Corica & Romano, 2015; Pardi, 1998). Various forms of kidney disease in conjunction with IBD have been reported, GN among others (Katsanos & Tsianos, 2002; Lakatos et al., 2003; Thomas et al., 1990). Tubulointerstitial nephritis (TIN) is a well-known, yet an uncommon EIM of IBD and traditionally attributed to 5-ASA therapy (Birketvedt et al., 2000; Colvin et al., 2014; De Jong et al., 2005; Gisbert et al., 2007; Ransford & Langman, 2002; Van Staa et al., 2004). Other medications used to treat IBD can also cause kidney injury, cyclosporin A and tumour necrosis factor inhibitors being among the most common ones (Corica & Romano, 2015). Kidney recovery may be incomplete after withdrawal of 5-ASA (Heap et al., 2016).

The most common urological manifestations in IBD are urine stones (urolithiasis), enterovesical fistulas and ureteral obstruction (Katsanos & Tsianos, 2002; Pardi, 1998). The prevalence of urolithiasis in IBD varies between 3.0% and 6.7% (Fagagnini et al., 2017; Herbert et al., 2022). The lifetime risk for urolithiasis in IBD is estimated to be 9 to 18% (Van Hoeve & Hoffman, 2022). Asymptomatic urine stones were found in 38% of surgery-naïve IBD patients in a Brazilian single-centre study (Cury et al., 2013). Various mechanisms lead to urine stone formation of different origin; uric acid, calcium oxalate and calcium phosphate (Katsanos & Tsianos, 2002; Parks et al., 2003). Uric acid stones form as a result of intestinal fluid and bicarbonate losses leading to concentrated and acidic urine, especially after colon resection (Parks et al., 2003). Calcium oxalate stones are related to increased urinary oxalate excretion caused by increased intestinal oxalate absorption due to different mechanisms (Corica & Romano, 2015; Katsanos & Tsianos, 2002).

Tubular injury has likewise frequently been seen in the absence of 5-ASA and tubular proteinuria has been shown to depend on the disease activity in both CrD and UC (Fraser et al., 2001; Herrlinger et al., 2001; Poulou et al., 2006; Schreiber et al., 1997; Van Staa et al., 2004). An older study concluded that IBD patients treated with higher doses of 5-ASA suffered from an increased prevalence of tubular proteinuria, but in fact tubular proteinuria may also have been merely associated with the activity of IBD (Schreiber et al., 1997). In a small study with only six weeks of

follow-up, patients treated with 5-ASA were found to have both lower IBD activity indices and lower urinary excretion of a sensitive enzyme of tubular injury, β-N-acetyl-D-glucosaminidase (Dehmer et al., 2003). Interestingly, microalbuminuria has also been detected in IBD patients, and it too has correlated with the severity of colonic inflammation (Mahmud et al., 1994, 1996).

### 2.5.7 Inflammatory bowel disease and IgA nephropathy

IgAN was the most frequent kidney biopsy diagnosis among IBD patients in a large American study, the prevalence being about 3-fold higher compared to that in all other native kidney biopsies (Ambruzs et al., 2014). GWAS have identified shared susceptibility loci for both IgAN and IBD (Gharavi et al., 2011; Kiryluk et al., 2014; Shi et al., 2020). A Mendelian randomization study recently conducted on patients with European ancestry showed a positive causal relationship of both CrD and UC with IgAN (Xiao et al., 2022).

IBD patients with active intestinal inflammation have been shown to have significantly increased numbers of IgA-producing cells in the gut. The finding was found to be accompanied with more haematuria and elevated serum levels of IgA (Wang et al., 2004). The activity of IBD, both UC and CrD, has been shown in many case reports to affect the clinical course of concomitant IgAN (Choi et al., 2012; Forshaw et al., 2005; Onime et al., 2006).

Various forms of GN have been reported in conjunction with IBD (Corica & Romano, 2015; Doumas et al., 2023). The possible association with other GN and IBD is less conclusive (Corica & Romano, 2015). There is probably a generalized breakdown of intestinal tolerance in various primary GN (Rostoker et al., 2001). Renal amyloidosis is a rare complication of IBD, usually associated with longlasting disease and persistent inflammation (Corica & Romano, 2015). However, in an Egyptian single-centre study, amyloidosis was surprisingly the most common kidney biopsy finding, followed by IgAN (Elaziz & Fayed, 2016).

The risk of ESKD was found to be doubled in IgAN patients with IBD compared to IgAN patients without IBD in a Swedish population-based register study. Conversely, compared to IBD patients without IgAN, the risk of ESKD was about 30-fold in patients having both IBD and IgAN (Rehnberg et al., 2021). In a small single-centre Japanese study comparing IgAN patients with and without CrD, the kidney lesions were more advanced according to the Oxford classification in patients with CrD (Akiyama et al., 2022). In a French study kidney survival was similar in

IgAN patients with and without IBD in a mean follow-up of 82 months (Joher et al., 2021).

### 2.5.8 Coeliac disease and IgA nephropathy

According to a Swedish nationwide population study the risk of IgAN among biopsy-verified CeD patients was 3-fold compared to that among reference individuals (0.026% vs. 0.008%) (Welander et al., 2013). A meta-analysis of eight studies showed increased risks of IgAN, diabetic nephropathy and ESKD in patients suffering from CeD (Wijarnpreecha et al., 2016).

The prevalence of CeD in IgAN was found to be about 4-fold compared to that in the general population of Finland (Collin et al., 2002b). Nevertheless, coeliac-type HLA-DQ2/8 was not found to be increased in IgAN (Collin et al., 2002b). Nor has IgAN been consistently linked to any other HLA-DQ allele among Caucasian populations (Fennessy et al., 1996). Conversely, there is no evidence that IgAN is particularly common among patients with CeD (Bottaro et al., 1999; Collin et al., 1994; Moeller et al., 2014).

Despite the lack of irrefutable associations between IgAN and CeD, there are many intriguing phenomena conjoining the two diseases. Significantly higher serum levels of Gd-IgA1 have been found in male CeD patients compared to healthy individuals and the IgA1-type TG2Abs were also aberrantly glycosylated in CeD patients (Lindfors et al., 2011). Glomerular mesangial IgA deposits have been found in a substantial proportion of both CeD and DH patients (Pasternack et al., 1990; Reunala et al., 1983). However, no clinically overt GN was induced, most likely because of the lack of complement activation (Pasternack et al., 1990). A correlation between glomerular TG2 staining and histological signs of advanced kidney disease has been reported in IgAN patients (Ikee et al., 2007). It should nevertheless be born in mind, that TG2 most likely plays an important role in scarring and fibrosis formation in CKD in general (Johnson et al., 2003).

IgA-class antigliadin antibodies (IgA-AGA) have been found to varying extents in IgAN patients, ranging from 3% to up to 70% (Almroth et al., 2006; Fornasieri et al., 1987; Laurent et al., 1987; Nagy et al., 1988; Ots et al., 1999; Sategna-Guidetti et al., 1992). On the one hand, the discrepancy between the studies is most likely attributable to different methods (Sategna-Guidetti et al., 1992). On the other hand, IgA-AGA have been more elevated in IgAN patients with longer disease duration (Ots et al., 1999). Even though elevated IgA-AGA levels are frequently present in

IgAN, the more specific EmAs have been tested negative multiple times (Almroth et al., 2006; Ots et al., 1999; Rostoker et al., 1988; Sategna-Guidetti et al., 1992). In one study, EmAs were found in IgAN patients, yet in most cases this was seen when tested for immunoglobulin G1-class autoantibodies instead of the widely used IgA-class autoantibodies (Pierucci et al., 2002).

Gluten has been shown to be capable of exacerbating IgAN in humanized mice (Papista et al., 2015). Gluten may act as a toxic lectin, increasing the permeability of the intestinal mucosa in IgAN (Coppo, 1988). This hypothesis was supported by the finding of decreased levels of antibodies against other alimentary components in IgAN patients on GFD (Coppo, 2015). Interestingly, GFD has also been shown to be associated with a decrease in IgA immune complex levels in IgAN patients (Coppo et al., 1986, 1990) and further to reduce the amount of proteinuria and haematuria in an uncontrolled trial of a minimum duration of six months (Coppo et al., 1990). In a more recent study, rectal mucosal sensitivity to gluten was present in one third of IgAN patients (Smerud et al., 2009). In a case series, positive IgA-AGA led to CeD diagnosis in two out of the three asymptomatic IgAN patients who underwent gastroscopy (Fornasieri et al., 1987). On GFD, microscopic haematuria and IgA-AGAs disappeared in these two patients (Fornasieri et al., 1987). A Finnish case report confirmed total remission of IgAN on GFD (Koivuviita et al., 2009). GFD, however, has not been studied in randomized studies, probably due to the mounting interest in the benefits of corticosteroids in the early 1990s (Coppo, 2015).

# 3 AIMS OF THE STUDY

The aims of this dissertation were to assess the prevalence of diagnosed enteropathies among patients referred to kidney biopsy and to evaluate the presence of diagnosed enteropathies and subclinical intestinal damage or inflammation among IgAN patients according to the prevailing hypothesis of the pathogenesis of IgAN.

The specific aims were:

1. To evaluate the prevalence of IBD and the phenotypes of IBD in patients who have undergone kidney biopsies due to clinical indications. (Study I)
2. To elucidate whether IBD has an influence on kidney and patient outcomes among patients with biopsy-verified kidney diseases. (Study I)
3. To examine the prevalence of IBD in IgAN over time. (Study II)
4. To examine the prevalence of CeD, including screen-detected coeliac autoimmunity, in IgAN over time. (Study II)
5. To evaluate the prevalence of gastrointestinal symptoms and health-related quality of life among IgAN patients with no known enteropathies. (Study III)
6. To evaluate the presence of subclinical IBD or CeD in IgAN patients with faecal calprotectin and serum coeliac autoantibody tests. (Study IV)
7. To measure the serum levels of three indirect biomarkers of intestinal damage in IgAN patients with no known enteropathies and to compare the results to those of patients suffering from dyspepsia and to healthy people. (Study IV)
8. To evaluate the correlation between gastrointestinal symptoms and the serum levels of the indirect biomarkers of intestinal damage in IgAN patients with no known enteropathies. (Study IV)

# 4 MATERIALS AND METHODS

## 4.1 Study populations

### 4.1.1 Patients

All studies were conducted at the Celiac Disease Research Center (CeliRes), Tampere University and at the Department of Internal Medicine, Tampere University Hospital (TAUH). All patients were diagnosed in TAUH. Study populations are presented in Table 1.

Study I comprised 824 consecutive patients over 16 years of age who had undergone a kidney biopsy due to clinical indications between January 2000 and December 2012. Data was missing in five patients, yielding a study population of 819 patients. Follow-up was started from the time of kidney biopsy. Patients were divided into two groups depending on whether or not they had been diagnosed with IBD.

Study II comprised 629 patients over 16 years of age with a newly diagnosed IgAN between January 1976 and December 2012. Patients were divided into four groups according to the year when IgAN had been diagnosed (1976-1979, 1980-1989, 1990-1999, 2000-2012). Patients were also subdivided into three groups according to their enteropathy status: a) previously diagnosed CeD, b) screen-detected coeliac autoimmunity and c) previously diagnosed IBD. Follow-up was started from the time of kidney biopsy.

In Study III, 206 IgAN patients with no previous diagnosis of IBD or CeD and who had preserved kidney function received the study questionnaires and the study information by post. By replying to the questionnaires, 104 IgAN patients became enrolled in the study. Originally, the clinical histories of 533 patients diagnosed with IgAN from 1980 to 2018 were scrutinized. According to the predefined exclusion criteria 327 patients were excluded as follows: death (n=51), progression to ESKD (defined as eGFR < 15/ml/min/1.73m$^2$, initiation of maintenance dialysis or kidney transplantation, n=64), age under 18 or over 80 at recruitment (n=78), known chronic enteropathy (CeD or IBD, n=16), move to another hospital district (n=79),

or other obvious reason for exclusion (major GI surgery performed, missing contact information, short life-expectancy for any reason, or a labile mental disorder, n=39).

Eighty-five of the 104 IgAN patients in Study III volunteered to give biological samples forming the study group for Study IV. Blood samples were taken from all 85 patients and faecal samples from 57 IgAN patient volunteers.

**Table 1.** Brief overview of the study patients.

| | Study population | Diagnostic kidney biopsy conducted | Age at kidney biopsy, years, median (min-max) | Time since kidney biopsy, years, median (min-max) |
|---|---|---|---|---|
| Study I | 819 patients referred to kidney biopsy, including 151 IgA nephropathy patients | 2000-2012 | 59 (16-85) | 5 (0-15) |
| Study II | 629 IgA nephropathy patients | 1976-2012 | 42 (16-80) | 14 (0-37) |
| Study III | 104 IgA nephropathy patients<br>147 healthy controls* | 1980-2018 | 38 (8-70) | 11 (1-38) |
| Study IV | 85 IgA nephropathy patients<br>14 dyspepsia controls*<br>15 healthy controls* | 1980-2018 | 41 (8-68) | 11 (1-38) |

*kidney biopsy had not been conducted for controls

### 4.1.2 Controls

In Study I, comparisons were made between the two kidney disease patient groups, those with IBD and those without. In Study II, the prevalence rates of CeD, screen-detected coeliac autoimmunity and IBD in IgAN patients were compared to those of general Finnish population (Collin et al., 1997; Ilus et al., 2014; Jussila et al., 2013; Lohi et al., 2007; Manninen et al., 2010).

The healthy controls in Study III were participants from an earlier study in CeliRes (Laurikka et al., 2016). The control group of originally 160 people was limited to those of the same age as the IgAN patients (18 to 80 years), leaving 147

people as the healthy controls. The controls had no known intestinal diseases, nor had they first-degree relatives with CeD. The controls were used for the comparison of the questionnaires and no biological information except age and sex was available.

Dyspepsia controls and healthy controls in Study IV were participants from earlier studies in CeliRes (Kurppa et al., 2009; Laine et al., 2018). The dyspepsia controls had undergone gastroscopies with normal findings, excluding CeD. The healthy controls were relatives of CeD patients but had tested negative for CeD. No other clinical information except age and sex was available on the controls.

## 4.2 Kidney biopsies

Kidney biopsies were taken and processed using standard methods. All specimens were studied with light and immunofluorescence microscopy by two renal pathologists. Both native kidney biopsies and biopsies from transplanted kidneys were included. The diagnosis of IgAN was based on the presence of glomerular IgA as the sole or predominant finding on immunofluorescence microscopy (Mustonen et al., 1985).

Based on the histopathological findings, five kidney disease groups were categorized in Study I: glomerular diseases, tubulointerstitial diseases, vascular diseases, other findings (e.g. cystic and congenital diseases) and no glomeruli (inadequate sample). If a patient had undergone multiple kidney biopsies during the study period, the first diagnostic biopsy was included in both Studies I and II.

Prior to Study I, the kidney biopsy indications had been classified in hierarchical order to seven as follows: 1) kidney insufficiency (elevated creatinine level), 2) nephritic syndrome (haematuria and daily urinary excretion exceeding 1.5 g of protein), 3) proteinuria and haematuria (haematuria and daily urinary excretion of less than 1.5 g of protein), 4) nephrotic syndrome (daily urinary excretion of more than 3.5 g of protein without haematuria), 5) proteinuria (daily urinary excretion of protein 0.3–3.5 g without haematuria), 6) haematuria (daily urinary excretion of protein less than 0.3 g), or 7) any other indication (Wirta et al., 2008). This classification was used in Study II. In Study I, the biopsy indications were further classified into three groups: 1) abnormal urinary findings: including nephritic syndrome, nephrotic syndrome, proteinuria and haematuria; 2) kidney failure; and 3) any other indication.

## 4.3 Clinical data

### 4.3.1 General data

In Study I, the histories of all 819 patients were scrutinized from the medical records of TAUH between 2014 and 2016. Information regarding other diagnosed diseases, including IBD, was collected systematically. Detailed data on the activity of IBD, medication used, location of IBD, GI surgery performed and possible EIMs were collected. Location of IBD was determined by means of endoscopy or GI imaging reports and grouped into five different categories as follows: proctitis, left-sided colitis (including proctosigmoiditis), pancolitis or ileocolonic colitis, small intestinal disease (no colonic affliction) and unknown. EIMs comprised diseases of organs commonly accepted to be involved in IBD; diseases of the joints, eyes, skin, liver, biliary tract and urinary tract.

In Study II, there was no access to the medical records of 77 IgAN patients diagnosed in the 1970s, but data on IBD and CeD diagnosed before 1983 were available from a previous report (Mustonen, 1984). For the remaining 552 IgAN patients diagnosed from 1980 onwards, the clinical data were systematically collected from the medical records with similar principles by two investigators from 2014 to 2018. Data on diagnosis of IBD and CeD as well as data on relevant comorbidities including type 1 and 2 diabetes, hypertension and hypercholesterolemia were collected.

In Study III, the medical histories of all available 533 IgAN patients were selectively reviewed with regard to the predefined exclusion criteria in 2019. For the participating 104 patients the medical histories were read in more detail and data on relevant comorbidities, medications, abdominal surgery, outpatient and inpatient visits to the nephrological unit and selected laboratory results were collected between 2019 and 2020. The 85 IgAN patients in Study IV were volunteer patients from Study III and no new data from the medical records were collected.

### 4.3.2 Kidney function

In Study I, data on plasma creatinine concentration, quantitative 24-hour urinary protein excretion and haematuria proven by dipstick test were gathered from the medical records at the time of kidney biopsy and at the most recent follow-up. Data

on chronic dialysis treatment or kidney transplantation during follow-up were moreover recorded and collectively named as ESKD. Only patients followed up for at least one year after the kidney biopsy and with no new kidney transplantation or chronic dialysis initiated during follow-up were included in the kidney function calculations at the most recent follow-up.

In Study II, data on plasma creatinine concentration, dipstick test proven haematuria and proteinuria, and daily urinary protein excretion rate at the time of the kidney biopsy were gathered from the medical records.

In Study III, data on plasma creatinine concentration, dipstick test proven haematuria and proteinuria at the time of kidney biopsy and at the latest control (no more than one year preceding study enrollment) were collected from the medical records. Data were collected at the stable phase of kidney disease, excluding possible acute situations. Current kidney function was evaluated from the latest plasma creatinine measurement. The same data were utilized in Study IV.

The urine dipstick tests for haematuria and proteinuria were dichotomized as negative (values 0 or +) or positive (++ or +++) similarly in all four studies. eGFR was defined using the CKD-EPI 2009 equation (Levey et al., 2009). eGFR > 60 ml/min/1.73m$^2$ was categorized as preserved kidney function and eGFR < 60 ml/min/1.73m$^2$ as impaired kidney function in Studies III and IV.

Annual change in eGFR (Studies I and IV) was calculated by dividing the difference between the latest eGFR and the eGFR at the kidney biopsy by the number of years of follow-up.

## 4.4 Questionnaires

Both the IgAN patients and the healthy controls in Study III completed the Gastrointestinal Symptom Rating Scale (GSRS) to systematically evaluate current GI symptoms (Dimenäs et al., 1995, 1996; Svedlund et al., 1988). The questionnaire has been translated into Finnish (Appendix 1) but not validated in a Finnish population. The questionnaire evaluates five sub-dimensions of GI symptoms: indigestion, diarrhoea, abdominal pain, reflux and constipation. It comprises altogether 15 separate items. The scoring goes from one to seven points, where one point signifies no symptoms, and seven points signifies the most severe symptoms. The values for each of the five sub-dimension scores were calculated as means of the respective items and the total GSRS score as a mean of all 15 items.

A person was deemed to suffer from 'increased GI symptoms' if the total GSRS score exceeded plus 1 standard deviation (SD) of the mean of the total score in the healthy controls. The same principle was applied to the GSRS sub-scores: 'increased symptoms' were taken to be present if an individual's score exceeded plus 1 SD of the mean of the corresponding sub-score in the healthy controls (Laurikka et al., 2016).

All participants also completed the Psychological General Well-Being (PGWB) index to measure health-related quality of life. The questionnaire has been translated into Finnish (Appendix 2) but not validated in a Finnish population. The questionnaire consists of 22 separate items covering six different sub-dimensions: anxiety, depression, wellbeing, self-control, general health and vitality. The scoring goes from 1 to 6 points, higher score indicating better quality of life (Dimenäs et al., 1995). The sub-dimension scores are calculated as a sum of the items in each sub-dimension and the total PGWB score as a sum of all 22 items (Dimenäs et al., 1996).

If a patient failed to answer one or two items in the GSRS or PGWB questionnaires, the missing answer was replaced by the mean value of the other scores for the same subject. If more than two answers were missing, the questionnaire was rejected.

IgAN patients' diagnosed co-morbidities and current height and weight were elicited with a short questionnaire created for Study III (Appendix 3). Self-reported body mass index (BMI) was calculated according to numbers reported, by dividing the weight (kilogrammes) by the square of height (metres). In this questionnaire, smoking status and alcohol consumption were elicited with standardized tools: The Fagerström Test for Nicotine Dependence (Fagerström & Schneider, 1989; Pomerleau et al., 1994) and the Alcohol Use Disorders Identification Test - Consumption (Higgins-Biddle & Babor, 2018) questionnaire respectively.

The GSRS scores from Study III were reused for the IgAN patients in Study IV as the scores were correlated with the indirect biomarkers of intestinal damage (see in more detail Chapter 4.5).

## 4.5 Laboratory testing

Blood samples have been taken for study purposes from all volunteer patients undergoing kidney biopsies in TAUH since 1980. These samples have been centrifuged at 1,500 G for 10 minutes and subsequently frozen and stored at -80°C until analysis. In Study II, 484 stored serum samples from the patients diagnosed

from 1980 onwards were available for the analyses of TG2Ab levels. IgA class TG2Ab was investigated by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Celikey®; Phadia, GmbH, Freiburg, Germany). Values > 7.0 U/ml were defined as screen-detected CeD autoimmunity.

In Study IV, blood samples were taken from all 85 IgAN patients. Faecal samples were taken from 57 IgAN patient volunteers. Blood samples were centrifuged and serum stored frozen at -80°C until analysed. Fresh faecal samples were collected in a sterile container and immediately stored at -80°C. Coeliac autoantibodies were measured from the serum samples by measuring IgA class TG2Ab and EmA. TG2Ab levels were determined according to manufacturers' instructions with EliA Celikey assay (ThermoFisher Scientific, Waltham, MA, USA, cut-off for positivity 7.0 U/ml). EmA was determined by an in-house indirect immunofluorescence method using human umbilical cord as a substrate. A serum dilution of 1: ≥ 5 was considered positive. Faecal calprotectin was measured by ELISA kit (Calpro AS, Oslo, Norway) following instructions provided by the manufacturers. The cut-off value was 50 μg/g.

In Study IV, serum levels of I-FABP, sCD14 and LBP were determined with commercially available kits following the instructions provided by the manufacturer. For the I-FABP ELISA kit (Hycult Biotech, Uden, The Netherlands) the cut-off limit was 47 pg/ml, for the sCD14 ELISA kit (Hycult Biotech, Uden, The Netherlands) 1.56 ng/ml and for the LBP ELISA kit (Hycult Biotech, Uden, The Netherlands) 4.4 ng/ml.

## 4.6 Statistical methods

The data are presented as medians and interquartile ranges (IQR) for most of the continuous variables and as percentages for the categorical variables. Groups were compared using the Chi-square test, the Kruskal-Wallis test, Fisher's exact test, the independent *t*-test or the Mann-Whitney *U*-test as appropriate. All tests were two-sided, and *p*-values less than 0.05 were considered statistically significant.

In Study I, survival (ESKD as event) was performed using Kaplan-Meier curves, and differences between IBD (yes/no) were compared by logrank test. Univariate and multivariable analyses were performed using Cox proportional hazards regression. Hazard ratios and their 95% confidence intervals (95% CI) are presented.

In Study III, binary logistic regression analysis was applied to identify factors for increased GI symptoms. Three covariates were used to avoid overfitting the model. The associations are presented as odds ratios with 95% CI.

In Study IV, Spearman's correlation coefficient ($r_S$) was used to evaluate correlations between continuous variables.

All statistical testing was performed using SPSS versions 23.0, 25.0 or 27.0 (IBM SPSS, NY, USA).

## 4.7 Ethical considerations

The study protocols were approved by the Ethics Committee of TAUH. All subjects had given written informed consent at the time of the kidney biopsy and again at enrollment in Studies III and IV.

# 5 RESULTS

## 5.1 Patients and demographic data

In Study I, the median age at the time of the kidney biopsy was 49 years in those having a past or future diagnosis of IBD and 59 years in those without IBD. Patients with and also without IBD were more often males, 57% and 63% respectively ($p$=0.593). Information on both height and weight at the time of kidney biopsy was available for 372 patients with IBD and for 17 patients without IBD. Patients without IBD were more obese at the time of kidney biopsy (median BMI 27.4 vs. 23.5 kg/m$^2$, $p$=0.005). Two IBD patients had a transplanted kidney at the time of kidney biopsy (5.7%), the corresponding percentage being 7.1% in those without IBD. Median follow-up time was 59 months for IBD patients and 66 months for those without IBD.

In Study II, there was no access to the medical records of 77 patients diagnosed with IgAN from 1976 to 1979. For 552 patients diagnosed with IgAN from 1980 onwards the median age was 42 years. Two thirds of the patients were males. Median follow-up time was 14 years.

In Study III, median age of the IgAN patients at the time of study enrollment was 55 years (IQR 42-68 years) and 54% of them were males. Median time from kidney biopsy was 11 years (IQR 5-20 years). Female patients were younger (52 vs. 59 years, $p$<0.001) and their reported BMI was lower than that reported by male patients (27 vs. 29 kg/m$^2$, $p$=0.048). The healthy controls were predominantly women (72%). Also, female controls were younger (median 49 years, IQR 40-62 years) than male controls (median 66 years, IQR 52-70 years). However there was no age difference between healthy controls and IgAN patients.

In Study IV, median age of the IgAN patients was 55 years (IQR 46-68 years) and 54% were males. Median time from kidney biopsy was 11 years (IQR 6-20 years). The fourteen dyspepsia controls were on average 59 (34-67) years old and 21% of them were males. The fifteen healthy controls were 57 (47-63) years old and 47% of them were males. The three groups did not differ in age ($p$=0.861) or sex distribution ($p$=0.075).

## 5.2 Kidney function

In Study I, information on current kidney function was available in 70% of all patients. At the latest follow-up, median eGFR among patients with IBD was 78 ml/min/1.73m$^2$ and 57 ml/min/1.73m$^2$ among those without IBD ($p$=0.118). At the time of kidney biopsy, eGFR had been 44 ml/min/1.73m$^2$ and 51 ml/min/1.73m$^2$. Two patients with IBD (5.7%) had progressed to ESKD during follow-up and both had received a kidney transplant. Progression to ESKD occurred in 18.1% of the patients without IBD. Annual lowering of eGFR was slow both in patients without IBD (median -1 ml/min/1.73m$^2$) and in patients with IBD (median 0 ml/min/1.73m$^2$).

In Study II, no data were gathered on current kidney function. Median eGFR at kidney biopsy among IgAN patients biopsied from 1980 onwards was 78 ml/min/1.73m$^2$. No change over decades was seen in eGFR at biopsy. The most common indication for the diagnostic kidney biopsy of IgAN was proteinuria and haematuria (42.2%) followed by nephritic syndrome (25.5%) (Table 1 in the original publication). The indications for kidney biopsy changed over time. The patients whose kidney biopsies were taken from 2000 to 2012 had more proteinuria at the time of biopsy (1.2 g/day) compared to those whose biopsy had been taken in earlier decades (0.6 g/day in the 1980s and 0.7 g/day in the 1990s). Haematuria as the sole indication for kidney biopsy became rarer over time; from 22% in the 1980s to 12% in the 1990s and further to 9% in the 21$^{st}$ century.

In Study III, data on kidney function from the year preceding study recruitment were available on 79% of the IgAN patients. Median eGFR was 63 ml/min/1.73m$^2$ and kidney function was regarded as being preserved in 56% of the patients on whom the information was available. Female IgAN patients had better kidney function than male patients (eGFR 78 vs. 54 ml/min/1.73m$^2$, $p$<0.001). No data on kidney function were available for the healthy controls.

In Study IV, median time from the diagnostic kidney biopsy was 11 years (IQR 6-20 years). Data on current kidney function were available for 80% of the IgAN patients. Median eGFR was 63 ml/min/1.73m$^2$ and kidney function were deemed preserved in 57% of the patients on whom the information was available. The median of the annual change of eGFR was -0.7 ml/min/1.73m$^2$ (IQR -2.1-+0.5 ml/min/1.73m$^2$). No data on kidney function were available for the controls.

## 5.3 Inflammatory bowel disease in kidney diseases

### 5.3.1 Inflammatory bowel disease in patients referred to kidney biopsy (Study I)

Altogether 35 out of 819 (4.3%) kidney-biopsied patients had IBD, of whom 28 (3.4%) were known cases at the time of the kidney biopsy. An additional seven patients were diagnosed with IBD during follow-up. Fourteen cases of both CrD and UC were found, and seven patients had an unclassified IBD. Characteristics of patients according to IBD types are presented in Table 2.

**Table 2.** Characteristics of inflammatory bowel disease (IBD) in patients undergoing kidney biopsy. Data is presented as medians (interquartile range) for continuous variables and as percentages for categorical variables.

| | Crohn's disease | Ulcerative colitis | IBD unclassified |
|---|---|---|---|
| | n=14 | n=14 | n=7 |
| Female | 36 | 50 | 43 |
| Age at kidney biopsy, years | 49 (24-70) | 41 (18-76) | 64 (21-74) |
| Diagnosis of IBD before kidney biopsy | 86 | 79 | 71 |
| Months since IBD diagnosis | 69 (6-249) | 106 (22-726) | 68 (4-491) |
| Prior or ongoing 5-ASA medication | 100 | 100 | 80 |
| IBD relapse during the preceding year | 25 | 27 | 20 |
| Extraintestinal manifestation of IBD | 43 | 29 | 14 |
| IBD-related surgery performed | 36 | 29 | 14 |

Among the patients with a former diagnosis of IBD (diagnosed over one year before the kidney biopsy, n=23), the diagnosis had been set a median of six years before the kidney biopsy and the maximum preceding disease duration was 60 years.

### 5.3.2 Kidney biopsy findings in inflammatory bowel disease and the prevalence of inflammatory bowel disease in different kidney biopsy findings (Study I)

Glomerular diseases were the most common group of kidney diseases found in IBD (Table 1 in the original publication). Seven patients (20.0%) had IgAN. Other glomerular diseases were diverse (Table 2 in the original publication). Kidney biopsy findings according to IBD types are presented in Table 3.

**Table 3.** Kidney biopsy findings in inflammatory bowel disease (IBD) patients undergoing kidney biopsy. Data presented as percentages.

| | Crohn's disease | Ulcerative colitis | IBD unclassified |
|---|---|---|---|
| | n=14 | n=14 | n=7 |
| *Kidney biopsy findings* | | | |
| Glomerular disease | 57 | 50 | 29 |
| IgA nephropathy* | 29 | 21 | 0 |
| Tubulointerstitial disease | 21 | 36 | 29 |
| Tubulointerstitial nephritis* | 21 | 29 | 14 |
| Vascular diseases | 7 | 0 | 0 |
| Other findings | 14 | 14 | 43 |

*percentage of all kidney biopsy findings in the corresponding IBD group

Tubulointerstitial diseases were the second most common (28.6%) group found in IBD patients' kidney biopsies. More specifically, acute (four patients) or chronic (four patients) TIN represented together 22.9% of the kidney biopsy findings among IBD patients. Eight patients (22.9%) had findings categorized as vascular diseases or other findings.

There were no differences in the indications for biopsy between the patients with and without IBD. Tubulointerstitial diseases were more common in IBD patients (28.6%) than in patients without IBD (12.5%). The prevalence of IBD was highest among patients diagnosed with TIN, 13.3%. In IgAN, the prevalence of IBD was 4.6% and 2.6% in patients with other GN.

### 5.3.3 Phenotypes of inflammatory bowel disease in patients referred to kidney biopsy (Study I)

Pancolitis or ileocolonic disease was the most common (54%) location of IBD, irrespective of the kidney biopsy finding (Table 4). All patients diagnosed with TIN had a previous diagnosis of IBD and all of them had used 5-ASA prior to kidney biopsy. One quarter of the patients had had an IBD flare-up during the year preceding the kidney biopsy. Immunomodulatory medication was used by 37% of the IBD patients at the time of kidney biopsy.

**Table 4.** Characteristics of inflammatory bowel disease (IBD) according to kidney biopsy findings. Data presented as medians (interquartile range) for continuous variables and as percentages for categorical variables.

| | Tubulointerstitial nephritis | IgA nephropathy | Glomerular disease* | Other kidney biopsy findings |
|---|---|---|---|---|
| | n=8 | n=7 | n=10 | n=10 |
| Female | 88 | 29 | 10 | 50 |
| Age at kidney biopsy, years | 50 (26-76) | 49 (18-69) | 45 (20-70) | 49 (24-67) |
| IBD diagnosed before kidney biopsy | 100 | 86 | 70 | 70 |
| Months since IBD diagnosis | 58 (19-491) | 64 (6-171) | 68 (4-320) | 121 (35-726) |
| Prior or ongoing 5-ASA | 100 | 100 | 100 | 71 |
| IBD relapse during the preceding year | 25 | 33 | 2 | 14 |
| IBD type | | | | |
| Crohn's disease | 37 | 57 | 40 | 30 |
| Ulcerative colitis | 50 | 43 | 40 | 30 |
| IBD unclassified | 13 | 0 | 20 | 40 |
| Location of IBD | | | | |
| Proctitis | 0 | 0 | 14 | 22 |
| Left-sided colitis | 29 | 29 | 0 | 22 |
| Pancolitis/ileocolonic | 57 | 71 | 86 | 44 |
| Small intestinal | 14 | 0 | 0 | 11 |
| Extraintestinal manifestation of IBD | 13 | 71 | 20 | 30 |

*glomerular disease other than IgA nephropathy

### 5.3.4 Kidney outcomes in inflammatory bowel disease (Study I)

The median follow-up was 59 months in patients with IBD and 66 months in patients without IBD. There was no difference between the groups in eGFR at the time of kidney biopsy or at the most recent follow-up.

Patients with IBD had significantly less proteinuria at the time of kidney biopsy than those without IBD (median 0.8 g/day, IQR 0.1-6.4 g/day vs. 1.5, 0.1-24.2 g/day, $p$=0.040). Nine out of the 26 IBD patients (34.6%) in whom the 24-hour urinary protein excretion had been quantified were taking immunomodulatory medication at the time of kidney biopsy. However, the amount of proteinuria did not differ between those on immunomodulatory medication and those who were not (median of the 24-hour excretion 0.8 and 0.9 g respectively).

During follow-up, two patients with IBD (5.7%) and 142 patients without IBD (18.1%) progressed to ESKD. Male sex was found to be a strong and independent predictor of ESKD, but IBD was not associated with the risk of ESKD (Table 4 in the original publication).

## 5.4 Inflammatory bowel disease in patients with IgA nephropathy (Studies I, II and IV)

In Study I, seven patients with IgAN had been diagnosed with IBD: four with UC and three with CrD (Table 4). In six of them IBD had been diagnosed before the diagnosis of IgAN, a median of 64 months before. Two out of the six IgAN patients with an earlier diagnosis of IBD had had a relapse of IBD during the year before the diagnostic kidney biopsy. Five of the seven IBD patients with IgAN also had another EIM.

Of the 629 IgAN patients in Study II, 15 (2.4%) had IBD; ten patients had received the diagnosis of IBD before the diagnosis of IgAN and five afterwards. IBD had not been diagnosed in any of the patients diagnosed with IgAN in the 1970s. From the 1980s to the 1990s to the 21st century the prevalence of IBD in IgAN increased steadily from 2.0% to 2.7% to 4.4% accordingly (Table 2 in the original publication). Altogether, nine patients had UC and six had CrD.

The four IBD patients diagnosed with IgAN in the 1980s all had UC, giving a UC prevalence of 2.0% in IgAN in the 1980s and of 0% for that of CrD. Among patients diagnosed with IgAN in the 1990s, two patients had CrD and two had UC, yielding a prevalence of 1.4% for each. In the 21st century four out of the seven

patients diagnosed with IgAN had CrD (2.5%) and the remaining three had UC (1.9%).

One half of the CrD patients with IgAN were diagnosed after the diagnosis of IgAN and the earliest diagnosis of CrD had been set in 1999. Twenty-two percent of UC diagnoses had been set after that of IgAN. Four out of the six (67%) CrD patients were diagnosed with CrD in the 21st century, compared with 22% of the UC cases.

In Studies III and IV, diagnosed IBD had been excluded by thoroughly scrutinizing the medical histories of all participants. Possible IBD diagnosis was also surveyed in the questionnaire created for Study III, with no positive responses. All 57 IgAN patients voluntarily providing faecal samples in Study IV tested negative for faecal calprotectin, further diminishing the possibility of subclinical IBD in participants.

## 5.5 Coeliac autoimmunity in IgA nephropathy (Studies II and IV)

In Study II, the prevalence of diagnosed CeD among IgAN patients decreased from its highest level of 2.9% in the 1980s to 0.7% in the 1990s and further to 0.6% by the 21st century (Table 2 in the original publication). Likewise, the prevalence of screen-detected coeliac autoimmunity in IgAN patients decreased from 2.8% to 0.7% over time.

Low positive TG2Ab values ranging from 3.1 to 7.0 U/ml were found in 4.3% of the total of 484 IgAN patients tested for TG2Ab between 1980 and 2012 in Study II (4.7% in 1980s, 0.8% in 1990s and 6.9% in 2000-2012). Low TG2Ab positivity, screen-detected autoimmunity and diagnosed CeD combined gave a total prevalence of 6.5% of coeliac autoimmunity among the 552 IgAN patients evaluated.

In Study IV, one IgAN patient had a borderline elevation (7.1 U/ml) in TG2Ab, which could be regarded as screen-detected CeD according to the criteria in Study II. Median of TG2Ab was 1.3 U/ml (IQR 0.8-1.9) in IgAN patients (Figure 1). None was EmA positive. Low positive TG2Ab values were found in eight patients. Altogether, TG2Ab positivity, either as low positive values or as screen-detected CeD was found in 10.6% of IgAN patients. Among the two control groups, two out of 29 (6.9%) had a low positive TG2Ab. TG2Ab levels did not differ between IgAN patients and dyspepsia controls ($p$=0.077) but were higher in IgAN patients than in healthy controls ($p$<0.001).

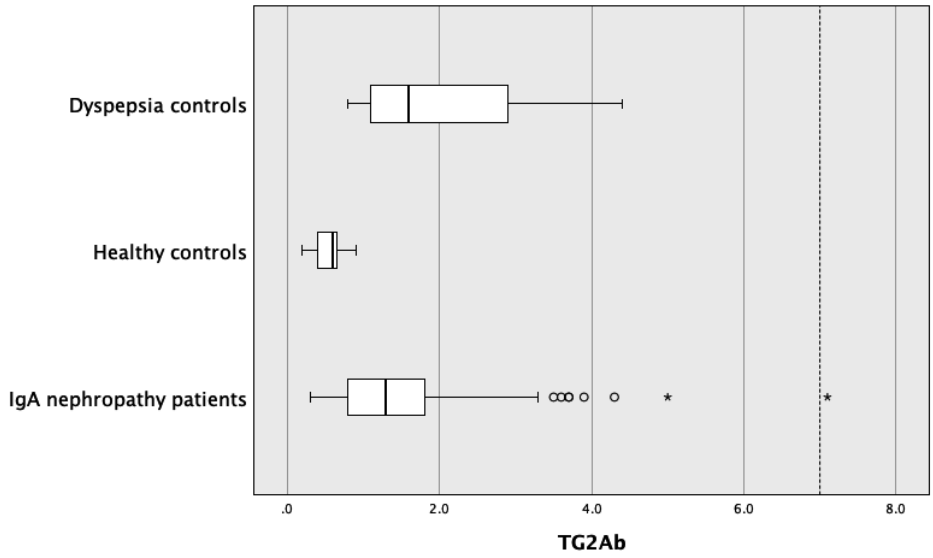


**Figure 1.** Transglutaminase 2 antibody (TG2Ab) levels (U/ml) in IgA nephropathy patients, healthy controls and dyspepsia controls.

## 5.6 Gastrointestinal symptoms and health-related quality of life in IgA nephropathy (Study III)

GSRS was rejected for one IgAN patient and two healthy controls due to incomplete questionnaires. IgAN patients reported more GI symptoms than did healthy controls. The median of the total GSRS score was 2.0 (IQR 1.5-2.7) in IgAN patients and 1.7 (IQR 1.4-2.2) in healthy controls ($p<0.001$). Of the five GSRS sub-scores IgAN patients scored higher on all but one (constipation) than did the healthy controls (Table 2 in the original publication). When IgAN patients were evaluated by sex, female patients had higher GSRS total scores and sub-scores for indigestion, constipation and abdominal pain than did male patients (Table 3 in the original publication).

The GSRS total scores did not differ between male patients and healthy males (median 1.7, IQR 1.5-2.3 vs. 1.7, 1.3-2.3, accordingly, $p=0.411$), and only the sub-score for diarrhoea was higher among male patients (1.7 vs. 1.3, $p=0.025$). In contrast to males, female patients scored higher than healthy females on all sub-scores and so also had higher overall scores. The GSRS scores and the PGWB scores for healthy controls are presented in Table 5.

**Table 5.** The Gastrointestinal Symptom Rating Scale (GSRS) scores and the Psychological General Well-Being Index (PGWB) scores in healthy controls. Values are given as medians and interquartile ranges.

| | Female | Male | *p*-value |
|---|---|---|---|
| GSRS, n | 104 | 41 | |
| Total score | 1.7 (1.4-2.2) | 1.7 (1.3-2.3) | 0.763 |
| *Diarrhoea* | 1.2 (1.0-1.7) | 1.3 (1.0-2.0) | 0.631 |
| *Indigestion* | 2.3 (1.8-2.8) | 2.3 (1.5-2.8) | 0.462 |
| *Constipation* | 1.3 (1.0-2.0) | 1.3 (1.0-2.3) | 0.697 |
| *Abdominal pain* | 1.7 (1.1-2.0) | 1.3 (1.0-2.2) | 0.468 |
| *Reflux* | 1.0 (1.0-1.5) | 1.0 (1.0-2.0) | 0.028 |
| PGWB, n | 104 | 38 | |
| Total score | 109 (101-114) | 113 (100-118) | 0.144 |
| *Anxiety* | 25 (23-27) | 25 (23-28) | 0.473 |
| *Depression* | 17 (16-18) | 17 (15-18) | 0.467 |
| *Wellbeing* | 17 (16-19) | 18 (16-20) | 0.293 |
| *Self-control* | 16 (14-17) | 16 (15-17) | 0.111 |
| *General health* | 15 (13-16) | 14 (11-17) | 0.987 |
| *Vitality* | 19 (17-20) | 20 (18-21) | 0.026 |

PGWB was excluded for one IgAN patient and five healthy controls due to incomplete questionnaire. PGWB total score as well as general health and vitality sub-scores were significantly lower in IgAN patients than in healthy controls (Table 2 in the original publication). More severe GI symptoms were more often present in female than male IgAN patients (Table 6). However, no sex-based difference in PGWB scores was seen in IgAN patients (Table 3 in the original publication).

**Table 6.** Prevalence (%) of increased gastrointestinal symptoms (defined as GSRS scores > 1 SD compared to mean values of healthy controls) in IgA nephropathy patients.

| | Female n=47 | Male n=56 | *p*-value |
|---|---|---|---|
| Gastrointestinal Symptom Rating Scale | | | |
| Total score | 45 | 20 | 0.010 |
| *Diarrhoea* | 38 | 29 | 0.400 |
| *Indigestion* | 30 | 14 | 0.090 |
| *Constipation* | 38 | 7 | <0.001 |
| *Abdominal pain* | 35 | 7 | <0.001 |
| *Reflux* | 31 | 21 | 0.272 |

IgAN patients with preserved kidney function reported increased GI symptoms more often than did IgAN patients with reduced kidney function in the GSRS sub-scores for diarrhoea, constipation and reflux (Table 7). IgAN patients with preserved kidney function were most often women (63%). In a multivariable logistic regression analysis of risk factors for increased GI symptoms among IgAN patients, female sex was positively and PGWB total score negatively associated with higher GSRS total score (Table 4 in the original publication).

**Table 7.** Prevalence (%) of increased gastrointestinal symptoms (defined as Gastrointestinal Symptom Rating Scale scores > 1 SD compared to mean values of healthy controls) in patients with IgA nephropathy, according to kidney function.

| | eGFR < 60 n=35 | eGFR > 60 n=46 | *p*-value |
|---|---|---|---|
| Gastrointestinal Symptom Rating Scale | | | |
| Total score | 22 | 37 | 0.327 |
| *Diarrhoea* | 17 | 41 | 0.028 |
| *Indigestion* | 11 | 26 | 0.158 |
| *Constipation* | 8 | 28 | 0.046 |
| *Abdominal pain* | 14 | 26 | 0.272 |
| *Reflux* | 8 | 37 | 0.004 |

## 5.7 Indirect biomarkers of intestinal damage in IgA nephropathy (Study IV)

Median serum I-FABP level among IgAN patients was 830 pg/ml, 289 pg/ml in healthy controls and 510 pg/ml in dyspepsia controls (Table 8). Also, sCD14 was lower in dyspepsia controls than in IgAN patients and healthy controls. LBP did not differ between the three groups.

Serum I-FABP was higher in IgAN patients with impaired kidney function than in patients with preserved kidney function (median 1100 pg/ml, IQR 868-1949 pg/ml vs. 650, IQR 419-880, $p<0.001$). Thus, IgAN patients with preserved kidney function also had higher I-FABP levels than healthy controls ($p<0.001$). Serum I-FABP level correlated inversely with current eGFR ($r_S=-0.598$, $p<0.001$) but did not correlate with the annual change in eGFR ($r_S=0.095$, $p=0.454$).

**Table 8.** Test results of the indirect markers for intestinal damage, presented as medians and interquartile range.

| | IgA nephropathy patients | Dyspepsia controls | Healthy controls |
|---|---|---|---|
| | n=85 | n=14 | n=15 |
| I-FABP, pg/ml | 830 (475 – 1378) | 510 (380 – 724) | 289 (199 – 568)* |
| sCD14, µg/ml | 2.9 (2.4 – 3.6) | 1.6 (1.0 – 2.3)* | 2.8 (2.5 – 3.7) |
| LBP, µg/ml | 11.7 (8.2 – 18.3) | 15.1 (10.5 – 25.2) | 14.8 (7.6 – 21.4) |

* $p<0.05$ compared to IgA nephropathy patients

Soluble CD14 was higher in IgAN patients with impaired kidney function than in those with preserved kidney function (3.4 µg/ml, IQR 2.6-3.9 µg/ml vs. 2.7 µg/ml, IQR 2.3-3.4 µg/ml, $p=0.003$). Also, sCD14 correlated inversely with current eGFR ($r_S=-0.332$, $p=0.006$), but not with the annual change in eGFR ($r_S=-0.029$, $p=0.822$). There was no difference in serum LBP levels between IgAN patients with reduced versus preserved kidney function (median 13.7 µg/ml, IQR 10.6-19.5 µg/ml vs. 11.0 µg/ml, IQR 7.1-18.7 µg/ml, $p=0.165$).

As faecal calprotectin had not been tested in 28 IgAN patients, the levels of the three biomarkers were compared among IgAN patients based on performed calprotectin test (Table 9). I-FABP and sCD14 levels did not differ between those IgAN patients who had been tested and those who had not been tested with faecal calprotectin. On the contrary, LBP was higher among those IgAN patients who had not been tested with calprotectin.

**Table 9.** Test results of the indirect markers for intestinal damage in IgA nephropathy patients, based on tested faecal calprotectin. Results are presented as medians and interquartile range.

| | Calprotectin tested<br>n=57 | Calprotectin not tested<br>n=28 | *p*-value |
|---|---|---|---|
| I-FABP, pg/ml | 830 (468 – 1157) | 835 (541 – 1876) | 0.443 |
| sCD14, ng/ml | 2.8 (2.4 – 3.8) | 3.0 (2.3 – 3.4) | 0.540 |
| LBP, ng/ml | 10.5 (7.2 – 14.9) | 17.5 (11.7 – 21.8) | <0.001 |

## 5.8 Correlation of gastrointestinal symptoms with indirect biomarkers of intestinal damage (Study IV)

Serum I-FABP levels did not correlate with total GSRS score in IgAN patients ($r_S$=-0.106, $p$=0.393). Nor did I-FABP correlate with any of the subscores of GSRS: diarrhoea ($r_S$=-0.143, $p$=0.194), indigestion ($r_S$=0.002, $p$=0.985), constipation ($r_S$=-0.034, $p$=0.758), abdominal pain ($r_S$=-0.100, $p$=0.365) and reflux ($r_S$=-0.084, $p$=0.445). The same was also found for both LBP and sCD14 serum levels and the GSRS scores.

# 6 DISCUSSION

## 6.1 Inflammatory bowel disease in kidney diseases

Before Study I, IBD was regarded as a rare finding in conjunction with kidney diseases, especially with glomerular diseases including IgAN (Floege & Feehally, 2016; Katsanos & Tsianos, 2002; Shaer et al., 2003). Urological complications on the other hand were well known and regarded as significant EIMs of IBD (Corica & Romano, 2015; Katsanos & Tsianos, 2002; Pardi, 1998).

IBD prevalence as high as 3.4% in patients undergoing clinically indicated kidney biopsies was a new finding in Study I, yielding about 5-fold higher prevalence for IBD in kidney patients compared to contemporary general population (Jussila et al., 2013). During the follow-up the prevalence of diagnosed IBD in these patients was further elevated to 4.3%. A large biopsy register-based study from the United States had been published before Study I. It had been conducted with kidney biopsies performed between 2001 and 2012, and showed an IBD prevalence of 0.2% at the time of kidney biopsy (Ambruzs et al., 2014). The patient data in the study by Ambruzs et al. were provided at the time kidney biopsy was requested, probably explaining the small number of IBD cases. The incidence of IBD does not differ between the United States and Finland on a population level (Keyashian et al., 2019; Kontola et al., 2023).

Prevalence of IBD in different kidney biopsy findings varied in Study I. The prevalence was highest in TIN (13.3%) and also significant in IgAN (4.6%) and other GN (2.6%). Prevalence of IBD in patients with biopsy-confirmed TIN has not been published before or after Study I. The prevalence of IBD in IgAN is discussed in more detail in the next chapter. IBD was most often located in pancolitis or ileocolonic forms, irrespective of the kidney biopsy findings in Study I. One case with TIN had a CrD restricted in a small intestinal form. None of the patients with IgAN or other glomerular diseases had such a form of IBD. Two patients diagnosed with IgAN had a left-sided colitis and the rest had the more extensive form.

Whether TIN was related to 5-ASA usage could not be determined in Study I as all the patients diagnosed with TIN were either actively using or had used 5-ASA preparations before kidney biopsy. The association between TIN and 5-ASA has

long been contested. Tubular injury also occurs in IBD without 5-ASA (Fraser et al., 2001; Herrlinger et al., 2001; Izzedine et al., 2002). Treatment with 5-ASA may even alleviate tubular inflammation (Dehmer et al., 2003). The risk of nephrotoxicity of 5-ASA in general is deemed low and most likely idiosyncratic (Gisbert et al., 2007; Van Staa et al., 2004). Since Study I, the low risk of nephrotoxicity has been corroborated and other clinical factors like IBD flare-ups emphasized as more important risk factors for kidney injury (Jairath et al., 2019; Menon & Bressler, 2019).

According to earlier case reports, a detrimental coexistence between IBD and kidney diseases seemed possible, or even likely (Koçak et al., 2010; Shaer et al., 2003; Tokuyama et al., 2010). On the other hand, previously published studies and case reports had created an impression of active IBD leading to kidney injury, which would in many cases be at least partly reversible if properly treated and if remission in IBD were achieved (Choi et al., 2012; Forshaw et al., 2005; Lewis et al., 2013; Onime et al., 2006). The behaviour of IBD among the patients in Study I most likely represented average course of the disease, as less than half of the patients had had an IBD flare-up during the preceding year or had been taking immunomodulatory medication at the time of the kidney biopsy. Historically about half of patients with UC will be in remission at any given time (Langholz et al., 1994).

The disease activity of IBD seems to subside with longer disease duration and also the remission rate increases (Langholz et al., 1994). In Study I, median disease duration of IBD before the kidney biopsy was six years in those with earlier diagnosis of IBD. As the median follow-up time was five years beginning from the kidney biopsy, the duration of IBD in most cases was not particularly long. In any case, IBD was not related to an elevated risk of ESKD in Study I. Since then, a nationwide population study from South Korea has been published concluding that IBD may be associated with a minor elevation in risk of ESKD, especially in case of CrD (Park S et al., 2018). The risk of CKD also seems elevated, especially among younger IBD patients (Vajravelu et al., 2020). Thus, a yearly follow-up of kidney function is recommended in general, and some experts recommend even more vigilant follow-up in cases where 5-ASA is used (Guillo et al., 2022; Kumar et al., 2022).

Only recently a large Swedish register study was published in which an association between reduced eGFR and the risk of developing IBD, especially CrD, was shown to exist and the association was stronger, yet modest, with more reduced eGFR (Yang et al., 2023). The authors speculated with the possibility of intestinal permeability and small-bowel inflammation of CKD being linked to the pathogenesis of IBD. As the authors concluded, an observational analysis cannot determine whether a kidney disease is a risk factor for IBD as such, or whether the

two diseases have genetic risk factors in common, or whether there is a yet unknown environmental factor or a condition that predisposes to both diseases.

In conclusion, IBD was present in a notable percentage of patients with clinical signs of kidney disease. Kidney biopsy findings did not differ in different phenotypes of IBD, but the small study population limits this interpretation. IBD should be kept in mind especially when the kidney biopsy shows TIN or IgAN. IBD was not associated with an increased risk of ESKD.

## 6.2 Inflammatory bowel disease in IgA nephropathy

Before Study I, published prevalence of IBD in IgAN was 0.6% to 0.7% (Ambruzs et al., 2014; Makdassy et al., 1984). A Swedish population-based register study has subsequently reported an IBD prevalence of 2.5% in IgAN at kidney biopsy, and an overall prevalence of 7.4% after median follow-up of 12.6 years (Rehnberg et al., 2021). In Study II, the prevalence of IBD in IgAN at the time of kidney biopsy was 1.8%. The overall prevalence of IBD in IgAN was 2.4%, 2.7% if only patients diagnosed after 1980 were included and 4.4% in those biopsied in the 21st century.

Clinical indications for kidney biopsy have changed over time and accordingly the annual incidence of biopsy-verified IgAN has decreased since the 1980s (Wirta et al., 2008). As the amount of proteinuria in Study I was lower in patients with IBD compared to those without IBD, it seems unlikely that the increase seen in the prevalence of IBD in IgAN in Study II would only be associated with different biopsy criteria. One explanation for the increasing IBD prevalence in IgAN could be the cumulative incidence of IBD over a long follow-up time. The risk of future IBD was found to be tripled in IgAN patients compared to controls in the aforementioned Swedish study with a median follow-up of 12.6 years (Rehnberg et al., 2021).

As Finns and Swedes do not differ markedly in ethnicity, nor in IBD prevalence (Büsch et al., 2014; Jussila et al., 2013) and most likely the kidney biopsy practices are also largely similar (Peters et al., 2020; Wirta et al., 2008) the increasing IBD prevalence in IgAN is true and most likely reflects a rise in IBD incidence. A Japanese retrospective single-centre study published in 2020 reported a biopsy-verified IgAN in 1.6% of IBD patients enrolled, all of whom had CrD (Hayashi et al., 2020). In a retrospective multicentre study, French colleagues examined 24 IgAN patients with IBD, ¾ of whom suffered from CrD (Joher et al., 2021). As the diagnosed CrD cases doubled each decade in Study II, the increasing prevalence of

CrD seems to explain the increasing IBD prevalence found in IgAN. The prevalence of UC in IgAN was at most stable. In the nationwide Swedish study, UC was more common than CrD in conjunction with IgAN in patients having received a diagnosis of CrD between 1974 and 2011 (Rehnberg et al., 2021). They found no similar increase in the incidence of CrD in conjunction with IgAN over time as was found in Study II. Increase in CrD prevalence reportedly follows that of UC by one decade (Ananthakrishnan, 2015).

The rising prevalence of IBD has been explained, for example, by dietary habits, use of antibiotics and diminishing parasite infections (Malik, 2015). In the pathogenesis of IgAN, antigen processing and presentation, and regulation of mucosal IgA production have likewise been implicated as potential pathways (Magistroni et al., 2015). Also, direct genetic associations between IBD and IgAN have been found (Kiryluk et al., 2014). Still, a recent finding of an association between reduced kidney function and the risk of developing CrD (Yang et al., 2023) must also be taken into account as a possible explanation for the rising prevalence of CrD in IgAN.

The high percentage (71%) of IBD patients suffering an EIM in addition to IgAN was an interesting finding of Study I. EIMs have been reported to be more common in CrD than in UC with multiple EIMs found in less than 10% of IBD patients (Fumery et al., 2018; Lakatos et al., 2003; Vavricka et al., 2015). Patient cases and a small case series of multiple EIMs, including IgAN, have been published (De Moura et al., 2006; Peeters et al., 1990; Vegh et al., 2017). Even though IgAN is not regarded as a systemic disease or syndrome, concomitant diseases have been found in more than 50% of IgAN cases (Mustonen, 1984). In the early 1980s IgAN was actually classified as a GN of systemic diseases (Mustonen & Pasternack, 1987). Some researchers regard IgAN in conjunction with IBD as a secondary form of IgAN (Tota et al., 2023; Wang M et al., 2020).

In Study IV, none of the 57 IgAN patients volunteering to give faecal samples had positivity in faecal calprotectin, interpreted as having had an undiagnosed IBD excluded. Even though a low level of faecal calprotectin cannot totally exclude a small bowel IBD, it yields an excellent sensitivity of over 95% (Mattila et al., 2022).

In conclusion, IBD was present in a notable percentage of IgAN patients and the prevalence of IBD in IgAN increased over time. The rising co-prevalence of IgAN and IBD is most likely linked to the genetic associations between the two diseases and the true rising prevalence of IBD, especially that of CrD. A subclinical IBD in IgAN seems unlikely, but it cannot be excluded.

## 6.3 Coeliac disease and coeliac autoimmunity in IgA nephropathy

The prevalence of CeD in IgAN was shown to be 4-fold that of general population in Finland at the end of the 20th century (Collin et al., 2002b). Similarly, the risk of IgAN in CeD was 3-fold compared that of general population in a Swedish nationwide population-study (Welander et al., 2013). The incidence and prevalence of CeD have constantly increased in Finland (Lohi et al., 2007; Mäki et al., 2003; Vilppula et al., 2009). Nevertheless, in Study II an opposite direction was found in the prevalence of both diagnosed and screen-detected CeD in IgAN.

CeD has reportedly been associated with an elevated risk of kidney disease and IgAN, but no elevated risk was seen in DH patients (Nurmi et al., 2022). It was hypothesized that the finding might be linked to the less prevalent intestinal inflammation seen in DH compared with CeD, but also to the Finnish DH patients' strict adherence to GFD (Nurmi et al., 2022). GFD as a possible treatment for IgAN has long been hypothesized, but not tested in a randomized controlled trial (Coppo et al., 1986, 1990). Thus, the finding of decreasing prevalence of CeD in IgAN in Study II could be partly associated with GFD, which could also alleviate IgAN. Still, it remained unexplained, why also screen-detected coeliac autoimmunity in Study II decreased over time as those patients most likely were not on GFD.

TG2 is regarded as one of the molecular links between IgAN and CeD (Abbad 2020). TG2-targeted IgA deposits have been found in kidney biopsies of gluten-consuming IgAN patients (Nurmi et al., 2021). Binding of IgA to CD71 on mesangial cells is facilitated and amplified by TG2 (Berthelot et al., 2012; Haddad et al., 2003). In Study IV, serum TG2Ab levels were higher among IgAN patients than among healthy people, yet the more specific EmAs were negative in all patients. Elevated TG2Ab levels have also been reported in IgAN patients before (Collin et al., 2002b; Nurmi et al., 2018).

In conclusion, the prevalence of CeD in IgAN was found to decrease over time and finally come close to that of CeD in general Finnish population today. Levels of TG2Ab were higher in IgAN patients than in healthy people, yet EmAs were negative in all study participants. A subclinical CeD in IgAN seems unlikely despite the many interesting connections between the two diseases.

## 6.4 Gastrointestinal symptoms and health-related quality of life in IgA nephropathy

Before Study III, GI symptoms in kidney diseases had only been reported in advanced CKD, most often in patients with ESKD and dialysis treatment (Cano et al., 2007; Costa-Moreira et al., 2020; Strid et al., 2002). Study III was the first to focus on kidney patients with less advanced CKD, even those with preserved kidney function (eGFR > 60 ml/min/1.73m$^2$). IgAN patients with diagnosed enteropathies had been excluded to avoid bias caused by symptoms associated with known enteropathies.

In Study III, IgAN patients experienced more GI symptoms than did healthy subjects in regard to GSRS total score and in regard to four out of the five sub-scores of GSRS (diarrhoea, indigestion, abdominal pain and reflux). Noteworthy, the GSRS total score of IgAN patients (median 2.0, IQR 1.5-2.7) were about the same as those of Swedish patients undergoing either haemodialysis (median 1.9, IQR 1.4-2.7) or peritoneal dialysis (median 2.1, IQR 1.5-3.1)(Strid et al., 2002).

Female IgAN patients were more symptomatic than male patients. Female patients also experienced increased GI symptoms more often than did healthy women. Male patients also had more symptoms of diarrhoea than did healthy men. The role of sex in experienced GI symptoms has been controversial in published studies; some showing women having more symptoms (Chan S et al., 2021; Kahvecioglu et al., 2005), others reporting no differences (Strid et al., 2002; Yi et al., 2022). IBS may be more common in women and thus also in female IgAN patients (Chang et al., 2006). The finding of increased symptoms of diarrhoea, constipation and reflux among IgAN patients with preserved kidney function compared to those with reduced kidney function was most likely associated with the preponderance of females among patients with preserved kidney function.

Patients with IgAN experienced poorer health-related quality of life than did the healthy controls in Study III, especially regarding general health and vitality. Furthermore, poorer quality of life was associated with increased GI symptoms. Interestingly, even though female patients had more GI symptoms than did male patients, health-related quality of life did not differ between sexes.

In conclusion, IgAN patients and especially female IgAN patients experienced more GI complaints than healthy people did. Also, IgAN patients with preserved kidney function experienced notable numbers of GI symptoms. Paying attention to these troubles would be desirable as a part of good patient care, especially as the GI complaints were found to be associated with poorer health-related quality of life.

## 6.5 Signs of intestinal damage in IgA nephropathy

The patients in Study IV had not progressed to ESKD, in which intestinal barrier function would most likely be impaired due to uremia and alterations in the gut microbiome (Vaziri et al., 2012a, 2016). Therefore, the results of Study IV can be interpreted without the confounding interference caused by the presence of obvious intestinal damage or increased intestinal permeability.

Serum I-FABP levels in untreated CeD patients (Adriaanse et al., 2013) were essentially the same as they were among the IgAN patients in Study IV, also in patients with preserved kidney function. As small-bowel mucosal damage with villous atrophy and crypt hyperplasia are the characteristic features of CeD, the finding of elevated I-FABP in IgAN patients possibly indicates the presence of intestinal damage in IgAN. This was the first published study of serum I-FABP levels in a well-defined kidney disease population.

LBP did not differ between the three groups studied. Soluble CD14 was lower in dyspepsia patients than in IgAN patients, a finding which still lacks an explanation. Neither I-FABP, nor LBP or sCD14 levels correlated with the GSRS total score or sub-scores in IgAN patients. Thus, clinically apparent GI inflammation or damage is unlikely in IgAN patients in whom the known enteropathies IBD and CeD have been excluded.

The serum level of I-FABP rises with declining kidney function (Okada et al., 2018). The finding of higher I-FABP levels in IgAN patients with kidney failure compared to patients with preserved kidney function in Study IV was most likely due to impaired kidney function. However, I-FABP levels did not correlate with the annual change in eGFR. This could be interpreted to mean that the subclinical intestinal damage present in IgAN, of which increased I-FABP would be a marker, does not correlate with the rate of decline in kidney function. As I-FABP was not solely linked to the level of kidney function, the possibility remains that increased I-FABP in IgAN represents a phenomenon related to the pathogenesis of IgAN.

In a Chinese study, LBP and sCD14 were higher among 52 patients with IgAN than among healthy controls (Zhong et al., 2020). Among paediatric patients with generally inactive IBD, LBP was elevated compared with controls, whereas sCD14 levels did not differ between patients and controls (Pasternak et al., 2010). Among adult patients with CrD, sCD14 levels were decreased while LBP levels were elevated compared to controls (Lakatos et al., 2011). The finding of no significant increase in sCD14 and LBP levels in IgAN patients compared to controls in Study IV may be a sign of less prevalent intestinal permeability. Gut microbiome composition varies

geographically (Gupta et al., 2017), thus one can hypothesize the role of microbiome when the results of Chinese and Finnish patients are compared.

It is intriguing that there is a possible correlation between LPS exposure and defective galactosylation of IgA (Qin et al., 2008). CD14 as the LPS binding receptor is one of the major components of cellular LPS signalling in response to various microbes (Coppo, 2015). Gene polymorphism of CD14 may be an important factor in the risk of progression of IgAN (Yoon, 2003). The genetic modification of the LPS receptor could logically modulate the level of inflammatory response (Coppo, 2015; Yoon, 2003).

It is possible that the increased permeability known to exist in IgAN is not present throughout the GI tract (Seikrit et al., 2023). Li and colleagues evaluated the presence of intestinal permeability in IgAN patients with serum zonulin levels and found higher levels in IgAN patients than in healthy people (Li Q et al., 2023). The major problem with the interpretation of the results of Li et al. is the lack of consensus as to exactly what the zonulin test measures (Ajamian et al., 2019; Meira de-Faria et al., 2021).

In conclusion, the possibility of a subclinical intestinal damage in IgAN cannot be excluded. The discrepancy in the levels of the three indirect biomarkers of intestinal damage may be linked to the possibility that the intestinal inflammation present in IgAN is limited to some parts of the GI tract only. Clinically relevant GI symptoms did not correlate with the damage markers.

## 6.6 Strengths and limitations

In this study, it was possible to collect real-life data from large patient cohorts with long follow-up times. The data in Study I were available for over 800 patients referred to kidney biopsy due to a clinical indication and in Study II the follow-up covered over 500 IgAN patients from four decades. Due to the retrospective nature of the study, however, some of the information collected may be inaccurate or insufficient. Even though the whole cohort in Study I was large, the number of IBD patients was small, which limits the reliability of interpretations regarding e.g. possible correlations in kidney biopsy findings and IBD phenotypes.

In Studies II, III and IV, well-defined and sizeable groups of patients with a confirmed diagnosis of IgAN is one of the major strengths of this study. The kidney biopsies had been taken at one centre and analysed by two renal pathologists, providing both unified clinical indications for the kidney biopsies as well as

consistent interpretation of the kidney samples. Yet a study conducted in a single centre limits the generalizability of the results.

The diagnostics of both IBD and CeD in Finland is good, as corroborated in the rising prevalence of both diseases (Kontola et al., 2023; Vilppula et al., 2009). Thus, it is unlikely that there would have been any notable percentage of undiagnosed CeD or IBD patients in the study populations of any of the four substudies. The same applies to the controls.

Another strength of the study is that the study group was familiar with the GSRS and PGWB questionnaires from several earlier studies conducted in CeliRes. It is possible that symptomatic patients may have been more eager to participate than asymptomatic patients in Studies III and IV. Yet this seems unlikely as more than half of the participating IgAN patients were males and their GSRS scores were comparable to those of the male controls. Also, the patients in Studies III and IV had IgAN diagnosed a median of 10 years before recruitment. It is thus possible that these patients do not represent those IgAN patients with more aggressive phenotype and the findings might have been different if the studies had been conducted with IgAN patients suffering from an actively progressive kidney disease.

The most important limitation of Studies III and IV is the lack of control groups with other primary GN. This leaves it uncertain whether the IgAN patients, for example, experienced an excess of GI symptoms due to a kidney disease in general or if the symptoms were related to IgAN. Likewise, the results of the indirect biomarkers of intestinal damage might have been similarly elevated in other kidney diseases too, especially as the findings of increased intestinal permeability are not confined to IgAN (Rostoker et al., 1993; Seikrit et al., 2023).

The controls in Study IV had not tested negative for IBD. The dyspepsia controls had undergone gastroscopies and the healthy controls had tested negative with coeliac serology, yet faecal calprotectin had not been tested. It is also important to note that not all IgAN patients in Study IV had tested negative with faecal calprotectin. However, the serum levels of the tested biomarkers did not differ significantly between the groups. The difference found in the levels of LBP among IgAN patients based on their test status with calprotectin is most likely mere coincidence. Also, blood samples were taken separately from the questionnaires, a fact that should be noted when interpreting the findings on the lack of correlation between experienced GI symptoms and the serum levels of the three biomarkers of intestinal damage.

It is possible that the chosen biomarkers of intestinal damage do not represent the kind of damage possibly present in IgAN. I-FABP for example originates in the

small intestine and thus probably does not cover the whole of the intestine as a damage marker (Okada et al., 2018). In this study, however, the finding of elevated I-FABP in IgAN patients compared with healthy controls could point to a subclinical intestinal damage in the small intestine in IgAN. LBP and sCD14 are mentioned as endotoxin-related markers (Lakatos et al., 2011). Based on earlier studies showing increased intestinal permeability in IgAN (Kovács et al., 1996; Rostoker et al., 1993), it would be logical to expect a rise in LBP and sCD14 levels. Yet again, the low levels of LBP and sCD14 could be explained by the affected area of gut. In a study showing elevation of LBP and sCD14 in active CrD, 85% of the patients had CrD either in colonic or ileocolonic form (Lakatos et al., 2011). Moreover, there was a confusing finding of lower levels of sCD14 both in the active and inactive CrD when compared with blood donor controls. Despite this, sCD14 was higher in active CrD than in inactive CrD (Lakatos et al., 2011). An important finding in the study by Rojo et al. was the higher LBP levels in CrD compared to those of UC (Rojo et al., 2007). As the inflammation in CrD is in transmural form, this may suggest a need for more extensive damage to cause a clear elevation in LBP and sCD14.

In Studies III and IV, kidney function was regarded as current although the laboratory tests had in many cases been taken months before study participation, and information was not available at all on one fifth of the IgAN patients. Taking the generally slowly progressive or stable nature of IgAN into account, it is nevertheless unlikely that a significant proportion of the study patients would have had a rapidly progressive kidney disease.

# 7 SUMMARY AND CONCLUSIONS

The main conclusions of this dissertation are as follows.

First, IBD was present in a notable percentage of patients referred to kidney biopsy for any clinical reason. CrD and UC were equally common in these patients. IBD was especially prevalent in kidney biopsy findings of tubulointerstitial nephritis and IgAN. Before the start of this project, IBD was regarded as a rare disease in conjunction with IgAN. The connection between TIN and IBD was well known and mainly regarded to be explained by use of 5-ASA medication.

Second, IBD was not associated with an increased risk of ESKD in patients referred to kidney biopsy. One should be cautious about generalizing this conclusion as the study population was limited and selected. Bigger register studies have shown an increased risk of ESKD with IBD and CrD (Park S et al., 2018; Rehnberg et al., 2021).

Third, IBD will most likely become even more prevalent in IgAN if the rise in the incidence of IBD, and especially that of CrD, continues.

Fourth, the prevalence of both diagnosed CeD and that of screen-detected coeliac autoimmunity decreased in IgAN patients over time. Even though in normal limits, TG2Ab levels in sera were higher in IgAN patients than in healthy individuals in Study IV. Although a subclinical CeD in IgAN seems unlikely as a notable phenomenon, the idea of connections between the two diseases gained further support. The most recent data shows the combined prevalence of different enteropathies in IgAN to be as high as 17% (Suzuki Y et al., 2021).

Fifth, patients with IgAN experienced more GI symptoms than did healthy people. This finding was especially prevalent among female IgAN patients. Health-related quality of life was lower in IgAN patients than in healthy people and in this there was no difference between the sexes. Clinicians should actively elicit possible GI complaints from IgAN patients to provide better patientcare.

Sixth, presence of subclinical IBD in IgAN was not directly supported by the findings in this study. However, faecal calprotectin is good for finding inflammation of the colon, but not equally good for finding inflammation present in ileal CrD (Abraham & Kane, 2012).

Seventh, based on the findings with the three biomarkers of intestinal damage, the possibility cannot be excluded that IgAN patients had true intestinal inflammation.

Eighth, there was no correlation between experienced GI symptoms and the serum levels of the three biomarkers of intestinal damage. The reliability of this finding is limited due to methodological limitations in this study. On the other hand, subclinical inflammation would presumably be asymptomatic.

# 8 FUTURE PERSPECTIVES

It is intriguing to hypothesize that the big picture in this dissertation could uniformly point to the small intestine as the source of inflammation and as a crucial contributor to the pathogenesis of IgAN. Future studies should be directed to study the small intestines of IgAN patients in greater detail. The confirmatory methods to show the presence of intestinal inflammation or damage in IgAN are so far invasive. Technical advances will most likely also yield non-invasive tools for measuring intestinal inflammation, positron-emission tomography being one example (Gelston et al., 2021). Also, other available noninvasive intestine-related biomarkers should be studied in IgAN patients (Lalande et al., 2020; Ok et al., 2020). It would be especially interesting to study these phenomena in the early stages of IgAN and in progressive kidney disease.

The obvious role of the gut microbiome in IgAN likewise calls for more studies on the topic. Preliminary studies have shown differences in the composition of gut microbiome between IgAN patients and healthy people (De Angelis et al., 2014; Tan et al., 2022; Zhong et al., 2020). Associations between the gut microbiome and the phenotype of IgAN may exist (Zhong et al., 2020). Some bacteria may confer a causal link with IgAN (Wang F et al., 2023). Host genetics possibly affect the composition of the gut microbiome in IgAN (He J.W. et al., 2021).

Gut bacteria have been shown to promote IgA class-switching and an abnormal production of Gd-IgA1 was found to be associated with specific faecal microbiota metabolites (He B et al., 2007; Sallustio et al., 2020). Gut-targeted therapies could offer new options to treat kidney diseases (Lehto & Groop, 2018). Antibiotic treatment targeted at the intestine has been shown to reduce the formation of immune complexes and to prevent the development of glomerular inflammation in a mouse model of IgAN (Chemouny et al., 2019). Also, probiotic treatment with *Bifidobacterium* was shown to lead to a decreased glomerular density of IgA and to a lesser amount of proteinuria in mice (Tan et al., 2022).

Ultimately, all research conducted on the topic should aim at inhibiting or stopping the pathogenetic process of IgAN, which still today leads to ESKD and human suffering in a substantial proportion of patients.

# REFERENCES


Abbad, L., Monteiro, R.C., Berthelot, L. (2020). Food antigens and Transglutaminase 2 in IgA nephropathy: Molecular links between gut and kidney. *Mol Immunol. 121*;1–6. doi:10.1016/j.molimm.2020.02.019

Abraham, B. P., Kane, S. (2012). Fecal Markers: Calprotectin and Lactoferrin. *Gastroenterol Clin North Am. 41*(2);483–95. doi:10.1016/j.gtc.2012.01.007

Adriaanse, M. P. M., Tack, G. J., Passos, V. L. et al. (2013). Serum I-FABP as marker for enterocyte damage in coeliac disease and its relation to villous atrophy and circulating autoantibodies. *Aliment Pharmacol Therap. 37*(4);482–90. doi:10.1111/apt.12194

Adriaanse, M. P. M., Leffler, D. A., Kelly, C. P. et al. (2016). Serum I-FABP Detects Gluten Responsiveness in Adult Celiac Disease Patients on a Short-Term Gluten Challenge. *Am J Gastroenterol. 111*(7);1014–22. doi:10.1038/ajg.2016.162

Ajamian, M., Steer, D., Rosella, G., Gibson, P. R. (2019) Serum zonulin as a marker of intestinal mucosal barrier function: May not be what it seems. *PLoS One. 14*(1), e0210728. doi:10.1371/journal.pone.0210728

Akiyama, M., Shimomura, K., Yoshimoto, H. (2022). et al. Crohn's disease may promote inflammation in IgA nephropathy: A case–control study of patients undergoing kidney biopsy. *Virchows Arch. 2481*(4);553–63. doi:10.1007/s00428-022-03373-w

Almroth, G., Axelsson, T., Müssener, E., Grodzinsky, E., Midhagen, G., Olcén, P. (2006). Increased prevalence of anti-gliadin IgA-antibodies with aberrant duodenal histopathological findings in patients with IgA-nephropathy and related disorders. *Ups J Med Sci. 111*(3);339–52. doi:10.3109/2000-1967-060

Ambruzs, J. M., Walker, P. D., Larsen, C. P. (2014). The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol. 9*(2);265–70. doi:10.2215/CJN.04660513

Ananthakrishnan, A. N. (2015). Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol. 12*(4);205–17. doi:10.1038/nrgastro.2015.34

Anders, H. J., Andersen, K., Stecher, B. (2013). The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int. 83*(6);1010-6. doi:10.1038/ki.2012.440

Aronov, P.A., Luo, F. J. G., Plummer, N. S. et al. (2011). Colonic Contribution to Uremic Solutes. *J Am Soc Nephrol. 22*(9), 1769–76. doi:10.1681/ASN.2010121220

Atkinson, J. P., Goodship, T. H. J. (2007). Complement factor H and the hemolytic uremic syndrome. *J Exp Med. 204*(6);1245–8. doi:10.1084/jem.20070664

Barbour, S. J., Reich, H. N. (2012). Risk stratification of patients with IgA nephropathy. *Am J Kidney Dis. 59*(6);865–73. doi:10.1053/j.ajkd.2012.02.326

Barbour, S. J., Cattran, D. C., Espino-Hernandez, G., Hladunewich, M. A., Reich, H. N. (2015). Identifying the ideal metric of proteinuria as a predictor of renal outcome in idiopathic glomerulonephritis. *Kidney Int. 88*(6);1392–401. doi:10.1038/ki.2015.241

Barbour, S. J., Espino-Hernandez, G., Reich, H. N. et al. (2016). The MEST score provides earlier risk prediction in lgA nephropathy. *Kidney Int. 89*(1);167–75. doi:10.1038/ki.2015.322

Barbour, S. J., Coppo, R., Zhang, H. et al. (2019). Evaluating a New International Risk-Prediction Tool in IgA Nephropathy. *JAMA Int Med.* 179(7);942–52. doi:10.1001/jamainternmed.2019.0600

Barbour, S. J., Canney, M., Coppo, R. et al. (2020). International IgA Nephropathy Network. Improving treatment decisions using personalized risk assessment from the International IgA Nephropathy Prediction Tool. *Kidney Int. 98*(4);1009–19. doi:10.1016/j.kint.2020.04.042

Barbour, S. J., Coppo, R., Zhang, H. et al. (2022) Application of the International IgA Nephropathy Prediction Tool one or two years post-biopsy. *Kidney Int. 102*(1);160–72. doi:10.1016/j.kint.2022.02.042

Barratt, J., Bailey, E. M., Buck, K. S. et al. (1999). Exaggerated systemic antibody response to mucosal Helicobacter pylori infection in IgA nephropathy. *Am J Kidney Dis. 33*(6);1049–57. doi:10.1016/S0272-6386(99)70141-1

Barratt, J., Rovin, B. H., Cattran, D. et al. (2020). Why Target the Gut to Treat IgA Nephropathy? *Kidney Int Rep. 5*(10);1620–4. doi:10.1016/j.ekir.2020.08.009

Barratt, J., Floege, J. (2021). SGLT-2 inhibition in IgA nephropathy: The new standard of care? *Kidney Int. 100*(1);24–6. doi:10.1016/j.kint.2021.04.002

Bartosik, L. P., Lajoie, G., Sugar, L., Cattran, D. C. (2001). Predicting progression in IgA nephropathy. *Am J Kidney Dis. 38*(4);728–35. doi:10.1053/ajkd.2001.27689

Baumgart, D. C., Carding, S. R. (2007). Inflammatory bowel disease: Cause and immunobiology. *Lancet. 369*(9573);1627–40. doi:10.1016/S0140-6736(07)60750-8

Baumgart, D. C., Sandborn, W. J. (2007). Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet. 369*(9573);1641–57. doi:10.1016/S0140-6736(07)60751-X

Bellur, S. S., Troyanov, S., Cook, H. T., Roberts, I. S. D. (2011). Immunostaining findings in IgA nephropathy: Correlation with histology and clinical outcome in the Oxford classification patient cohort. *Nephrol Dial Transplant. 26*(8);2533–6. doi:10.1093/ndt/gfq812

Berg, D. F., Bahadursingh, A. M., Kaminski, D. L., Longo, W. E. (2002). Acute surgical emergencies in inflammatory bowel disease. *Am J Surg. 184*(1);45–51. doi:10.1016/S0002-9610(02)00879-6

Berger J, Hinglais N. (1968). Les depots intercapillaires d'IgA-IgG. J Urol Nephrol. 74:694-5.

Bernstein, C. N., Blanchard, J. F., Rawsthorne, P., Yu, N. (2001). The prevalence of extraintestinal diseases in inflammatory bowel disease: A population-based study. *Am J Gastroenterol. 96*(4);1116–22. doi:10.1016/S0002-9270(01)02319-X

Bernstein, C. N., Shanahan, F. (2008). Disorders of a modern lifestyle: Reconciling the epidemiology of inflammatory bowel diseases. *Gut. 57*(9);1185–91. doi:10.1136/gut.2007.122143

Berthelot, L., Papista, C., Maciel, T. T. et al. (2012). Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J Exp Med. 209*(4);793–806. doi:10.1084/jem.20112005

Berthoux, F. C., Mohey, H., Afiani, A. (2008). Natural History of Primary IgA Nephropathy. *Semin Nephrol. 28*(1);4–9. doi:10.1016/j.semnephrol.2007.10.001

Berthoux, F., Mohey, H., Laurent, B., Mariat, C., Afiani, A., Thibaudin, L. (2011). Predicting the risk for dialysis or death in IgA nephropathy. *J Am Soc Nephrol. 22*(4);752–61. doi:10.1681/ASN.2010040355

Berthoux, F., Suzuki, H., Thibaudin, L. et al. (2012). Autoantibodies Targeting Galactose-Deficient IgA1 Associate with Progression of IgA Nephropathy. *J Am Soc Nephrol. 23*(9);1579–87. doi:10.1681/ASN.2012010053

Bibbins-Domingo, K., Grossman, D. C., Curry, S. J., et al. (2017). Screening for Celiac Disease: US Preventive Services Task Force Recommendation Statement. *JAMA. 317*(12);1252-7. doi:10.1001/jama.2017.1462

Bikbov, B., Purcell, C. A., Levey, A. S. et al. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet. 395*(10225);709–33. doi:10.1016/S0140-6736(20)30045-3

Birketvedt, G. S., Berg, K. J., Fausa, O., Florholmen, J. (2000). Glomerular and Tubular Renal Functions After Long-Term Medication of Sulphasalazine, Olsalazine, and Mesalazine in Patients with Ulcerative Colitis. *Inflamm Bowel Dis. 6*(4);275–9. doi:10.1097/00054725-200011000-00003

Bossola, M., Sanguinetti, M., Scribano, D. et al. (2009). Circulating Bacterial-Derived DNA Fragments and Markers of Inflammation in Chronic Hemodialysis Patients. *Clin J Am Soc Nephrol. 4*(2);379–85. doi:10.2215/CJN.03490708

Bottaro, G., Cataldo, F., Rotolo, N., Spina, M., Corazza, G. R. (1999). The clinical pattern of subclinical/silent celiac disease: An analysis on 1026 consecutive cases. *Am J Gastroenterol. 94*(3);691–6. doi:10.1016/S0002-9270(98)00819-3

Boyd, J. K., Cheung, C. K., Molyneux, K., Feehally, J., Barratt, J. (2012). An update on the pathogenesis and treatment of IgA nephropathy. *Kidney Int. 81*(9);833–43. doi:10.1038/ki.2011.501

Buck, K. S., Smith, A. C., Molyneux, K., El-Barbary, H., Feehally, J., Barratt, J. (2008). B-cell O-galactosyltransferase activity, and expression of O-glycosylation genes in bone marrow in IgA nephropathy. *Kidney Int. 73*(10);1128–36. doi:10.1038/sj.ki.5002748

Büsch, K., Ludvigsson, J. F., Ekström-Smedby, K., Ekbom, A., Askling, J., Neovius, M. (2014). Nationwide prevalence of inflammatory bowel disease in Sweden: A population-based register study. *Aliment Pharmacol Therap. 39*(1);57–68. doi:10.1111/apt.12528

Camilleri, M. (2019). Leaky gut: Mechanisms, measurement and clinical implications in humans. *Gut. 68*(8);1516–26. doi:10.1136/gutjnl-2019-318427

Campbell, K. N. (2022). Oral Glucocorticoids for IgA Nephropathy. *JAMA. 327*(19);1872. doi:10.1001/jama.2022.4638

Canney, M., Barbour, S. J., Zheng, Y. et al for the International IgA Nephropathy Network. (2021). Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy. *J Am Soc Nephrol. 32*(2);436–47. doi:10.1681/ASN.2020030349

Cano, A. E., Neil, A. K., Kang, J. Y. et al. (2007). Gastrointestinal symptoms in patients with end-stage renal disease undergoing treatment by hemodialysis or peritoneal dialysis. *Am J Gastroenterol. 102*(9);1990–7. doi:10.1111/j.1572-0241.2007.01321.x

Carr, I., Mayberry, J. F. (1999). The Effects of Migration on Ulcerative Colitis: A Three-Year Prospective Study Among Europeans and First- and Second-Generation South

Asians in Leicester (1991–1994). *Am J Gastroenterol. 94*(10);2918–22. doi:10.1111/j.1572-0241.1999.01438.x

Cassol, C. A., Bott, C., Nadasdy, G. M. et al. (2020). Immunostaining for galactose-deficient immunoglobulin A is not specific for primary immunoglobulin A nephropathy. *Nephrol Dial Transplant. 35*(12);2123–9. doi:10.1093/ndt/gfz152

Cattran, D. C., Coppo, R., Cook, H. T. et al. (2009). The Oxford classification of IgA nephropathy: Rationale, clinicopathological correlations, and classification. *Kidney Int. 76*(5);534–45. doi:10.1038/ki.2009.243

Cattran, D. C., Reich, H. N., Beanlands, H. J., Miller, J. A., Scholey, J. W., Troyanov, S. (2008). The impact of sex in primary glomerulonephritis. *Nephrol Dial Transplant. 23*(7);2247–53. doi:10.1093/ndt/gfm919

Celiac disease. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Gastroenterology. *The Finnish Medical Society Duodecim*. 2018. www.kaypahoito.fi

Cenit, M. C., Olivares, M., Codoñer-Franch, P., Sanz, Y. (2015). Intestinal microbiota and celiac disease: Cause, consequence or co-evolution? *Nutrients. 7*(8);6900–23. doi:10.3390/nu7085314

Cerf-Bensussan, N., Gaboriau-Routhiau, V. (2010). The immune system and the gut microbiota: Friends or foes? *Nat Rev Immunol. 10*(10);735–44. doi:10.1038/nri2850

Chan, L. Y. Y., Leung, J. C. K., Tsang, A. W. L., Tang, S. C. W., Neng Lai, K. (2005). Activation of tubular epithelial cells by mesangial-derived TNF-α: Glomerulotubular communication in IgA nephropathy. *Kidney Int. 67*(2);602-12. doi:10.1111/j.1523-1755.2005.67116.x

Chan, S., Cao, C., Pascoe, E. M. et al. (2021). Patient-Reported Gastrointestinal Symptoms and the Association With Quality of Life Following Kidney Transplantation. *Kidney Int Rep. 6*(1);138–45. doi:10.1016/j.ekir.2020.10.013

Chang, L., Toner, B. B., Fukudo, S. et al. (2006). Gender, Age, Society, Culture, and the Patient's Perspective in the Functional Gastrointestinal Disorders. *Gastroenterology. 130*(5);1435–46. doi:10.1053/j.gastro.2005.09.071

Chemouny, J. M., Gleeson, P. J., Abbad, L. et al. (2019). Modulation of the microbiota by oral antibiotics treats immunoglobulin A nephropathy in humanized mice. *Nephrol Dial Transplant. 34*(7);1135–44. doi:10.1093/ndt/gfy323

Cheung, C. K., Barratt, J. (2020). Should we STOP immunosuppression for IgA nephropathy? Long-term outcomes from the STOP-IgAN trial. *Kidney Int. 98*(4);836–8. doi:10.1016/j.kint.2020.05.033

Choi, J. Y., Yu, C. H., Jung, H. Y. et al. (2012). A case of rapidly progressive IgA nephropathy in a patient with exacerbation of Crohns disease. *BMC Nephrol. 13*(1);1. doi: 10.1186/1471-2369-13-84

Clayton, P., McDonald, S., Chadban, S. (2011). Steroids and recurrent IgA nephropathy after kidney transplantation. *Am J Transplant. 11*(8);1645–9. doi:10.1111/j.1600-6143.2011.03667.x

Collin, P., Reunala, T., Pukkala, E., Laippala, P., Keyriläinen, O., Pasternack, A. (1994). Coeliac disease—Associated disorders and survival. *Gut. 35*(9);1215–8. doi:10.1136/gut.35.9.1215

Collin, P., Reunala, T., Rasmussen, M. et al. (1997). High Incidence and Prevalence of Adult Coeliac Disease Augmented Diagnostic Approach. *Scand J Gastroenterol. 32*(11);1129–33. doi:10.3109/00365529709002992

Collin, P., Kaukinen, K., Välimäki, M., Salmi, J. (2002a). Endocrinological disorders and celiac disease. *Endocr Rev. 23*(4);464–83. doi:10.1210/er.2001-0035

Collin, P., Syrjänen, J., Partanen, J., Pasternack, A., Kaukinen, K., Mustonen, J. (2002b). Celiac disease and HLA DQ in patients with IgA nephropathy. *Am J Gastroenterol. 97*(10);2572-6. doi:10.1016/S0002-9270(02)04383-6

Colvin, R. B., Traum, A. Z., Taheri, D., Jafari, M., Dolatkhah, S. (2014). Granulomatous interstitial nephritis as a manifestation of crohn disease. *Arch Path Lab. 138*(1);125–7. doi:10.5858/arpa.2012-0224-CR

Coppo, R., Basolo, B., Rollino, C. et al. (1986). Dietary Gluten and Primary IgA Nephropathy. *N Engl J Med. 315*(18);1167–8. doi:10.1056/NEJM198610303151819

Coppo, R. (1988). The Pathogenetic Potential of Environmental Antigens in IgA Nephropathy. *Am J Kidney Dis. 12*(5);420–4. doi:10.1016/S0272-6386(88)80038-6

Coppo, R., Roccatello, D., Amore, A. et al. (1990). Effects of a gluten-free diet in primary IgA nephropathy. *Clin Nephrol. 33*(2);72–86.

Coppo, R., Amore, A., Roccatello, D. (1992). Dietary antigens and primary immunoglobulin A nephropathy. *J Am Soc Nephrol. 2*(10 Suppl);S173-80. doi:10.1681/ASN.V210s173

Coppo, R. (2013). Is a legacy effect possible in IgA nephropathy? *Nephrol Dial Transplant. 28*(7);1657–62. doi:10.1093/ndt/gft016

Coppo, R. (2015). The intestine-renal connection in IgA nephropathy. *Nephrol Dial Transplant. 30*(3);360–6. doi:10.1093/ndt/gfu343

Coppo, R. (2017). Biomarkers and targeted new therapies for IgA nephropathy. *Pediatr Nephrol. 32*(5);725–31. doi: 10.1007/s00467-016-3390-9

Coppo, R. (2018). The gut–kidney axis in IgA nephropathy: Role of microbiota and diet on genetic predisposition. *Pediat Nephrol. 33*(1);53–61. doi:10.1007/s00467-017-3652-1

Coppo, R. (2019). Towards a personalized treatment for IgA nephropathy considering pathology and pathogenesis. *Nephrol Dial Transplant. 34*(11);1832–8. doi:10.1093/ndt/gfy338

Coppo, R., D'Arrigo, G., Tripepi, G. et al. (2020). Is there long-term value of pathology scoring in immunoglobulin A nephropathy? A validation study of the Oxford Classification for IgA Nephropathy (VALIGA) update. *Nephrol Dial Transplant. 35*(6);1002–9. doi:10.1093/ndt/gfy302

Coresh, J. (2017). Update on the Burden of CKD. *J Am Soc Nephrol. 28*(4);1020–2. doi:10.1681/ASN.2016121374

Corica, D., Romano, C. (2015). Renal involvement in inflammatory bowel diseases. *J Crohns Colitis. 10*(2);1–10. doi:10.1093/ecco-jcc/jjv138

Corthésy, B. (2007). Roundtrip Ticket for Secretory IgA: Role in Mucosal Homeostasis? *J Immunol. 178*(1);27–32. doi:10.4049/jimmunol.178.1.27

Cosnes, J., Cattan, S., Blain, A. et al. (2002). Long-Term Evolution of Disease Behavior of Crohn's Disease: *Inflamm Bowel Dis. 8*(4);244–50. doi:10.1097/00054725-200207000-00002

Costa-Moreira, P., Vilas-Boas, F., Teixeira Fraga, A., Macedo, G. (2020). Particular aspects of gastroenterological disorders in chronic kidney disease and end-stage renal disease patients: A clinically focused review. *Scand J Gastroenterol. 55*(2);129–38. doi:10.1080/00365521.2020.1722217

Crohn, BB., Ginzburg, L., Oppenheimer, GD. (1932). Regional ileitis: A pathologic and clinical entity. *JAMA*. 99:132.

Cury, D., Moss, A., Schor, N. (2013). Nephrolithiasis in patients with inflammatory bowel disease in the community. *Int J Nephrol Renovasc Dis. 6;*139-42. doi:10.2147/IJNRD.S45466

Czerkinsky, C., Koopman, W., Jackson, S. et al. (1986). Circulating immune complexes and immunoglobulin A rheumatoid factor in patients with mesangial immunoglobulin A nephropathies. *J Clin Investig. 77*(6);1931–8. doi:10.1172/JCI112522

D'Amico, G. (2000). Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. *Am J Kidney Dis. 36*(2);227–37. doi:10.1053/ajkd.2000.8966

De Angelis, M., Montemurno, E., Piccolo, M. et al. (2014). Microbiota and metabolome associated with Immunoglobulin A Nephropathy (IgAN). *PLoS ONE. 9*(6). doi: 10.1371/journal.pone.0099006

De Jong, D. J., Tielen, J., Habraken, C. M., Wetzels, J. F. M., Naber, A. H. J. (2005). 5-Aminosalicylates and effects on renal function in patients with Crohn's disease. *Inflamm Bowel Dis. 11*(11);972–6. doi:10.1097/01.MIB.0000185402.65288.19

De Moura, C. G., De Moura, T. G. G., De Souza, S. P., Testagrossa, L. (2006). Inflammatory bowel disease, ankylosing spondylitis, and IgA nephropathy. *J Clin Rheumatol. 12*(2);106–7. doi:10.1097/01.rhu.0000209619.00364.05

Dehmer, C., Greinwald, R., Löffler, J. et al. (2003). No dose-dependent tubulotoxicity of 5-aminosalicylic acid: A prospective study in patients with inflammatory bowel diseases. *Int J Colorect Dis. 18*(5);406-12. doi:10.1007/s00384-002-0467-7

Delanghe, S. E., Speeckaert, M. M., Segers, H. et al. (2013). Soluble transferrin receptor in urine, a new biomarker for IgA nephropathy and Henoch-Schönlein purpura nephritis. *Clin Biochem. 46*(7–8);591–7. doi:10.1016/j.clinbiochem.2013.01.017

Derikx, J. P. M., Vreugdenhil, A. C. E., Van den Neucker, A. M. et al. (2009). A Pilot Study on the Noninvasive Evaluation of Intestinal Damage in Celiac Disease Using I-FABP and L-FABP. *J Clin Gastroenterol. 43*(8);727–33. doi:10.1097/MCG.0b013e31819194b0

Dicke, W. K. (1950). Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease *(Thesis)*. University of Utrecht.

Dimenäs, E., Glise, H., Hallerbäck, B., Hernqvist, H., Svedlund, J., Wiklund, I. (1995). Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. *Scand J Gastroenterol. 30*(11);1046–52. doi:10.3109/00365529509101605

Dimenäs, E., Carlsson, G., Glise, H., Israelsson, B., Wiklund, I. (1996). Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol. Suppl 31*(221);8–13. doi:10.3109/00365529609095544

Dong, R., Guo, Z. Y., Ding, J. R., Zhou, Y. Y., Wu, H. (2014). Gastrointestinal symptoms: A comparison between patients undergoing peritoneal dialysis and hemodialysis. *World J Gastroenterol. 20*(32); 11370–5. doi:10.3748/wjg.v20.i32.11370

Doumas, S. A., Tsironis, C., Bolaji, A. A., Garantziotis, P., Frangou, E. (2023). Glomerulonephritis and inflammatory bowel disease: A tale of gut-kidney axis dysfunction. *Autoimm Rev. 22*(6);103327. doi:10.1016/j.autrev.2023.103327

Dubois, P. C. A., Trynka, G., Franke, L. et al. (2010). Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet. 42*(4);295–302. doi:10.1038/ng.543

Eijgenraam, J. W., Oortwijn, B. D., Kamerling, S. W. A. et al. (2008). Secretory immunoglobulin A (IgA) responses in IgA nephropathy patients after mucosal immunization, as part of a polymeric IgA response. *Clin Exp Immunol. 152*(2);227–32. doi:10.1111/j.1365-2249.2008.03616.x

Ekberg, H., Kyllönen, L., Madsen, S., Grave, G., Solbu, D., Holdaas, H. (2007). Increased Prevalence of Gastrointestinal Symptoms Associated with Impaired Quality of Life in Renal Transplant Recipients. *Transplantation. 83*(3);282–9. doi:10.1097/01.tp.0000251923.14697.f5

Elaziz, M. M. A., Fayed, A. (2016). Patterns of renal involvement in a cohort of patients with inflammatory bowel disease in Egypt. *Acta Gastroenterol Belg. 81*(3);381–5.

Endoh, M., Suga, T., Miura, M., Tomino, Y., Nomoto, Y., Sakai, H. (1984). In vivo alteration of antibody production in patients with IgA nephropathy. *Clin Exp Immunol. 57*(3);564–70.

Eronen, H., Kolehmainen, S., Koffert, J. et al. (2022). Combining biological therapies in patients with inflammatory bowel disease: A Finnish multi-centre study. *Scand J Gastroenterol. 57*(8);936–41. doi:10.1080/00365521.2022.2045350

Espinosa, M., Ortega, R., Gómez-Carrasco, J. M. et al. (2009). Mesangial C4d deposition: A new prognostic factor in IgA nephropathy. *Nephrol Dial Transplant. 24*(3);886–91. doi:10.1093/ndt/gfn563

Espinosa, M., Ortega, R., Sanchez, M. et al. (2014). Association of C4d deposition with clinical outcomes in IgA nephropathy. *Clin J Am Soc Nephrol. 9*(5);897–904. doi:10.2215/CJN.09710913

Evenepoel, P., Meijers, B. K. I., Bammens, B. R. M., Verbeke, K. (2009). Uremic toxins originating from colonic microbial metabolism. *Kidney Int. 76*;S12–9. doi:10.1038/ki.2009.402

Fagagnini, S., Heinrich, H., Rossel, J-B. et al. (2017). Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. *PLoS One. 12*(10);e0185193. doi:10.1371/journal.pone.0185193

Fagerström, K. O., Schneider, N. G. (1989). Measuring nicotine dependence: A review of the Fagerstrom Tolerance Questionnaire. *J Behav Med. 12*(2);159–82. doi:10.1007/BF00846549

Falk, M. C., Ng, G., Zhang, G. Y., Fanning, G. C. et al. (1995). Infiltration of the kidney by αβ and γδ T cells: Effect on progression in IgA nephropathy. *Kidney Int. 47*(1);177–85. doi:10.1038/ki.1995.21

Feehally, J., Farrall, M., Boland, A. et al. (2010). HLA has strongest association with IgA nephropathy in genome-wide analysis. *J Am Soc Nephrol. 21*(10);1791–7. doi:10.1681/ASN.2010010076

Feehally, J., Cameron, J. (2011). IgA nephropathy: Progress before and since Berger. *Am J Kidney Dis. 58*(2);310–9. doi:10.1053/j.ajkd.2011.03.024

Feehally, J., Levy, M., Monteiro, R. C. (2011). Jean Berger (1930–2011). *Kidney Int. 80*(5);437–8. doi:10.1038/ki.2011.239

Feehally, J., Floege, J., Tonelli, M., Johnson, R. (2019). *Comprehensive Clinical Nephrology, 6th Edition*. Elsevier Inc.

Fellström, B. C., Barratt, J., Cook, H. et al. (2017). Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): A double-blind, randomised, placebo-controlled phase 2b trial. *Lancet. 389*(10084);2117–27. doi:10.1016/S0140-6736(17)30550-0

Fennessy, M., Hitman, G. A., Moore, R. H. et al. (1996). HLA-DQ gene polymorphism in primary IgA nephropathy in three European populations. *Kidney Int. 49*(2);477–80. doi:10.1038/ki.1996.67

Ferrante, M., Panaccione, R., Baert, F. (2022). Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet.* 399:2031-46. doi:10.1016/S0140-6736(22)00466-4

Ferrara, F., Quaglia, S., Caputo, I. et al. (2009). Anti-transglutaminase antibodies in non-coeliac children suffering from infectious diseases. *Clin Exp Immunol. 159*(2);217–23. doi:10.1111/j.1365-2249.2009.04054.x

Finnish Registry for Kidney Diseases: Report 2021. (2021). muma.fi/files/5997/Finnish_Registry_for_Kidney_Diseases_Report_2021.pdf

Floege, J., Feehally, J. (2016). The mucosa-kidney axis in IgA nephropathy. *Nat Rev Nephrol. 12*(3);147–56. doi:10.1038/nrneph.2015.208

Floege, J., Rauen, T., Tang, S. C. W. (2021). Current treatment of IgA nephropathy. *Semin Immunopathol. 43*(5);717–28. doi:10.1007/s00281-021-00888-3

Fornasieri, A., Sinico, R. A., Maldifassi, P., Bernasconi, P., Vegni, M., D'Amico, G. (1987). IgA-Antigliadin antibodies in IgA mesangial nephropathy (Berger's disease). *BMJ. 295*(6590);78–80. doi:10.1136/bmj.295.6590.78

Forshaw, M. J., Guirguis, O., Hennigan, T. W. (2005). IgA nephropathy in association with Crohn's disease. *Int J Colorect Dis. 20*(5);463–5. doi:10.1007/s00384-004-0696-z

Fortune, F., Courteau, M., Williams, D. G., Lehner, T. (1992). T and B cell responses following immunization with tetanus toxoid in IgA nephropathy. *Clin Exp Immunol. 88*(1);62–7. doi:10.1111/j.1365-2249.1992.tb03040.x

Fraser, J. S., Muller, A. F., Smith, D. J., Newman, D. J., Lamb, E. J. (2001). Renal tubular injury is present in acute inflammatory bowel disease prior to the introduction of drug therapy. *Aliment Pharmacol Therap. 15*(8);1131–7. doi:10.1046/j.1365-2036.2001.01041.x

Fumery, M., Singh, S., Dulai, P. S., Gower-Rousseau, C., Peyrin-Biroulet, L., & Sandborn, W. J. (2018). Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol. 16*(3);343-56. doi:10.1016/j.cgh.2017.06.016

Gaber, L. W., Khan, F. N., Graviss, E. A., et al. (2020). Prevalence, Characteristics, and Outcomes of Incidental IgA Glomerular Deposits in Donor Kidneys. *Kidney Int Rep. 5*(11);1914–24. doi:10.1016/j.ekir.2020.08.018

Gale, D. P., Molyneux, K., Wimbury, D., et al. (2017). Galactosylation of IgA1 Is Associated with Common Variation in C1GALT1. *J Am Soc Nephrol. 28*(7);2158–66. doi:10.1681/ASN.2016091043

Gasche, C., Scholmerich, J., Brynskov, J., et al. (2000). A Simple Classification of Crohn's Disease: Report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998: *Inflamm Bowel Dis. 6*(1);8–15. doi:10.1097/00054725-200002000-00002

Geddes, C. C., Rauta, V., Gronhagen-Riska, C., et al. (2003). A tricontinental view of IgA nephropathy. *Nephrol Dial Transplant. 18*(8);1541–8. doi:10.1093/ndt/gfg207

Gee, S. (1888). On the celiac affection. Saint Bartholomew's Hospital Reports. 24:17-20.

Gelston, D., Brosler, S., Vazquez, J. (2021). Utility of FDG PET/CT in assessing bowel inflammation. *Am J Nucl Med Mol Imaging.* 11(4):271-9.

Gharavi, A. G., Moldoveanu, Z., Wyatt, R. J., et al. (2008). Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. *J Am Soc Nephrol. 19*(5);1008–14. doi:10.1681/ASN.2007091052

Gharavi, A. G., Kiryluk, K., Choi, M., et al. (2011). Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet. 43*(4);321–7. doi:10.1038/ng.787

Gisbert, J. P., González-Lama, Y., Maté, J. (2007). 5-Aminosalicylates and renal function in inflammatory bowel disease: A systematic review. *Inflamm Bowel Dis. 13*(5);629–38. doi:10.1002/ibd.20099

Grossetête, B., Launay, P., Lehuen, A., Jungers, P., Bach, J. F., Monteiro, R. C. (1998). Down-regulation of Fcα receptors on blood cells of IgA nephropathy patients: Evidence for a negative regulatory role of serum IgA. *Kidney Int. 53*(5);1321–35. doi:10.1046/j.1523-1755.1998.00885.x

Guillo, L., Delanaye, P., Flamant, M., et al. (2022). Kidney function monitoring in inflammatory bowel disease: The MONITORED consensus. *Dig Liver Dis. 54*(3);309–15. doi:10.1016/j.dld.2021.11.008

Gupta, V. K., Paul, S., Dutta, C. (2017). Geography, Ethnicity or Subsistence-Specific Variations in Human Microbiome Composition and Diversity. *Frontiers in Microbiology*, *8*, 1162. doi:10.3389/fmicb.2017.01162

Gutieŕrez, E., Zamora, I., Ballarín, J., et al. (2012). Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. *J Am Soc Nephrol. 23*(10);1753–60. doi:10.1681/ASN.2012010063

Gutiérrez, E., Praga, M., Rivera, F., et al. (2018). Changes in the clinical presentation of immunoglobulin A nephropathy: Data from the Spanish Registry of Glomerulonephritis. *Nephrol Dial Transplant. 33*(3);472–7. doi:10.1093/ndt/gfx058

Haas, M. (1997). Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. *Am J Kidney Dis. 29*(6);829–42. doi:10.1016/S0272-6386(97)90456-X

Haas, M., Verhave, J. C., Liu, Z. H., et al. (2017). A multicenter study of the predictive value of crescents in IgA nephropathy. *J Am Soc Nephrol. 28*(2);691–701. doi:10.1681/ASN.2016040433

Haddad, E., Moura, I. C., Arcos-Fajardo, M., et al. (2003). Enhanced expression of the CD71 mesangial IgA1 receptor in Berger disease and Henoch-Schönlein nephritis: Association between CD71 expression and IgA deposits. *J Am Soc Nephrol. 14*(2);327–37. doi:10.1097/01.ASN.0000046961.04917.83

Haraldsson, B., Jeansson, M. (2009). Glomerular filtration barrier. *Curr Opin Nephrol Hypertens. 18*(4);331–5. doi:10.1097/MNH.0b013e32832c9dba

Harper, S. J., Pringle, J. H., Wicks, A. C. B., et al. (1994). Expression of J chain mRNA in duodenal IgA plasma cells in IgA nephropathy. *Kidney Int. 45*(3);836–44. doi:10.1038/ki.1994.110

Harper, S. J., Allen, A. C., Pringle, J. H., Feehally, J. (1996). Increased dimeric IgA producing B cells in the bone marrow in IgA nephropathy determined by in situ hybridisation for J chain mRNA. *J Clin Pathol. 49*(1);38–42. doi:10.1136/jcp.49.1.38

Hastings, M. C., Bursac, Z., Julian, B. A., et al. (2018). Life Expectancy for Patients From the Southeastern United States With IgA Nephropathy. *Kidney Int Rep. 3*(1);99–104. doi:10.1016/j.ekir.2017.08.008

Hayashi, R., Ueno, Y., Tanaka, S., et al. (2020). Clinical characteristics of inflammatory bowel disease patients with immunoglobulin A nephropathy. *Intest Res.* doi:10.5217/ir.2020.00067

He, B., Xu, W., Santini, P. A., et al. (2007). Intestinal Bacteria Trigger T Cell-Independent Immunoglobulin A2 Class Switching by Inducing Epithelial-Cell Secretion of the Cytokine APRIL. *Immunity. 26*(6);812–26. doi:10.1016/j.immuni.2007.04.014

He, J. W., Zhou, X. J., Li, Y. F., et al. (2021). Associations of Genetic Variants Contributing to Gut Microbiota Composition in Immunoglobin A Nephropathy. *mSystems. 6*(1);1–13. doi:10.1128/msystems.00819-20

Heap, G. A., So, K., Weedon, M., et al. (2016). Clinical Features and HLA Association of 5-Aminosalicylate (5-ASA)-induced Nephrotoxicity in Inflammatory Bowel Disease. *J Crohns Colitis. 10*(2);149–58. doi:10.1093/ecco-jcc/jjv219

Hein, R., Köster, I., Bollschweiler, E., Schubert, I. (2014). Prevalence of inflammatory bowel disease: Estimates for 2010 and trends in Germany from a large insurance-based regional cohort. *Scand J Gastroenterol. 49*(11);1325–35. doi:10.3109/00365521.2014.962605

Helve, J., Sund, R., Arffman, M., et al. (2018). Incidence of End-Stage Renal Disease in Patients With Type 1 Diabetes. *Diabetes Care. 41*(3);434–9. doi:10.2337/dc17-2364

Henriksen, M., Jahnsen, J., Lygren, I. et al. (2007) Clinical course in Crohn's disease: Results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol.* 42:602-10. doi:10.1080/00365520601076124

Herbert, J., Teeter, E., Burstiner, L. S., et al. (2022). Urinary manifestations in African American and Caucasian inflammatory bowel disease patients: A retrospective cohort study. *BMC Urology. 22*(1);1. doi:10.1186/s12894-021-00951-z

Herrlinger, K. R., Noftz, M. K., Fellermann, K., Schmidt, K., Steinhoff, J., Stange, E. F. (2001). Minimal renal dysfunction in inflammatory bowel disease is related to disease activity but not to 5-ASA use. *Aliment Pharmacol Therap. 15*(3);363–9. doi:10.1046/j.1365-2036.2001.00940.x

Higgins-Biddle, J. C., Babor, T. F. (2018). A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions. *Am J Drug Alcohol Abuse. 44*(6);578–86. doi:10.1080/00952990.2018.1456545

Hiki, Y., Odani, H., Takahashi, M., et al. (2001). Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. *Kidney Int. 59*(3);1077–85. doi:10.1046/j.1523-1755.2001.0590031077.x

Hogan, M. C., Norby, S. M. (2010). Evaluation and Management of Pain in Autosomal Dominant Polycystic Kidney Disease. *Adv Chronic Kidney Dis. 17*(3);e1–e16. doi:10.1053/j.ackd.2010.01.005

Honkanen, T., Mustonen, J., Kainulainen, H., et al. (2005). Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. *Kidney Int. 67*(6);2187–95. doi:10.1111/j.1523-1755.2005.00324.x

Hotta, O., Furuta, T., Chiba, S., Tomioka, S., Taguma, Y. (2002). Regression of IgA nephropathy: A repeat biopsy study. *Am J Kidney Dis. 39*(3);493–502. doi:10.1053/ajkd.2002.31399

Huang, Z. Q., Raska, M., Stewart, T. J., et al. (2016). Somatic Mutations Modulate Autoantibodies against Galactose-Deficient IgA1 in IgA Nephropathy. *J Am Soc Nephrol. 27*(11);3278–84. doi:10.1681/ASN.2014101044

Hurley, J. C. (1995). Endotoxemia: Methods of detection and clinical correlates. *Clin Microbiol Rev. 8*(2);268–92. doi:10.1128/CMR.8.2.268

Husby, S., Koletzko, S., Korponay-Szabó, I. R., et al. (2012). European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease. *J Pediatr Gastroenterol Nutr. 54*(1);136–60. doi:10.1097/MPG.0b013e31821a23d0

Ibels, L. S., György, A. Z. (1994). IgA nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine. 73*(2);79–102.

Ikee, R., Kobayashi, S., Hemmi, N., et al. (2007). Involvement of transglutaminase-2 in pathological changes in renal disease. *Nephron Clin Pract. 105*(3);c139-46. doi:10.1159/000098646

Ilus, T., Kaukinen, K., Virta, L. J., et al. (2014). Refractory coeliac disease in a country with a high prevalence of clinically-diagnosed coeliac disease. *Aliment Pharmacol Therap. 39*(4);418–25. doi:10.1111/apt.12606

Ingle, S., Loftus, E. (2007) The natural history of perianal Crohn's disease. *Dig Liver Dis.* 39:963-9. doi:10.1016/j.dld.2007.07.154

Inker, L. A., Mondal, H., Greene, T., et al. (2016). Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis. 68*(3);392–401. doi:10.1053/j.ajkd.2016.02.042

Inker, L. A., Eneanya, N. D., Coresh, J., et al. (2021). New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *N Engl J Med. 385*(19);1737–49. doi:10.1056/NEJMoa2102953

Izzedine, H., Simon, J., Piette, A. M., et al. (2002). Primary chronic interstitial nephritis in crohn's disease. *Gastroenterology. 123*(5);1436–40. doi:10.1053/gast.2002.36613

Jacob, C. M. A., Pastorino, A. C., Fahl, K., Carneiro-Sampaio, M., Monteiro, R. C. (2008). Autoimmunity in IgA Deficiency: Revisiting the Role of IgA as a Silent Housekeeper. *J Clin Immunol. 28*(S1);56–61. doi:10.1007/s10875-007-9163-2

Jairath, V., Hokkanen, S. R. K., Guizzetti, L., Boxall, N., Campbell-Hill, S., Patel, H. (2019). No increased risk of nephrotoxicity associated with 5-aminosalicylic acid in IBD: A population-based cohort and nested case-control study. *Aliment Pharmacol Therap. 50*(4);416–24. doi:10.1111/apt.15408

Jarrick, S., Lundberg, S., Welander, A., et al. (2019). Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. *J Am Soc Nephrol. 30*(5);866–76. doi:10.1681/ASN.2018101017

Jericho, H., Sansotta, N., Guandalini, S. (2017). Extraintestinal Manifestations of Celiac Disease: Effectiveness of the Gluten-Free Diet. *J Pediatr Gastroenterol Nutr. 65*(1);75–9. doi:10.1097/MPG.0000000000001420

Johansson, M. E. V., Gustafsson, J. K., Holmén-Larsson, J., et al. (2014). Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut. 63*(2);281–91. doi:10.1136/gutjnl-2012-303207

Joher, N., Gosset, C., Guerrot, D., et al. (2021). Immunoglobulin A nephropathy in association with inflammatory bowel diseases: Results from a national study and systematic literature review. *Nephrol Dial Transplant. 37*(3);531-9. doi:10.1093/ndt/gfaa378

Johnson, T. S., El-Koraie, A. F., Skill, N. J., et al. (2003). Tissue transglutaminase and the progression of human renal scarring. *J Am Soc Nephrol. 14*(8);2052-62. doi:10.1097/01.ASN.0000079614.63463.DD

Johnson, T. S., Fisher, M., Haylor, J. L., et al. (2007). Transglutaminase inhibition reduces fibrosis and preserves function in experimental chronic kidney disease. *J Am Soc Nephrol. 18*(12);3078–88. doi:10.1681/ASN.2006070690

Jostins, L., Ripke, S., Weersma, R. K., et al. (2012). Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature. 491*(7422);119–24. doi:10.1038/nature11582

Jullien, P., Laurent, B., Claisse, G., et al. (2018). Deletion Variants of CFHR1 and CFHR3 Associate with Mesangial Immune Deposits but Not with Progression of IgA Nephropathy. *J Am Soc Nephrol. 29*(2);661–9. doi:10.1681/ASN.2017010019

Jussila, A., Virta, L. J., Kautiainen, H., Rekiaro, M., Nieminen, U., Färkkilä, M. A. (2012). Increasing incidence of inflammatory bowel diseases between 2000 and 2007: A nationwide register study in Finland: *Inflamm Bowel Dis. 18*(3);555–61. doi:10.1002/ibd.21695

Jussila, A., Virta, L. J., Salomaa, V., Mäki, J., Jula, A., Färkkilä, M. A. (2013). High and increasing prevalence of inflammatory bowel disease in Finland with a clear North-South difference. *J Crohns Colitis. 7*(7);256–62. doi:10.1016/j.crohns.2012.10.007

Jussila, A., Virta, L. J., Pukkala, E., Färkkilä, M. A. (2014). Mortality and causes of death in patients with inflammatory bowel disease: A nationwide register study in Finland. *J Crohns Colitis. 8*(9);1088–96. doi:10.1016/j.crohns.2014.02.015

Kaartinen, K., Syrjänen, J., Pörsti, I., et al. (2007). Insulin resistance and the progression of IgA glomerulonephritis. *Nephrol Dial Transplant. 22*(3);778–83. doi:10.1093/ndt/gfl704

Kaartinen, K., Safa, A., Kotha, S., Ratti, G., Meri, S. (2019). Complement dysregulation in glomerulonephritis. *Semin Immunol. 45*;101331. doi:10.1016/j.smim.2019.101331

Kahaly, G. J., Frommer, L., Schuppan, D. (2018). Celiac disease and endocrine autoimmunity – the genetic link. *Autoimmun Rev. 17*(12);1169–75. doi:10.1016/j.autrev.2018.05.013

Kahvecioglu, S., Akdag, I., Kiyici, M., et al. (2005). High prevalence of irritable bowel syndrome and upper gastrointestinal symptoms in patients with chronic renal failure. *J Nephrol. 18*(1);61–6.

Kalliomäki, M., Satokari, R., Lähteenoja, H., et al. (2012). Expression of Microbiota, Toll-like Receptors, and Their Regulators in the Small Intestinal Mucosa in Celiac Disease. *J Pediatr Gastroenterol Nutr. 54*(6);727–32. doi:10.1097/MPG.0b013e318241cfa8

Kaneko, Y., Otsuka, T., Tsuchida, Y., Gejyo, F., Narita, I. (2012). Integrin α1/β1 and α2/β1 as a receptor for IgA1 in human glomerular mesangial cells in IgA nephropathy. *Int Immunol. 24*(4);219–32. doi:10.1093/intimm/dxr125

Kang, H. S., Chin, R. K., Wang, Y., et al. (2002). Signaling via ltβr on the lamina propria stromal cells of the gut is required for iga production. *Nat Immunol. 3*(6);576–82. doi:10.1038/ni795

Kaplan, G. G., Seow, C. H., Ghosh, S., et al. (2012). Decreasing Colectomy Rates for Ulcerative Colitis: A Population-Based Time Trend Study. *Am J Gastroenterol. 107*(12);1879–87. doi:10.1038/ajg.2012.333

Kaplan, G. G. (2015). The global burden of IBD: From 2015 to 2025. *Nat Rev Gastroenterol Hepatol. 12*(12);720–7. doi:10.1038/nrgastro.2015.150

Kaplan, G. G., Ng, S. C. (2017). Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology. 152*(2);313-21. doi:10.1053/j.gastro.2016.10.020

Kastarinen, M., Juutilainen, A., Kastarinen, H., et al. (2010). Risk factors for end-stage renal disease in a community-based population: 26-year follow-up of 25 821 men and

women in eastern Finland. *J Intern Med. 267*(6);612–20. doi:10.1111/j.1365-2796.2009.02197.x

Katafuchi, R., Ninomiya, T., Nagata, M., Mitsuiki, K., Hirakata, H. (2011). Validation study of Oxford classification of IgA nephropathy: The significance of extracapillary proliferation. *Clin J Am Soc Nephrol. 6*(12);2806–13. doi:10.2215/CJN.02890311

Katsanos, K. H., Tsianos, E. V. (2002). The kidneys in inflammatory bowel disease. *Ann Gastroenterol. 15*(1);41–52.

Kaukinen, K., Partanen, J., Mäki, M., Collin, P. (2002). HLA-DQ typing in the diagnosis of celiac disease. *Am J Gastroenterol. 97*(3);695–9. doi:10.1016/S0002-9270(01)04033-3

Kaukinen, K., Lindfors, K., Collin, P., Koskinen, O., Mäki, M. (2010). Coeliac disease—A diagnostic and therapeutic challenge. *Clin Chem Lab Med. 48*(9);1205–16. doi:10.1515/CCLM.2010.241

Kerr, M. A. (1990). The structure and function of human IgA. *Biochem J. 271*(2);285–96. doi:10.1042/bj2710285

Keyashian, K., Dehghan, M., Sceats, L., Kin, C., Limketkai, B. N., Park, K. T. (2019). Comparative Incidence of Inflammatory Bowel Disease in Different Age Groups in the United States. *Inflamm Bowel Dis. 25*(12);1983–9. doi:10.1093/ibd/izz092

Khor, B., Gardet, A., Xavier, R. J. (2011). Genetics and pathogenesis of inflammatory bowel disease. *Nature. 474*(7351);307–17. doi:10.1038/nature10209

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter., Suppl.* 2013:*3*;1–150.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021*:100*(4S);S1–276. doi:10.1016/j.kint.2021.05.021

Kim, S. J., Koo, H. M., Lim, B. J., et al. (2012). Decreased Circulating C3 Levels and Mesangial C3 Deposition Predict Renal Outcome in Patients with IgA Nephropathy. *PLoS One.* doi:10.1371/journal.pone.0040495

Kirsner, J. B. (2001). Historical origins of current IBD concepts. *World J Gastroenterol. 7*(2);175. doi:10.3748/wjg.v7.i2.175

Kiryluk, K., Li, Y., Sanna-Cherchi, S., Rohanizadegan, M., et al. (2012). Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet. 8*(6). doi:10.1371/journal.pgen.1002765

Kiryluk, K., Li, Y., Scolari, F., Sanna-Cherchi, S., et al. (2014). Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet. 46*(11);1187–96. doi:10.1038/ng.3118

Kiryluk, K., Novak, J. (2014). The genetics and immunobiology of IgA nephropathy. *J Clin Invest. 124*(6);2325–32. doi:10.1172/JCI74475

Kitchens, R. L., Thompson, P. A. (2005). Modulatory effects of sCD14 and LBP on LPS-host cell interactions. *J Endotoxin Res. 11*(4);225–9. doi:10.1179/096805105X46565

Kleinman, L., Kilburg, A., Machnicki, G., et al. (2006). Using GI-specific patient outcome measures in renal transplant patients: Validation of the GSRS and GIQLI. *Qual Life Res. 15*(7);1223–32. doi:10.1007/s11136-006-0053-5

Knoop, T., Vikse, B. E., Svarstad, E., Leh, S., Reisæter, A. V., Bjørneklett, R. (2013). Mortality in patients with IgA nephropathy. *Am J Kidney Dis. 62*(5);883–90. doi:10.1053/j.ajkd.2013.04.019

Knoop, T., Vikse, B. E., Mwakimonga, A., Leh, S., Bjørneklett, R. (2017). Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. *Nephrol Dial Transplant. 32*(11);1841–50. doi:10.1093/ndt/gfx242

Knoppova, B., Reily, C., Maillard, N., et al. (2016). The origin and activities of IgA1-containing immune complexes in IGA nephropathy. *Front Immunol.* doi:10.3389/fimmu.2016.00117

Koçak, E., Köklü, S., Akbal, E., Huddam, B., Azak, A., Yilmaz, Ş. R. (2010). Development of glomerulonephritis early in the course of Crohn's disease. *Inflamm Bowel Dis. 16*(4);548–9. doi:10.1002/ibd.21044

Koivuviita, N., Tertti, R., Heiro, M., Metsärinne, K. (2009). A case report: A patient with IgA nephropathy and coeliac disease. Complete clinical remission following gluten-free diet. *NDT Plus. 2*(2);161–3. doi:10.1093/ndtplus/sfn205

Kontola, K., Oksanen, P., Huhtala, H., Jussila, A. (2023). Increasing Incidence of Inflammatory Bowel Disease, with Greatest Change Among the Elderly: A Nationwide Study in Finland, 2000–2020. *J Crohns Colitis. 17*(5);706–11. doi:10.1093/ecco-jcc/jjac177

Korponay-Szabó, I. R., Halttunen, T., Szalai, Z., et al. (2004). In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. *Gut. 53*(5);641–8. doi:10.1136/gut.2003.024836

Kosmadakis, G., Albaret, J., Da Costa Correia, E., Somda, F., Aguilera, D. (2018). Gastrointestinal Disorders in Peritoneal Dialysis Patients. *Am J Nephrol. 48*(5);319–25. doi:10.1159/000494145

Kovács, T., Kun, L., Schmelczer, M., Wagner, L., Davin, J. C., Nagy, J. (1996). Do intestinal hyperpermeability and the related food antigens play a role in the progression of IgA nephropathy? I. Study of intestinal permeability. *Am J Nephrol. 16*(6);500–5. doi:10.1159/000169050

Krebs, C. F., Paust, H. J., Krohn, S., et al. (2016). Autoimmune Renal Disease Is Exacerbated by S1P-Receptor-1-Dependent Intestinal Th17 Cell Migration to the Kidney. *Immunity. 45*(5);1078–92. doi:10.1016/j.immuni.2016.10.020

Krochmal, M., Cisek, K., Filip, S., et al. (2017). Identification of novel molecular signatures of IgA nephropathy through an integrative -omics analysis. *Sci Rep. 7*(1);9091. doi:10.1038/s41598-017-09393-w

Kumar, S., Pollok, R., Goldsmith, D. (2022). Renal and Urological Disorders Associated With Inflammatory Bowel Disease. *Inflamm Bowel Dis. 29*(8);1306-16. doi:10.1093/ibd/izac140

Kurppa, K., Collin, P., Viljamaa, M., et al. (2009). Diagnosing Mild Enteropathy Celiac Disease: A Randomized, Controlled Clinical Study. *Gastroenterology. 136*(3);816–23. doi:10.1053/j.gastro.2008.11.040

Lafayette, R. A., Canetta, P. A., Rovin, B. H., et al. (2017). A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J Am Soc Nephrol. 28*(4);1306–13. doi:10.1681/ASN.2016060640

Lafayette, R. A., Kelepouris, E. (2018). Immunoglobulin A Nephropathy: Advances in Understanding of Pathogenesis and Treatment. *Am J Nephrol. 47*(suppl 1);43–52. doi:10.1159/000481636

Lai, K. N. (2012). Pathogenesis of IgA nephropathy. *Nat Rev Nephrol. 8*(5);275–83. doi:10.1038/nrneph.2012.58

Laine, O., Pitkänen, K., Lindfors, K., et al. (2018). Elevated serum antiphospholipid antibodies in adults with celiac disease. *Dig Liver Dis. 50*(5);457–61. doi:10.1016/j.dld.2017.11.018

Lakatos, L., Pandur, T., David, G., et al. (2003). Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: Results of a 25-year follow-up study. *World J Gastroenterol. 9*(10);2300–7. doi:10.3748/wjg.v9.i10.2300

Lakatos, P. L., Kiss, L. S., Palatka, K., et al. (2011). Serum lipopolysaccharide-binding protein and soluble CD14 are markers of disease activity in patients with Crohn's disease. *Inflamm Bowel Dis. 17*(3);767–77. 10.1002/ibd.21402

Lalande, C., Drouin-Chartier, J-P., Tremblay, A., Couture, P., Veilleux, A. (2020). *Diabetol Metab Syndr.* 12:31. doi:10.1186/s13098-020-00530-6

Langholz, E., Munkholm, P., Davidsen, M., Binder, V. (1994). Course of ulcerative colitis: Analysis of changes in disease activity over years. *Gastroenterology. 107*(1);3–11. doi:10.1016/0016-5085(94)90054-X

Langhorst, J., Boone, J., Lauche, R., Rueffer, A., Dobos, G. (2016). Faecal lactoferrin, calprotectin, pmn-elastase, crp, and white blood cell count as indicators for mucosal healing and clinical course of disease in patients with mild to moderate ulcerative colitis: Post hoc analysis of a prospective clinical trial. *J Crohns Colitis. 10*(7);786–94. doi:10.1093/ecco-jcc/jjw044

Lau, W. L., Kalantar-Zadeh, K., Vaziri, N. D. (2015). The Gut as a Source of Inflammation in Chronic Kidney Disease. *Nephron. 130*(2);92–8. doi:10.1159/000381990

Launay, P., Grossetête, B., Arcos-Fajardo, et al. (2000). Fcα receptor (CD89) mediates the development of immunoglobulin a (IgA) nephropathy (Berger's disease): Evidence for pathogenic soluble receptor-IgA complexes in patients and CD89 transgenic mice. *J Exp Med. 191*(11);1999–2009. doi:10.1084/jem.191.11.1999

Laurent, J., Branellec, A., Heslan, J.-M., et al. (1987). An Increase in Circulating IgA Antibodies to Gliadin in IgA Mesangial Glomerulonephritis. *Am J Nephrol. 7*(3);178–83. doi:10.1159/000167460

Laurikka, P., Salmi, T., Collin, P., et al. (2016). Gastrointestinal symptoms in celiac disease patients on a long-term gluten-free diet. *Nutrients. 8*(7);1–11. doi:10.3390/nu8070429

Laurikka, P., Nurminen, S., Kivelä, L., Kurppa, K. (2018). Extraintestinal Manifestations of Celiac Disease: Early Detection for Better Long-Term Outcomes. *Nutrients. 10*(8);1015. doi:10.3390/nu10081015

Layward, L., Hattersley, J. M., Patel, H. R., Tanner, M. S., Feehally, J. (1990). Gut permeability in IgA nephropathy. *Nephrol Dial Transplant. 5*(8);569–71. doi:10.1093/ndt/5.8.569

Le, W. B., Liang, S. S., Hu, Y. L., et al. (2012). Long-term renal survival and related risk factors in patients with IgA nephropathy: Results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant. 27*(4);1479–85. doi:10.1093/ndt/gfr527

Le, W. B., Liang, S. S., Chen, H., et al. (2014). Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. *Am J Nephrol. 40*(1);43–50. doi:10.1159/000364954

Lebreton, C., Ménard, S., Abed, J., et al. (2012). Interactions among secretory immunoglobulin A, CD71, and transglutaminase-2 affect permeability of intestinal epithelial cells to gliadin peptides. *Gastroenterology. 143*(3);698-707. doi:10.1053/j.gastro.2012.05.051

Lechner, S. M., Papista, C., Chemouny, J. M., Berthelot, L., Monteiro, R. C. (2016). Role of IgA receptors in the pathogenesis of IgA nephropathy. *J Nephrol. 29*(1);5–11. doi:10.1007/s40620-015-0246-5

Lee, M., Suzuki, H., Kato, R., et al. (2021). Renal pathological analysis using galactose-deficient IgA1-specific monoclonal antibody is a strong tool for differentiation of primary IgA nephropathy from secondary IgA nephropathy. *CEN Case Rep. 10*(1);17–22. doi:10.1007/s13730-020-00508-3

Lee, S. H., Kwon, J. eun, Cho, M.-L. (2018). Immunological pathogenesis of inflammatory bowel disease. *Intest Res. 16*(1);26-42. doi:10.5217/ir.2018.16.1.26

Leffler, D. A., Green, P. H. R., Fasano, A. (2015). Extraintestinal manifestations of coeliac disease. *Nat Rev Gastroenterol Hepatol. 12*(10);561–71. doi:10.1038/nrgastro.2015.131

Lehmann, F. S., Burri, E., Beglinger, C. (2015). The role and utility of faecal markers in inflammatory bowel disease. *Therap Adv Gastroenterol. 8*(1);23–36. doi:10.1177/1756283X14553384

Lehto, M., Groop, P. H. (2018). The gut-kidney axis: Putative interconnections between gastrointestinal and renal disorders. *Front Endocrinol.* doi:10.3389/fendo.2018.00553

Leinikki, P. O., Mustonen, J., Pasternack, A. (1987). Immune response to oral polio vaccine in patients with IgA glomerulonephritis. *Clin Exp Immunol. 68*(1);33–8.

Levey, A. S., Stevens, L. A., Schmid, C. H., et al. (2009). A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med. 150*(9);604-12. doi:10.7326/0003-4819-150-9-200905050-00006

Lewis, B., Mukewar, S., Lopez, R., Brzezinski, A., Hall, P., Shen, B. (2013). Frequency and risk factors of renal insufficiency in inflammatory bowel disease inpatients. *Inflamm Bowel Dis. 19*(9);1846–51. doi:10.1097/MIB.0b013e31828a661e

Li, M., Wang, L., Shi, D.-C., et al. (2020). Genome-Wide Meta-Analysis Identifies Three Novel Susceptibility Loci and Reveals Ethnic Heterogeneity of Genetic Susceptibility for IgA Nephropathy. *J Am Soc Nephrol. 31*(12);2949–63. doi:10.1681/ASN.2019080799

Li, P. K. T., Leung, C. B., Chow, K. M., et al. (2006). Hong Kong Study Using Valsartan in IgA Nephropathy (HKVIN): A Double-Blind, Randomized, Placebo-Controlled Study. *Am J Kidney Dis. 47*(5);751–60. doi:10.1053/j.ajkd.2006.01.017

Li, Q., Yuan, X., Shi, S., et al. (2023). Zonulin, as a marker of intestinal permeability, is elevated in IgA nephropathy and IgA vasculitis with nephritis. *Clin Kidney J. 16*(1);184–91. doi:10.1093/ckj/sfac214

Li, X., Liu, Y., Lv, J., et al. (2014). Progression of IgA nephropathy under current therapy regimen in a chinese population. *Clin J Am Soc Nephrol. 9*(3);484–9. doi:10.2215/CJN.01990213

Lichtenstein, G. R., Loftus, E. V., Isaacs, K. L., Regueiro, M. D., Gerson, L. B., Sands, B. E. (2018). ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol. 113*(4);481–517. doi:10.1038/ajg.2018.27

Lindfors, K., Suzuki, H., Novak, J., et al. (2011). Galactosylation of serum IgA1 O-glycans in celiac disease. *J Clin Immunol. 31*(1);74–9. doi:10.1007/s10875-010-9473-7

Lindfors, K., Ciacci, C., Kurppa, K., et al. (2019). Coeliac disease. *Nat Rev Dis Primers. 5*(1);3. doi:10.1038/s41572-018-0054-z

Loftus, E., Panés, J., Lacerda, A. (2023). Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med.* 388:1966-80. doi:10.1056/NEJMoa2212728

Lohi, S., Mustalahti, K., Kaukinen, K., et al. (2007). Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther. 26*(9);1217–25. 10.1111/j.1365-2036.2007.03502.x

Louka, A. S., Sollid, L. M. (2003). HLA in coeliac disease: Unravelling the complex genetics of a complex disorder. *Tissue Antigens. 61*(2);105–17. doi:10.1034/j.1399-0039.2003.00017.x

Ludvigsson, J. F. J., Montgomery, S. M., Olén, O., Ekbom, A., Fored, M. (2006). Coeliac disease and risk of renal disease—A general population cohort study. *Nephrol Dial Transplant. 21*(7);1809–15. doi:10.1093/ndt/gfl117

Ludvigsson, J. F., Leffler, D. A., Bai, J. C., et al. (2013). The Oslo definitions for coeliac disease and related terms. *Gut. 62*(1);43–52. doi:10.1136/gutjnl-2011-301346

Ludvigsson, J. F., Bai, J. C., Biagi, F., et al. (2014). Diagnosis and management of adult coeliac disease: Guidelines from the British society of gastroenterology. *Gut. 63*(8);1210–28. doi:10.1136/gutjnl-2013-306578

Lundgren, D., Eklöf, V., Palmqvist, R., Hultdin, J., Karling, P. (2019). Proton pump inhibitor use is associated with elevatd faecal calprotectin levels. A cross-sectional study on subjects referred for colonoscopy. *Scand J Gastroenterol.* 54(2):152-7. doi:10.1080/00365521.2019.1566493

Lv, J., Shi, S., Xu, D., et al. (2013a). Evaluation of the oxford classification of IgA nephropathy: A systematic review and meta-analysis. *Am J Kidney Dis. 62*(5);891–9. doi:10.1053/j.ajkd.2013.04.021

Lv, J., Yang, Y., Zhang, H., et al. (2013b). Prediction of Outcomes in Crescentic IgA Nephropathy in a Multicenter Cohort Study. *J Am Soc Nephrol. 24*(12);2118–25. doi:10.1681/ASN.2012101017

Lv, J., Zhang, H., Wong, M. G., et al. (2017). Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomized clinical trial. *JAMA 318*(5);432–42. doi:10.1001/jama.2017.9362

Lv, J., Wong, M. G., Hladunewich, M. A., et al. (2022). Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA. 327*(19);1888-98. doi:10.1001/jama.2022.5368

Lycke, N. Y., Bemark, M. (2012). The role of Peyer's patches in synchronizing gut IgA responses. *Front Immunol.* doi:10.3389/fimmu.2012.00329

Lähdeaho, M.-L., Scheinin, M., Vuotikka, P., et al. (2019). Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: A phase 2a, randomised, double-blind, placebo-controlled study. *Lancet Gastroenterol Hepatol. 4*(12);948–59. doi:10.1016/S2468-1253(19)30264-X

Magistroni, R., D'Agati, V. D., Appel, G. B., Kiryluk, K. (2015). New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. *Kidney Int. 88*(5);974–89. doi:10.1038/ki.2015.252

Magnusson, M., Magnusson, K. E., Sundqvist, T., Denneberg, T. (1991). Impaired intestinal barrier function measured by differently sized polyethylene glycols in patients with chronic renal failure. *Gut. 32*(7);754–9. doi:10.1136/gut.32.7.754

Mahid, S. S., Minor, K. S., Soto, R. E., Hornung, C. A., Galandiuk, S. (2006). Smoking and Inflammatory Bowel Disease: A Meta-analysis. *Mayo Clin Proc. 81*(11);1462–71. doi:10.4065/81.11.1462

Mahmud, N., Stinson, J., O'Connell, M. A., et al. (1994). Microalbuminuria in inflammatory bowel disease. *Gut. 35*(11);1599–604. doi:10.1136/gut.35.11.1599

Mahmud, N., McDonald, G. S. A., Kelleher, D., Weir, D. G. (1996). Microalbuminuria correlates with intestinal histopathological grading in patients with inflammatory bowel disease. *Gut. 38*(1);99–103. doi:10.1136/gut.38.1.99

Maillard, N., Wyatt, R. J., Julian, B. A., et al. (2015). Current understanding of the role of complement in IgA nephropathy. *J Am Soc Nephrol. 26*(7);1503–12. doi:10.1681/ASN.2014101000

Maixnerova, D., Ling, C., Hall, S., et al. (2019). Correction: Galactose-deficient IgA1 and the corresponding IgG autoantibodies predict IgA nephropathy progression *PLoS One. 14*(7);1–9. doi:10.1371/journal.pone.0219947

Makdassy, R., Beaufils, M., Meyrier, A., Mignon, F., Moulonguet-Doleris, L., Richet, G. (1984). Pathologic conditions associated with IgA mesangial nephropathy: Preliminary results. *Contrib Nephrol. 40*;292–5. doi:10.1159/000409764

Makita, Y., Suzuki, H., Kano, T., et al. (2020). TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6–mediated pathways in IgA nephropathy. *Kidney Int. 97*(2);340–9. doi:10.1016/j.kint.2019.08.022

Malik, T. A. (2015). Inflammatory Bowel Disease. Historical Perspective, Epidemiology, and Risk Factors. *Surg Clin North Am. 95*(6);1105–22. doi:10.1016/j.suc.2015.07.006

Manninen, P., Karvonen, A. L., Huhtala, H., Rasmussen, M., Collin, P. (2010). The epidemiology of inflammatory bowel diseases in Finland. *Scand J Gastroenterol. 45*(9);1063–7. doi:10.3109/00365521.2010.485323

Manno, C., Torres, D. D., Rossini, M., Pesce, F., Schena, F. P. (2009). Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant. 24*(12);3694–701. doi:10.1093/ndt/gfp356

Mantis, N. J., Rol, N., Corthésy, B. (2011). Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol. 4*(6);603–11. doi:10.1038/mi.2011.41

Matousovic, K., Novak, J., Yanagihara, T., et al. (2006). IgA-containing immune complexes in the urine of IgA nephropathy patients. *Nephrol Dial Transplant. 21*(9);2478–84. doi:10.1093/ndt/gfl240

Matsushita, K. (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet. 375*(9731);2073–81. doi:10.1016/S0140-6736(10)60674-5

Mattila, J., Stenholm, T., Löyttyniemi, E., Koffert, J. (2022). Predictive Markers of Crohn's Disease in Small Bowel Capsule Endoscopy: A Retrospective Study of Small Bowel Capsule Endoscopy. *J Clin Med. 11*(15);4635. doi:10.3390/jcm11154635

Matysiak-Budnik, T., Moura, I. C., Arcos-Fajardo, M., et al. (2008). Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. *J Exp Med. 205*(1);143–54. doi:10.1084/jem.20071204

McGrogan, A., Franssen, C. F. M., De Vries, C. S. (2011). The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. *Nephrol Dial Transplant. 26*(2);414–30. doi:10.1093/ndt/gfq665

McIntyre, C. W., Harrison, L. E. A., Eldehni, M. T., et al. (2011). Circulating endotoxemia: A novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin J Am Soc Nephrol. 6*(1);133–41. doi:10.2215/CJN.04610510

McQuarrie, E. P., MacKinnon, B., Young, B., et al. (2009). Centre variation in incidence, indication and diagnosis of adult native renal biopsy in Scotland. *Nephrol Dial Transplant. 24*(5);1524–8. doi:10.1093/ndt/gfn677

Medjeral-Thomas, N. R., Lomax-Browne, H. J., Beckwith, H., et al. (2017). Circulating complement factor H–related proteins 1 and 5 correlate with disease activity in IgA nephropathy. *Kidney Int. 92*(4);942–52. doi:10.1016/j.kint.2017.03.043

Medjeral-Thomas, N. R., Troldborg, A., Constantinou, N., et al. (2018). Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin–Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H–Related Protein-5 (FHR5) Deposition. *Kidney Int Rep. 3*(2);426–38. doi:10.1016/j.ekir.2017.11.015

Meira de-Faria, F., Bednarska, O., Ström, M., Söderholm, J. D., Walter, S. A., Keita, Å. V. (2021). Colonic paracellular permeability and circulating zonulin-related proteins. *Scand J Gastroenterol. 56*(4);424–31. doi:10.1080/00365521.2021.1879247

Menon, S., Bressler, B. (2019). Editorial: Aminosalicylates and nephrotoxicity-an issue put to rest. *Aliment Pharmacol Ther. 50*(9);1059. doi:10.1111/apt.15474

Mikolajczyk, A. E., Te, H. S., Chapman, A. B. (2017). Gastrointestinal Manifestations of Autosomal-Dominant Polycystic Kidney Disease. *Clin Gastroenterol Hepatol. 15*(1);17–24. doi:10.1016/j.cgh.2016.06.017

Mizoguchi, E., Subramaniam, R., Okada, T., Mizoguchi, A. (2021). A Review of Selected IBD Biomarkers: From Animal Models to Bedside. *Diagnostics. 11*(2);207. doi:10.3390/diagnostics11020207

Moeller, S., Canetta, P. A., Taylor, A. K., et al. (2014). Lack of serologic evidence to link IgA nephropathy with celiac disease or immune reactivity to gluten. *PLoS One. 9*(4);1–6. doi:10.1371/journal.pone.0094677

Molberg, Ø., Mcadam, S. N., Körner, R., et al. (1998). Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. *Nat Med. 4*(6);713–7. doi:10.1038/nm0698-713

Molyneux, K., Wimbury, D., Pawluczyk, I., et al. (2017). B1,4-galactosyltransferase 1 is a novel receptor for IgA in human mesangial cells. *Kidney Int. 92*(6);1458–68. doi:10.1016/j.kint.2017.05.002

Monteiro, R. C., Berthelot, L. (2021). Role of gut-kidney axis in renal diseases and IgA nephropathy. *Curr Opin Gastroenterol. 37*(6);565–71. doi:10.1097/MOG.0000000000000789

Montenegro, V., Monteiro, R. C. (1999). Elevation of serum IgA in spondyloarthropathies and IgA nephropathy and its pathogenic role. *Curr Opin Rheumatol. 11*(4);265-72.

Moresco, R. N., Speeckaert, M. M., Delanghe, J. R. (2015). Diagnosis and monitoring of IgA nephropathy: The role of biomarkers as an alternative to renal biopsy. *Autoimm Rev. 14*(10);847–53. doi:10.1016/j.autrev.2015.05.009

Moresco, R. N., Speeckaert, M. M., Zmonarski, S. C., et al. (2016). Urinary myeloid IgA Fc alpha receptor (CD89) and transglutaminase-2 as new biomarkers for active IgA nephropathy and henoch-Schönlein purpura nephritis. *BBA Clin. 5*;79–84. doi:10.1016/j.bbacli.2016.02.002

Moroni, G., Longhi, S., Quaglini, S., et al. (2013). The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. *Nephrol Dial Transplant. 28*(5);1305–14. doi:10.1093/ndt/gfs472

Moura, I. C., Centelles, M. N., Arcos-Fajardo, et al. (2001). Identification of the Transferrin Receptor as a Novel Immunoglobulin (Ig)a1 Receptor and Its Enhanced Expression

on Mesangial Cells in Iga Nephropathy. *J Exp Med. 194*(4);417–26. doi:10.1084/jem.194.4.417

Moura, I. C., Arcos-Fajardo, M., Sadaka, C., et al. (2004). Glycosylation and Size of IgA1 Are Essential for Interaction with Mesangial Transferrin Receptor in IgA Nephropathy. *J Am Soc Nephrol. 15*(3);622–34. doi:10.1097/01.ASN.0000115401.07980.0C

Moura, I. C., Arcos-Fajardo, M., Gdoura, A., et al. (2005). Engagement of transferrin receptor by polymeric IgA1: Evidence for a positive feedback loop involving increased receptor expression and mesangial cell proliferation in IgA nephropathy. *J Am Soc Nephrol. 16*(9);2667–76. doi:10.1681/ASN.2004111006

Mustalahti, K., Catassi, C., Reunanen, A., et al. (2010). The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Ann Med. 42*(8);587–95. doi:10.3109/07853890.2010.505931

Mustonen, J., Pasternack, A., Rantala, I. (1983). The nephrotic syndrome in IgA glomerulonephritis: Response to corticosteroid therapy. *Clin Nephrol. 20*(4);172–6.

Mustonen, J. (1984). IgA glomerulonephritis and associated diseases. *Ann Clin Res.16*(3);161–6.

Mustonen, J., Pasternack, A., Helin, H., Nikkilä, M. (1985). Clinicopathologic correlations in a series of 143 patients with IgA glomerulonephritis. *Am J Nephrol. 5*(3);150–7. doi:10.1159/000166925

Mustonen, J., Pasternack, A. (1987). Associated Diseases in IgA Nephropathy. In A. R. Clarkson (Ed.), *IgA Nephropathy* (pp. 47–65). Springer US. doi:10.1007/978-1-4613-2039-5_5

Myllymäki, J., Honkanen, T., Syrjänen, J., et al. (2005). Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. *Nephrol Dial Transplant. 20*(1);89–95. doi:10.1093/ndt/gfh584

Mäki, M., Mustalahti, K., Kokkonen, J., et al. (2003). Prevalence of Celiac Disease among Children in Finland. *N Engl J Med. 348*(25);2517–24. doi:10.1056/NEJMoa021687

Nagy, J., Scott, H., Brandtzaeg, P. (1988). Antibodies to dietary antigens in IgA nephropathy. *Clin Nephrol. 29*(6);275–9.

Nam, K. H., Joo, Y. S., Lee, C., et al. (2020). Predictive value of mesangial C3 and C4d deposition in IgA nephropathy. *Clin Immunol. 211*;108331. doi:10.1016/j.clim.2019.108331

Natale, P., Palmer, S. C., Ruospo, M., et al. (2020). Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database Syst Rev. 2020*(3). doi:10.1002/14651858.CD003965.pub3

Neugarten, J., Acharya, A., Silbiger, S. R. (2000). Effect of Gender on the Progression of Nondiabetic Renal Disease: A Meta-Analysis. *J Am Soc Nephrol. 11*(2);319–29. doi:10.1681/ASN.V112319

Neuhaus, J., Bauer, F., Fitzner, C., et al. (2018). Urinary biomarkers in the prediction of prognosis and treatment response in IgA nephropathy. *Kidney Blood Press Res. 43*(5);1563–72. doi:10.1159/000494442

Novak, J., Vu, H. L., Novak, L., Julian, B. A., Mestecky, J., Tomana, M. (2002). Interactions of human mesangial cells with IgA and IgA-containing immune complexes. *Kidney Int. 62*(2);465–75. doi:10.1046/j.1523-1755.2002.00477.x

Novak, J., Tomana, M., Matousovic, K., et al. (2005). IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells. *Kidney Int. 67*(2);504–13. doi:10.1111/j.1523-1755.2005.67107.x

Nurmi, R., Metso, M., Pörsti, I., et al. (2018). Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies. *Dig Liver Dis. 50*(1);27–31. doi:10.1016/j.dld.2017.09.131

Nurmi, R., Korponay-Szabó, I., Laurila, K., et al. (2021). Celiac disease-type tissue transglutaminase autoantibody deposits in kidney biopsies of patients with iga nephropathy. *Nutrients. 13*(5). doi:10.3390/nu13051594

Nurmi, R., Pasternack, C., Salmi, T., et al. (2022). The risk of renal comorbidities in celiac disease patients depends on the phenotype of celiac disease. *J Intern Med.* 292;779-87. doi:10.1111/joim.13532

Ok, M., Ylidiz, R., Hatipoglu, F. (2020). Use of intestine-related biomarkers for detecting intestinal epithelial damage in neonatal calves with diarrhea. *Am J Vet Res.* 81(2):139-46. doi:10.2460/ajvr.81.2.139

Okada, K., Sekino, M., Funaoka, H., et al. (2018). Intestinal fatty acid-binding protein levels in patients with chronic renal failure. *J Surg Res. 230*;94–100. doi:10.1016/j.jss.2018.04.057

Olive, C., Allen, A. C., Harper, S. J., Wicks, A. C. B., Feehally, J., Falk, M. C. (1997). Expression of the mucosal γδ T cell receptor V region repertoire in patients with IgA nephropathy. *Kidney Int. 52*(4);1047–53. doi:10.1038/ki.1997.427

Onime, A., Agaba, E. I., Sun, Y., et al. (2006). Immunoglobulin A nephropathy complicating ulcerative colitis. *Int Urol Nephrol. 38*(2);349–53. doi:10.1007/s11255-006-0061-y

Oortwijn, B. D., Roos, A., Royle, L., et al. (2006a). Differential Glycosylation of Polymeric and Monomeric IgA: A Possible Role in Glomerular Inflammation in IgA Nephropathy. *J Am Soc Nephrol. 17*(12);3529–39. doi:10.1681/ASN.2006040388

Oortwijn, B. D., Van Der Boog, P. J. M., Roos, A., et al. (2006b). A pathogenic role for secretory IgA in IgA nephropathy. *Kidney Int. 69*(7);1131–8. doi:10.1038/sj.ki.5000074

Oortwijn, B. D., Rastaldi, M. P., Roos, A., Mattinzoli, D., Daha, M. R., Van Kooten, C. (2007). Demonstration of secretory IgA in kidneys of patients with IgA nephropathy. *Nephrol Dial Transplant. 22*(11);3191–5. doi:10.1093/ndt/gfm346

Ots, M., Uibo, O., Metsküla, K., Uibo, R., Salupere, V. (1999). IgA-Antigliadin Antibodies in Patients with IgA Nephropathy: The Secondary Phenomenon? *Am J Nephrol. 19*(4);453–8. doi:10.1159/000013497

Paavola, S., Lindfors, K., Kivelä, L., et al. (2021). Presence of high-risk HLA genotype is the most important individual risk factor for coeliac disease among at-risk relatives. *Aliment Pharmacol Ther. 54*(6);805–13. doi:10.1111/apt.16534

Paavola, S., Kurppa, K., Huhtala, H., Saavalainen, P., Lindfors, K., Kaukinen, K. (2022). Coeliac disease re-screening among once seronegative at-risk relatives: A long-term follow-up study. *United European Gastroenterol J. 10*(6);585–93. doi:10.1002/ueg2.12255

Papista, C., Berthelot, L., Monteiro, R. C. (2011). Dysfunctions of the Iga system: A common link between intestinal and renal diseases. *Cell Mol Immunol. 8*(2);126–34. doi:10.1038/cmi.2010.69

Papista, C., Lechner, S., Ben Mkaddem, S., et al. (2015). Gluten exacerbates IgA nephropathy in humanized mice through gliadin-CD89 interaction. *Kidney Int. 88*(2);276–85. doi:10.1038/ki.2015.94

Pardi, D. (1998). Renal and Urologic Complications of Inflammatory Bowel Disease. *Am J Gastroenterol. 93*(4);504–14. doi:10.1016/s0002-9270(98)00033-1

Pariente, B., Mary, J.-Y., Danese, S., et al. (2015). Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease. *Gastroenterology. 148*(1);52-63. doi:10.1053/j.gastro.2014.09.015

Park, J. H., Peyrin-Biroulet, L., Eisenhut, M., Shin, J. I. (2017). IBD immunopathogenesis: A comprehensive review of inflammatory molecules. *Autoimm Rev. 16*(4);416–26. doi:10.1016/j.autrev.2017.02.013

Park, S., Chun, J., Han, K. D., et al. (2018). Increased end-stage renal disease risk in patients with inflammatory bowel disease: A nationwide population-based study. *World J Gastroenterol. 24*(42);4798–808. doi:10.3748/wjg.v24.i42.4798

Park, S., Kim, H. W., Park, J. T., et al. (2020). Relationship between complement deposition and the Oxford classification score and their combined effects on renal outcome in immunoglobulin A nephropathy. *Nephrol Dial Transplant. 35*(12);2130–7. doi:10.1093/ndt/gfz161

Parks, J. H., Worcester, E. M., O'Connor, R. C., Coe, F. L. (2003). Urine stone risk factors in nephrolithiasis patients with and without bowel disease. *Kidney Int. 63*(1);255–65. doi:10.1046/j.1523-1755.2003.00725.x

Pasternack, A., Mustonen, J., Leinikki, P. (1986). Humoral immune response in patients with IgA and IgM glomerulonephritis. *Clin Exp Immunol. 63*(1);228–33.

Pasternack, A., Collin, P., Mustonen, J., et al. (1990). Glomerular IgA deposits in patients with celiac disease. *Clin Nephrol. 34*(2);56–60.

Pasternak, B. A., D'Mello, S., Jurickova, I. I., et al. (2010). Lipopolysaccharide exposure is linked to activation of the acute phase response and growth failure in pediatric Crohn's disease and murine colitis: *Inflamm Bowel Dis. 16*(5);856–69. doi:10.1002/ibd.21132

Peeters, A. J., Van Den Wall Bake, A. W. L., Daha, M. R., Breedveld, F. C. (1990). Inflammatory bowel disease and ankylosing spondylitis associated with cutaneous vasculitis, glomerulonephritis, and circulating IgA immune complexes. *Ann Rheum Dis. 49*(8);638–40. doi:10.1136/ard.49.8.638

Peters, B., Nasic, S., Segelmark, M. (2020). Clinical parameters predicting complications in native kidney biopsies. *Clin Kidney J. 13*(4);654–9. doi:10.1093/ckj/sfz132

Petrou, D., Kalogeropoulos, P., Liapis, G., Lionaki, S. (2023). IgA Nephropathy: Current Treatment and New Insights. *Antibodies. 12*(2);40. doi:10.3390/antib12020040

Pettersson, E., von Bonsdorff, M., Törnroth, T., Lindholm, H. (1984). Nephritis among young Finnish men. *Clin Nephrol. 22*(5);217–22.

Peyrin-Biroulet, L., Loftus, E. V., Colombel, J.-F., Sandborn, W. J. (2010). The Natural History of Adult Crohn's Disease in Population-Based Cohorts. *Am J Gastroenterol. 105*(2);289–97. doi:10.1038/ajg.2009.579

Pierucci, A., Fofi, C., Bartoli, B., et al. (2002). Antiendomysial antibodies in Berger's disease. *Am J Kidney Dis. 39*(6);1176–82. doi:10.1053/ajkd.2002.33387

Pillebout, E. (2021). IgA Vasculitis and IgA Nephropathy: Same Disease? *J Clin Med. 10*(11);2310. doi:10.3390/jcm10112310

Piovani, D., Danese, S., Peyrin-Biroulet, L., Nikolopoulos, G. K., Lytras, T., Bonovas, S. (2019). Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. *Gastroenterology. 157*(3);647-59. doi:10.1053/j.gastro.2019.04.016

Pippias, M., Stel, V. S., Aresté-Fosalba, N., et al. (2016). Long-term Kidney Transplant Outcomes in Primary Glomerulonephritis: Analysis From the ERA-EDTA Registry. *Transplantation. 100*(9);1955–62. doi:10.1097/TP.0000000000000962

Pomerleau, C. S., Carton, S. M., Lutzke, M. L., Flessland, K. A., Pomerleau, O. F. (1994). Reliability of the fagerstrom tolerance questionnaire and the fagerstrom test for nicotine dependence. *Addict Behav. 19*(1);33–9. doi:10.1016/0306-4603(94)90049-3

Ponticelli, C., Traversi, L., Feliciani, A., Cesana, B. M., Banfi, G., Tarantino, A. (2001). Kidney transplantation in patients with IgA mesangial glomerulonephritis. *Kidney Int. 60*(5);1948–54. doi:10.1046/j.1523-1755.2001.00006.x

Ponticelli, C., Colombo, D., Novara, M., Basilisco, G. (2010). Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are under-recognized by physicians. *Transpl Int. 23*(11);1126–34. doi:10.1111/j.1432-2277.2010.01115.x

Poulou, A. C., Goumas, K. E., Dandakis, D. C., et al. (2006). Microproteinuria in patients with inflammatory bowel disease: Is it associated with the disease activity or the treatment with 5-aminosalicylic acid? *World J Gastroenterol. 12*(5);739–46. doi:10.3748/wjg.v12.i5.739

Pouria, S., Barratt, J. (2008). Secondary IgA Nephropathy. *Semin Nephrol. 28*(1);27–37. doi:10.1016/j.semnephrol.2007.10.004

Pozzi, C., Bolasco, P. G., Fogazzi, G., et al. (1999). Corticosteroids in IgA nephropathy: A randomised controlled trial. *Lancet. 353*(9156);883–7. doi:10.1016/S0140-6736(98)03563-6

Praga, M., Gutiérrez, E., González, E., Morales, E., Hernandez, E. (2003). Treatment of IgA nephropathy with ace inhibitors: A randomized and controlled trial. *J Am Soc Nephrol. 14*(6);1578–83. doi:10.1097/01.ASN.0000068460.37369.DC

Qin, W., Zhou, Q., Yang, L. C., et al. (2005). Peripheral B lymphocyte β1,3-galactosyltransferase and chaperone expression in immunoglobulin A nephropathy. *J Int Med. 258*(5);467–77. doi:10.1111/j.1365-2796.2005.01558.x

Qin, W., Zhong, X., Fan, J. M., Zhang, Y. J., Liu, X. R., Ma, X. Y. (2008). External suppression causes the low expression of the Cosmc gene in IgA nephropathy. *Nephrol Dial Transplant. 23*(5);1608–14. doi:10.1093/ndt/gfm781

Radford, M. G., Donadio, J. V., Bergstralh, E. J., Grande, J. P. (1997). Predicting Renal Outcome in IgA Nephropathy. *J Am Soc Nephrol. 8*(2);199–207. doi:10.1681/asn.v82199

Raetz, C. R. H., Whitfield, C. (2002). Lipopolysaccharide Endotoxins. *Annu Rev Biochem. 71*(1);635–700. doi:10.1146/annurev.biochem.71.110601.135414

Ramezani, A., Raj, D. S. (2014). The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol. 25*(4);657–70. doi:10.1681/ASN.2013080905

Ransford, R. A. J., Langman, M. J. S. (2002). Sulphasalazine and mesalazine: Serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut. 51*(4);536–9. doi:10.1136/gut.51.4.536

Rantala, I., Collin, P., Holm, K., Kainulainen, H., Mustonen, J., Mäki, M. (1999). Small bowel T cells, HLA class II antigen DR, and GroEL stress protein in IgA nephropathy. *Kidney Int. 55*(6);2274–80. doi:10.1046/j.1523-1755.1999.00471.x

Rauen, T., Eitner, F., Fitzner, C., et al. (2015). Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med. 373*(23);2225–36. doi:10.1056/nejmoa1415463

Rauen, T., Wied, S., Fitzner, C., et al. (2020). After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. *Kidney Int. 98:*1044–52. doi:10.1016/j.kint.2020.04.046

Rehnberg, J., Symreng, A., Ludvigsson, J. F., Emilsson, L. (2021). Inflammatory Bowel Disease Is More Common in Patients with IgA Nephropathy and Predicts Progression of ESKD: A Swedish Population-Based Cohort Study. *J Am Soc Nephrol. 32*(2);411–23. doi:10.1681/ASN.2020060848

Reich, H. N., Troyanov, S., Scholey, J. W., Cattran, D. C. (2007). Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol. 18*(12);3177–83. doi:10.1681/ASN.2007050526

Repo, M., Lindfors, K., Mäki, M., et al. (2017). Anemia and Iron Deficiency in Children With Potential Celiac Disease. *J Pediatr Gastroenterol Nutr. 64*(1);56–62. doi:10.1097/MPG.0000000000001234

Reunala, T., Helin, H., Pasternack, A., Linder, E., Kalimo, K. (1983). Renal involvement and circulating immune complexes in dermatitis herpetiformis. *J Am Acad Dermatol. 9*(2);219–23. doi:10.1016/S0190-9622(83)70132-5

Reunala, T., Hervonen, K., Salmi, T. (2021). Dermatitis Herpetiformis: An Update on Diagnosis and Management. *Am J Clin Dermatol. 22*(3);329–38. doi:10.1007/s40257-020-00584-2

Rizk, D. V., Maillard, N., Julian, B. A., et al. (2019). The emerging role of complement proteins as a target for therapy of IgA nephropathy. *Front Immunol. 10*;1–14. doi:10.3389/fimmu.2019.00504

Rizk, D. V., Saha, M. K., Hall, S., et al. (2019). Glomerular immunodeposits of patients with IgA nephropathy are enriched for IgG autoantibodies specific for galactose-deficient IgA1. *J Am Soc Nephrol. 30*(10);2017–26. doi:10.1681/ASN.2018111156

Roberts, I. S. D., Cook, H. T., Troyanov, S., et al. (2009). The Oxford classification of IgA nephropathy: Pathology definitions, correlations, and reproducibility. *Kidney Int. 76*(5);546–56. doi:10.1038/ki.2009.168

Roberts, I. S. D. (2014). Pathology of IgA nephropathy. *Nat Rev Nephrol. 10*(8);445–54. doi:10.1038/nrneph.2014.92

Rodrigues, J. C., Haas, M., Reich, H. N. (2017). IgA nephropathy. *Clin J Am Soc Nephrol. 12*(4);677–86. doi:10.2215/CJN.07420716

Rogler, G., Singh, A., Kavanaugh, A., Rubin, D. T. (2021). Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology*. *161*(4);1118–32. doi:10.1053/j.gastro.2021.07.042

Rojo, Ó. P., Román, A. L. S., Arbizu, E. A., De La Hera Martínez, A., Sevillano, E. R., Martínez, A. A. (2007). Serum lipopolysaccharide-binding protein in endotoxemic patients with inflammatory bowel disease: *Inflamm Bowel Dis. 13*(3);269–77. doi:10.1002/ibd.20019

Roos, A., Rastaldi, M. P., Calvaresi, N., et al. (2006). Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephol. 17*(6);1724–34. doi:10.1681/ASN.2005090923

Røseth, A.G., Schmidt, P. N., Fagerhol, M. K. (1999). Correlation between Faecal Excretion of Indium-111-Labelled Granulocytes and Calprotectin, a Granulocyte Marker Protein, in Patients with Inflammatory Bowel Disease. *Scand J Gastroenterol. 34*(1);50–4. doi:10.1080/00365529950172835

Rostoker, G., André, C., Branellec, A., Bourhala, S., Laurent, J., Lagrue, G. (1988). Lack of antireticulin and IgA antiendomysium antibodies in sera of patients with primary IgA nephropathy associated with circulating IgA antibodies to gliadin. *Nephron. 48*(1);81. doi:10.1159/000184877

Rostoker, G., Wirquin, V., Terzidis, H., et al. (1993). Mucosal Immunity in Primary Glomerulonephritis. *Nephron. 63*(3);286–90. doi:10.1159/000187211

Rostoker, G., Delchier, J. C., Chaumette, M. T. (2001). Increased intestinal intra-epithelial T lymphocytes in primary glomerulonephritis. A role of oral tolerance breakdown in the pathophysiology of human primary glomerulonephritides? *Nephrol Dial Transplant. 16*(3);513–7. doi:10.1093/ndt/16.3.513

Rothfuss, K. S., Stange, E. F., Herrlinger, K. R. (2006). Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol. 12*(30);4819–31. doi:10.3748/wjg.v12.i30.4819

Rovin, B. H., Adler, S. G., Barratt, J., et al. (2021). Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int. 100*(4);753–79. doi:10.1016/j.kint.2021.05.015

Rubin, D. T., Ananthakrishnan, A. N., Siegel, C. A., Sauer, B. G., Long, M. D. (2019). ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol. 114*(3);384–413. doi:10.14309/ajg.0000000000000152

Rudnicki, M., Siwy, J., Wendt, R., et al. (2021). Urine proteomics for prediction of disease progression in patients with IgA nephropathy. *Nephrol Dial Transplant. 37*(1);42–52. doi:10.1093/ndt/gfaa307

Saha, M. K., Julian, B. A., Novak, J., Rizk, D. V. (2018). Secondary IgA nephropathy. *Kidney Int. 94*(4);674–81. doi:10.1016/j.kint.2018.02.030

Sallustio, F., Curci, C., Chaoul, N., et al. (2020). High levels of gut-homing immunoglobulin A–positive+B lymphocytes support the pathogenic role of intestinal mucosal hyperresponsiveness in immunoglobulin A nephropathy patients. *Nephrol Dial Transplant.* 36;452–64. doi:10.1093/ndt/gfaa264

Salmi, T. T., Hervonen, K., Kautiainen, H., Collin, P., Reunala, T. (2011). Prevalence and incidence of dermatitis herpetiformis: A 40-year prospective study from Finland: Dermatitis herpetiformis prevalence and incidence. *Br J Dermatol. 165*(2);354–9. doi:10.1111/j.1365-2133.2011.10385.x

Sanchez-Russo, L., Rajasekaran, A., Bin, S., Faith, J., Cravedi, P. (2022). The Gut and Kidney Crosstalk in Immunoglobulin A Nephropathy. *Kidney360. 3*(9);1630–9. doi:10.34067/KID.0002382022

Sandborn, W. J. (2008). Current Directions in IBD Therapy: What Goals Are Feasible With Biological Modifiers? *Gastroenterology. 135*(5);1442–7. doi:10.1053/j.gastro.2008.09.053

Sandborn, W. J., Feagan, B. G., D'Haens, G., et al. (2021). Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med. 385*(14);1280–91. doi:10.1056/NEJMoa2033617

Sategna-Guidetti, C., Ferfoglia, G., Bruno, M., et al. (1992). Do IgA antigliadin and IgA antiendomysium antibodies show there is latent coeliac disease in primary IgA nephropathy? *Gut. 33*(4);476–8. doi:10.1136/gut.33.4.476

Satsangi, J. (2006). The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. *Gut. 55*(6);749–53. doi:10.1136/gut.2005.082909

Schena, F. P., Cerullo, G., Rossini, M., Lanzilotta, S. G., D'Altri, C., Manno, C. (2002). Increased Risk of End-Stage Renal Disease in Familial IgA Nephropathy. *J Am Soc Nephrol. 13*(2);453–60. doi:10.1681/ASN.V132453

Schreiber, S., Hamling, J., Zehnter, E., et al. (1997). Renal tubular dysfunction in patients with inflammatory bowel disease treated with aminosalicylate. *Gut*, *40*(6);761–6. doi:10.1136/gut.40.6.761

Segarra, A., Romero, K., Agraz, I., et al. (2018). Mesangial C4d Deposits in Early IgA Nephropathy. *Clin J Am Soc Nephrol. 13*(2);258–64. doi:10.2215/CJN.02530317

Seikrit, C., Schimpf, J. I., Wied, S., et al. (2023). Intestinal permeability in patients with IgA nephropathy and other glomerular diseases: An observational study. *J Nephrol. 36*(2);463–74. doi:10.1007/s40620-022-01454-2

Shaer, A. J., Stewart, L. R., Cheek, D. E., Hurray, D., Self, S. E. (2003). IgA antiglomerular basement membrane nephritis associated with Crohn's disease: A case report and review of glomerulonephritis in inflammatory bowel disease. *Am J Kidney Dis. 41*(5);1097–109. doi:10.1016/S0272-6386(03)00208-7

Shehata, M., Bhandari, S., Venkat-Raman, G., et al. (2009). Effect of conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium on maximum tolerated dose and gastrointestinal symptoms following kidney transplantation. *Transpl Int. 22*(8);821–30. doi:10.1111/j.1432-2277.2009.00877.x

Shi, D., Zhong, Z., Wang, M., et al. (2020). Identification of susceptibility locus shared by IgA nephropathy and inflammatory bowel disease in a Chinese Han population. *J Hum Genet. 65*(3);241–9. doi:10.1038/s10038-019-0699-9

Shirazian, S., Radhakrishnan, J. (2010). Gastrointestinal disorders and renal failure: Exploring the connection. *Nat Rev Nephrol. 6*(8);480–92. doi:10.1038/nrneph.2010.84

Shivananda, S., Lennard-Jones, J., Logan, R., et al. (1996). Incidence of inflammatory bowel disease across Europe: Is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut. 39*(5);690–7. doi:10.1136/gut.39.5.690

Smerud, H. K., Fellstrom, B., Hallgren, R., Osagie, S., Venge, P., Kristjansson, G. (2009). Gluten sensitivity in patients with IgA nephropathy. *Nephrol Dial Transplant. 24*(8);2476–81. doi:10.1093/ndt/gfp133

Smerud, H. K., Barany, P., Lindstrom, K., et al. (2011). New treatment for IgA nephropathy: Enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant. 26*(10);3237–42. doi:10.1093/ndt/gfr052

Smith, A. C., Molyneux, K., Feehally, J., Barratt, J. (2006). O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. *J Am Soc Nephrol. 17*(12);3520–8. doi:10.1681/ASN.2006060658

Solberg, I. C., Lygren, I., Jahnsen, J., et al and the IBSEN Study Group. (2009). Clinical course during the first 10 years of ulcerative colitis: Results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol. 44*(4);431–40. doi:10.1080/00365520802600961

Strid, H., Simrén, M., Johansson, A. C., Svedlund, J., Samuelsson, O., Björnsson, E. S. (2002). The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being. *Nephrol Dial Transplant. 17*(8);1434–9. doi:10.1093/ndt/17.8.1434

Sumida, K., Yamagata, K., Kovesdy, C. P. (2020). Constipation in CKD. *Kidney Int Rep. 5*(2);121–34. doi:10.1016/j.ekir.2019.11.002

Suzuki, H., Moldoveanu, Z., Hall, S., et al. (2008). IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. *J Clin Investig. 118*(2);629–39. doi:10.1172/JCI33189

Suzuki, H., Fan, R., Zhang, Z., et al. (2009). Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. *J Clin Invest. 119*(6);1668–77. doi:10.1172/JCI38468

Suzuki, H., Kiryluk, K., Novak, J., et al. (2011). The pathophysiology of IgA nephropathy. *J Am Soc Nephrol. 22*(10);1795–803. doi:10.1681/ASN.2011050464

Suzuki, H., Raska, M., Yamada, K., et al. (2014). Cytokines Alter IgA1 O-Glycosylation by Dysregulating C1GalT1 and ST6GalNAc-II Enzymes. *J Biol Chem. 289*(8);5330–9. doi:10.1074/jbc.M113.512277

Suzuki, H., Allegri, L., Suzuki, Y., et al. (2016). Galactose-Deficient IgA1 as a Candidate Urinary Polypeptide Marker of IgA Nephropathy? *Dis Markers*. doi:10.1155/2016/7806438

Suzuki, H., Yasutake, J., Makita, Y., et al. (2018). IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis. *Kidney Int. 93*(3);700–5. doi:10.1016/j.kint.2017.10.019

Suzuki, H. (2019). Biomarkers for IgA nephropathy on the basis of multi-hit pathogenesis. *Clin Exp Nephrol. 23*(1);26–31. doi:10.1007/s10157-018-1582-2

Suzuki, K., Honda, K., Tanabe, K., Toma, H., Nihei, H., Yamaguchi, Y. (2003). Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int. 63*(6);2286–94. doi:10.1046/j.1523-1755.63.6s.2.x

Suzuki, Y., Monteiro, R. C., Coppo, R., Suzuki, H. (2021). The Phenotypic Difference of IgA Nephropathy and its Race/Gender-dependent Molecular Mechanisms. *Kidney360. 2*(8);1339–48. doi:10.34067/KID.0002972021

Svedlund, J., Sjödin, I., Dotevall, G. (1988). GSRS-A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci. 33*(2);129–34. doi:10.1007/BF01535722

Syrjänen, J., Mustonen, J., Pasternack, A. (2000). Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrol Dial Transplant. 15*(1);34–42. doi:10.1093/ndt/15.1.34

Szeto, C. C., Lai, F. M. M., To, K. F., et al. (2001). The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. *Am J Med. 110*(6);434–7. doi:10.1016/S0002-9343(01)00659-3

Tan, J., Dong, L., Jiang, Z., et al. (2022). Probiotics ameliorate IgA nephropathy by improving gut dysbiosis and blunting NLRP3 signaling. *J Transl Med. 20*(1);382. doi:10.1186/s12967-022-03585-3

Tang, X., Zheng, J., Jiang, X., et al. (2023). The significance of galactose-deficient immunoglobulin A1 staining in kidney diseases with IgA deposition. *Int Urol Nephrol. 55*(8);2119–29. doi:10.1007/s11255-023-03512-5

Thomas, D. M., Nicholls, A. J., Feest, T. G. (1990). Ulcerative Colitis and Glomerulonephritis: Is There an Association? *Nephrol Dial Transplant. 5*(8);628–9. doi:10.1093/ndt/5.8.628

Thompson, A., Carroll, K., Inker, L. A., et al. (2019). Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol. 14*(3);469–81. doi:10.2215/CJN.08600718

Tissandié, E., Morelle, W., Berthelot, L., et al. (2011). Both IgA nephropathy and alcoholic cirrhosis feature abnormally glycosylated IgA1 and soluble CD89-IgA and IgG-IgA complexes: Common mechanisms for distinct diseases. *Kidney Int. 80*(12);1352–63. doi:10.1038/ki.2011.276

Tokuyama, H., Wakino, S., Konishi, K., Hashiguchi, A., Hayashi, K., Itoh, H. (2010). Acute interstitial nephritis associated with ulcerative colitis. *Clin Exp Nephrol. 14*(5);483–6. doi:10.1007/s10157-010-0294-z

Tomana, M., Matousovic, K., Julian, B. A., Radl, J., Konecny, K., Mestecky, J. (1997). Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. *Kidney Int. 52*(2);509–16. doi:10.1038/ki.1997.361

Tomana, M., Novak, J., Julian, B. A., Matousovic, K., Konecny, K., Mestecky, J. (1999). Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Investig. 104*(1);73–81. doi:10.1172/JCI5535

Tortajada, A., Gutierrez, E., Pickering, M. C., Praga Terente, M., Medjeral-Thomas, N. (2019). The role of complement in IgA nephropathy. *Mol Immunol. 114*;123–32. doi:10.1016/j.molimm.2019.07.017

Tota, M., Baron, V., Musial, K., et al. (2023). Secondary IgA Nephropathy and IgA-Associated Nephropathy: A Systematic Review of Case Reports. *J Clin Med. 12*(7);2726. doi:10.3390/jcm12072726

Trimarchi, H., Barratt, J., Cattran, D. C., et al. (2017). Oxford Classification of IgA nephropathy 2016: An update from the IgA Nephropathy Classification Working Group. *Kidney Int. 91*(5);1014–21. doi:10.1016/j.kint.2017.02.003

Trimarchi, H., Coppo, R. (2019). Podocytopathy in the mesangial proliferative immunoglobulin A nephropathy: New insights into the mechanisms of damage and progression. *Nephrol Dial Transplant. 34*(8);1280–5. doi:10.1093/ndt/gfy413

Turner, D., Ricciuto, A., Lewis, A., et al. (2021). STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology*. 160:1570-83. doi:10.1053/j.gastro.2020.12.031

Tye-Din, J. A. (2022). Review article: Follow-up of coeliac disease. *Aliment Pharmacol Ther. 56*(S1). doi:10.1111/apt.16847

Vajravelu, R. K., Copelovitch, L., Osterman, M. T., et al. (2020). Inflammatory Bowel Diseases Are Associated With an Increased Risk for Chronic Kidney Disease, Which Decreases With Age. *Clin Gastroenterol Hepatol. 18*(10);2262–8. doi:10.1016/j.cgh.2019.10.043

Van Hoeve, K., Hoffman, I. (2022). Renal manifestations in inflammatory bowel disease: A systematic review. *J Gastroenterol. 57*(9);619–29. doi:10.1007/s00535-022-01903-6

Van Kruiningen, H. J., West, A. B., Freda, B. J., Holmes, K. A. (2002). Distribution of Peyer's Patches in the Distal Ileum: *Inflamm Bowel Dis. 8*(3);180–5. doi:10.1097/00054725-200205000-00004

Van Staa, T. P., Travis, S., Leufkens, H. G. M., Logan, R. F. (2004). 5-Aminosalicylic acids and the risk of renal disease: A large British epidemiologic study. *Gastroenterology. 126*(7);1733–9. doi:10.1053/j.gastro.2004.03.016

Van Wijck, K., Verlinden, T. J. M., Van Eijk, H. M. H., et al. (2013). Novel multi-sugar assay for site-specific gastrointestinal permeability analysis: A randomized controlled crossover trial. *Clin Nutr. 32*(2);245–51. doi:10.1016/j.clnu.2012.06.014

Varis, J., Rantala, I., Pasternack, A., et al. (1993). Immunoglobulin and complement deposition in glomeruli of 756 subjects who had committed suicide or met with a violent death. *J Clin Pathol. 46*(7);607–10. doi:10.1136/jcp.46.7.607

Vavricka, S. R., Rogler, G., Gantenbein, C., et al. (2015). Chronological Order of Appearance of Extraintestinal Manifestations Relative to the Time of IBD Diagnosis in the Swiss Inflammatory Bowel Disease Cohort. *Inflamm Bowel Dis. 21*(8);1794–800. doi:10.1097/MIB.0000000000000429

Vaziri, N. D., Goshtasbi, N., Yuan, J., et al. (2012a). Uremic Plasma Impairs Barrier Function and Depletes the Tight Junction Protein Constituents of Intestinal Epithelium. *Am J Nephrol. 36*(5);438–43. doi:10.1159/000343886

Vaziri, N. D., Yuan, J., Rahimi, A., Ni, Z., Said, H., Subramanian, V. S. (2012b). Disintegration of colonic epithelial tight junction in uremia: A likely cause of CKD-associated inflammation. *Nephrol Dial Transplant. 27*(7);2686–93. doi:10.1093/ndt/gfr624

Vaziri, N. D., Wong, J., Pahl, M., et al. (2013a). Chronic kidney disease alters intestinal microbial flora. *Kidney Int. 83*(2);308–15. doi:10.1038/ki.2012.345

Vaziri, N. D., Yuan, J., Nazertehrani, S., Ni, Z., Liu, S. (2013b). Chronic kidney disease causes disruption of gastric and small intestinal epithelial tight junction. *Am J Nephrol. 38*(2);99–103. doi:10.1159/000353764

Vaziri, N. D., Zhao, Y. Y., Pahl, M. V. (2016). Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: The nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant. 31*(5);737–46. doi:10.1093/ndt/gfv095

Vegh, Z., Vegh, Z., Macsai, E., Lakatos, L. (2017). The incidence of glomerulonephritis in a population-based inception cohort of patients with inflammatory bowel disease. *Di Liver Dis. 49*(6);718–19. doi:10.1016/j.dld.2017.03.029

Viljamaa, M., Collin, P., Huhtala, H., Sievänen, H., Mäki, M., Kaukinen, K. (2005). Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Aliment Pharmacol Therap. 22*(4);317–24. doi:10.1111/j.1365-2036.2005.02574.x

Vilppula, A., Kaukinen, K., Luostarinen, L., et al. (2009). Increasing prevalence and high incidence of celiac disease in elderly people: A population-based study. *BMC Gastroenterol. 9*(1);49. doi:10.1186/1471-230X-9-49

Virta, L. J., Kaukinen, K., Collin, P. (2009). Incidence and prevalence of diagnosed coeliac disease in Finland: Results of effective case finding in adults. *Scand J Gastroenterol. 44*(8);933–8. doi:10.1080/00365520903030795

Vreugdenhil, A. C., Wolters, V. M., Adriaanse, M. P., et al. (2011). Additional value of serum I-FABP levels for evaluating celiac disease activity in children. *Scand J Gastroenterol. 46*(12);1435–41. doi:10.3109/00365521.2011.627447

Wang, A. Y. M., Lai, F. M. M., Yu, A. W. Y., et al. (2001). Recurrent IgA nephropathy in renal transplant allografts. *Am J Kidney Dis. 38*(3);588–96. doi:10.1053/ajkd.2001.26885

Wang, F., Jiang, H., Shi, K., Ren, Y., Zhang, P., Cheng, S. (2012). Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients: Bacterial translocation in ESRD. *Nephrology. 17*(8);733–8. doi:10.1111/j.1440-1797.2012.01647.x

Wang, F., Li, N., Ni, S., et al. (2023). The Effects of Specific Gut Microbiota and Metabolites on IgA Nephropathy—Based on Mendelian Randomization and Clinical Validation. *Nutrients. 15*(10);2407. doi:10.3390/nu15102407

Wang, J., Anders, R. A., Wu, Q., et al. (2004). Dysregulated LIGHT expression on T cells mediates intestinal inflammation and contributes to IgA nephropathy. *J Clin Investig. 113*(6);826–35. doi:10.1172/JCI20096

Wang, M., Lv, J., Zhang, X., Chen, P., Zhao, M., Zhang, H. (2020). Secondary IgA Nephropathy Shares the Same Immune Features With Primary IgA Nephropathy. *Kidney Int Rep. 5*(2);165–72. doi:10.1016/j.ekir.2019.10.012

Webster, A. C., Nagler, E. V., Morton, R. L., Masson, P. (2017). Chronic Kidney Disease. *Lancet. 389*(10075);1238–52. doi:10.1016/S0140-6736(16)32064-5

Welander, A., Sundelin, B., Fored, M., Ludvigsson, J. F. (2013). Increased risk of IgA nephropathy among individuals with celiac disease. *J Clin Gastroenterol. 47*(8);678–83. doi:10.1097/MCG.0b013e318284792e

Wheeler, D. C., Toto, R. D., Stefánsson, B. V., et al. (2021). A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int. 100*(1);215–24. doi:10.1016/j.kint.2021.03.033

Wijarnpreecha, K., Thongprayoon, C., Panjawatanan, P., et al. (2016). Celiac disease and the risk of kidney diseases: A systematic review and meta-analysis. *Dig Liver Dis. 48*(12);1418–24. doi:10.1016/j.dld.2016.08.115

Wilks, S., Moxon, W. (1875). Lectures on Pathological Anatomy. 2nd Ed. Philadelphia Lindsay and Blakiston.

Wirta, O., Mustonen, J., Helin, H., Pasternack, A. (2008). Incidence of biopsy-proven glomerulonephritis. *Nephrol Dial Transplant. 23*(1);193–200. doi:10.1093/ndt/gfm564

Woof, J. M., Ken, M. A. (2006). The function of immunoglobulin A in immunity. *J Pathol. 208*(2);270–82. doi:10.1002/path.1877

Wyatt, R. J., Julian, B. A. (2013). Medical progress: IgA nephropathy. *N Engl J Med. 368*(25);2402–14. doi:10.1056/NEJMra1206793

Xavier, R., Podolsky, D. K. (2005). Commensal flora: Wolf in sheep's clothing. *Gastroenterology. 128*(4);1122–6. doi:10.1053/j.gastro.2005.02.053

Xavier, R. J., Podolsky, D. K. (2007). Unravelling the pathogenesis of inflammatory bowel disease. *Nature. 448*(7152);427–34. doi:10.1038/nature06005

Xiao, M., Ran, Y., Shao, J., Lei, Z., Chen, Y., Li, Y. (2022). Causal association between inflammatory bowel disease and IgA nephropathy: A bidirectional two-sample Mendelian randomization study. *Front Genet. 13*;1002928. doi:10.3389/fgene.2022.1002928

Yamada, K., Huang, Z.-Q., Raska, M., et al. (2017). Inhibition of STAT3 Signaling Reduces IgA1 Autoantigen Production in IgA Nephropathy. *Kidney Int Rep. 2*(6);1194–207. doi:10.1016/j.ekir.2017.07.002

Yanagawa, H., Suzuki, H., Suzuki, Y., et al. (2014). A Panel of Serum Biomarkers Differentiates IgA Nephropathy from Other Renal Diseases. *PLoS One. 9*(5);e98081. doi:10.1371/journal.pone.0098081

Yang, Y., Ludvigsson, J. F., Olén, O., Sjölander, A., Carrero, J. J. (2023). Estimated Glomerular Filtration Rate and the Risk of Inflammatory Bowel Disease in Adults: A Swedish Population-Based Study. *Inflamm Bowel Dis.* doi:10.1093/ibd/izac267

Yasuda, G., Shibata, K., Takizawa, T., et al. (2002). Prevalence of constipation in continuous ambulatory peritoneal dialysis patients and comparison with hemodialysis patients. *Am J Kidney Dis. 39*(6);1292–9. doi:10.1053/ajkd.2002.33407

Yi, C., Wang, X., Ye, H., Lin, J., Yang, X. (2022). Patient-reported gastrointestinal symptoms in patients with peritoneal dialysis: The prevalence, influence factors and association with quality of life. *BMC Nephrol. 23*(1). doi:10.1186/s12882-022-02723-9

Yoon, H. J. (2003). Association of the CD14 gene -159C polymorphism with progression of IgA nephropathy. *J Med Genet. 40*(2);104–8. 10.1136/jmg.40.2.104

Yu, G. zhen., Guo, L., Dong, J. feng, et al. (2020). Persistent Hematuria and Kidney Disease Progression in IgA Nephropathy: A Cohort Study. *Am J Kidney Dis. 76*(1);90–9. doi:10.1053/j.ajkd.2019.11.008

Yu, X. Q., Li, M., Zhang, H., et al. (2012). A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. *Nat Genet. 44*(2);178–82. doi:10.1038/ng.1047

Zhai, Y. L., Zhu, L., Shi, S. F., Liu, L. J., Lv, J. C., Zhang, H. (2016). Increased April expression induces IgA1 aberrant glycosylation in IgA nephropathy. *Medicine. 95*(11);1–7. doi:10.1097/MD.0000000000003099

Zhang, J., Xu, L., Liu, G., Zhao, M., Wang, H. (2007). The level of serum secretory IgA of patients with IgA nephropathy is elevated and associated with pathological phenotypes. *Nephrol Dial Transplant. 23*(1);207–12. doi:10.1093/ndt/gfm492

Zhang, J., Huang, B., Liu, Z., et al. (2020). External Validation of the International IgA Nephropathy Prediction Tool. *Clin J Am Soc Nephrol. 15*(8);1112–20. doi:10.2215/CJN.16021219

Zhang, W., Lachmann, P. J. (1994). Glycosylation of IgA is required for optimal activation of the alternative complement pathway by immune complexes. *Immunology. 81*(1);137–41.

Zhang, X., Bansal, N., Go, A. S., Hsu, C. Y. (2015). Gastrointestinal symptoms, inflammation and hypoalbuminemia in chronic kidney disease patients: A cross-sectional study. *BMC Nephrol. 16*(1);1–8. doi:10.1186/s12882-015-0209-z

Zhao, N., Hou, P., Lv, J., et al. (2012). The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. *Kidney Int. 82*(7);790–6. doi:10.1038/ki.2012.197

Zhernakova, A., Van Diemen, C. C., Wijmenga, C. (2009). Detecting shared pathogenesis from the shared genetics of immune-related diseases. *Nat Rev Genet. 10*(1);43–55. doi:10.1038/nrg2489

Zhong, Z. X., Tan, J. X., Tan, L., et al. (2020). Modifications of gut microbiota are associated with the severity of IgA nephropathy in the Chinese population. *Int Immunopharmacol.* doi:10.1016/j.intimp.2020.107085

Zhou, Y. H., Tang, L. G., Guo, S. L., et al. (2011). Steroids in the treatment of iga nephropathy to the improvement of renal survival: A systematic review and meta-analysis. *PLoS One. 6*(4). doi:10.1371/journal.pone.0018788

Zhu, L., Zhai, Y. L., Wang, F. M., et al. (2015). Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA nephropathy. *J Am Soc Nephrol. 26*(5);1195–204. doi:10.1681/ASN.2014010096

Zimmermann, J., Herrlinger, S., Pruy, A., Metzger, T., Wanner, C. (1999). Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int. 55*(2);648–58. doi:10.1046/j.1523-1755.1999.00273.x

Zuvela, J., Trimingham, C., Le Leu, R., et al. (2018). Gastrointestinal symptoms in patients receiving dialysis: A systematic review. *Nephrology*. *23*(8);718–27. doi:10.1111/nep.13243

# APPENDIX 1: GSRS QUESTIONNAIRE

R_____

THE GASTROINTESTINAL SYMPTOM RATING SCALE

(GSRS)

Lue tämä ensin:

Tutkimus sisältää kysymyksiä voinnistasi ja tilastasi kuluneen viikon aikana. Merkitse rastilla (X) se vaihtoehto, joka sopii parhaiten sinuun ja tilaasi.

1. Onko Sinulla ollut VATSAKIPUJA kuluneen viikon aikana? (Vatsakivuilla tarkoitetaan kaikenlaista kipua tai särkyä vatsassa.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

2. Onko Sinulla ollut NÄRÄSTYSTÄ kuluneen viikon aikana? (Närästyksellä tarkoitetaan kirvelevää tai polttavaa pahanolontunnetta rintalastan takana.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

3. Onko Sinulla ollut HAPPAMIA RÖYHTÄISYJÄ kuluneen viikon aikana? (Happamilla röyhtäisyillä tarkoitetaan äkillisiä, hapanta vatsanestettä sisältäviä röyhtäisyjä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

4. Onko Sinua HIUKAISSUT kuluneen viikon aikana? (Hiukaisulla tarkoitetaan vatsassa olevaa hiukovaa tunnetta, johon liittyy tarve syödä aterioiden välillä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

5. Onko Sinulla ollut PAHOINVOINTIA kuluneen viikon aikana? (Pahoinvoinnilla tarkoitetaan pahanolontunnetta, joka saattaa muuttua kuvotukseksi tai oksentamiseksi.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

6. Onko vatsasi KURISSUT kuluneen viikon aikana? (Kurinalla tarkoitetaan vatsassa tuntuvaa värinää tai ”murinaa”.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

7. Onko vatsaasi TURVOTTANUT kuluneen viikon aikana? (Turvotuksella tarkoitetaan vatsassa tuntuvaa pingotusta, johon usein liittyy tuntemuksia ilmavaivoista.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

8. Onko Sinua vaivannut RÖYHTÄILY kuluneen viikon aikana? (Röyhtäilyllä tarkoitetaan tarvetta päästää ilmaa suun kautta, minkä yhteydessä vatsassa tuntuva pingotus usein helpottuu.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

9. Onko Sinulla ollut ILMAVAIVOJA kuluneen viikon aikana? (Ilmavaivoilla tarkoitetaan tässä tarvetta päästää ilmaa, jonka yhteydessä vatsassa tuntuva pingotus usein helpottuu.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

10. Onko Sinua vaivannut UMMETUS kuluneen viikon aikana? (Ummetuksella tarkoitetaan ulostuskertojen harventumista.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

11. Onko Sinua vaivannut RIPULI kuluneen viikon aikana? (Ripulilla tarkoitetaan ulostuskertojen lisääntymistä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

12. Onko Sinua vaivannut LÖYSÄ VATSA kuluneen viikon aikana? (Jos ulosteesi on välillä ollut kovaa ja välillä löysää, ilmoita vain, missä määrin ulosteesi löysyys on Sinua vaivannut.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

13. Onko Sinua vaivannut KOVA VATSA kuluneen viikon aikana? (Jos ulosteesi on välillä ollut kovaa ja välillä löysää, ilmoita vain, missä määrin ulosteesi kovuus on Sinua vaivannut.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

14. Onko Sinua vaivannut kuluneen viikon aikana PAKOTTAVA ULOSTAMISEN TARVE? (Pakottavalla ulostamisen tarpeella tarkoitetaan äkillistä tarvetta käydä WC:ssä. Siihen liittyy usein puutteellisen pidättämiskyvyn tunne.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

15. Onko Sinulla kuluneen viikon aikana ollut ULOSTAMISEN YHTEYDESSÄ TUNNE, ETTÄ SUOLI EI OLE TYHJENTYNYT KOKONAAN? (Tällä tarkoitetaan, että suoli ei ponnistuksista huolimatta tunnu tyhjentyneen kunnolla.)

☐ Ei minkäänlaisia vaivoja

☐ Vähäpätöisiä vaivoja

☐ Lieviä vaivoja

☐ Kohtalaisia vaivoja

☐ Melko pahoja vaivoja

☐ Pahoja vaivoja

☐ Erittäin pahoja vaivoja

16. ONKO SINULLA VIIMEISEN KUUKAUDEN AIKANA ESIINTYNYT SEURAAVIA OIREITA

(rengasta sopivat vaihtoehdot)

a. kielikipuja

b. haavaumia suussa

c. luustokipuja

d. puutumista

e. muuta, mitä _____

TARKISTAKAA, ETTÄ OLETTE VASTANNUT KAIKKIIN KYSYMYKSIIN.

KIITOS HYVÄSTÄ YHTEISTYÖSTÄ.

# APPENDIX 2: PGWB QUESTIONNAIRE

R_____

PGWB INDEX

Tutkimuksen tämä osa sisältää kysymyksiä siitä, miltä Teistä tuntuu ja kuinka Teillä on mennyt VIIMEKSI KULUNEEN VIIKON AIKANA. Jokaisen kysymyksen osalta rastittakaa (X) se vaihtoehto, joka parhaiten sopii Teidän kohdallenne.

1. Miltä Teistä on YLEISESTI ottaen TUNTUNUT viimeksi kuluneen viikon aikana?
   - ☐ Mielialani on ollut erinomainen
   - ☐ Mielialani on ollut oikein hyvä
   - ☐ Mielialani on ollut enimmäkseen hyvä
   - ☐ Mielialani on vaihdellut paljon
   - ☐ Mielialani on ollut enimmäkseen huono
   - ☐ Mielialani on ollut hyvin huono

2. Kuinka usein Teitä on VAIVANNUT JOKIN SAIRAUS, RUUMIILLINEN VAIVA, SÄRYT tai KIVUT viimeksi kuluneen viikon aikana?
   - ☐ Joka päivä
   - ☐ Melkein joka päivä
   - ☐ Noin puolet ajasta
   - ☐ Silloin tällöin, mutta vähemmän kuin puolet ajasta
   - ☐ Harvoin
   - ☐ Ei koskaan

3. Tunsitteko itsenne MASENTUNEEKSI viimeksi kuluneen viikon aikana?

   ☐ Kyllä – niin paljon, että minusta tuntui siltä, että ottaisin itseni hengiltä

   ☐ Kyllä – niin paljon, etten välittänyt mistään

   ☐ Kyllä – hyvin masentuneeksi melkein joka päivä

   ☐ Kyllä – melko masentuneeksi useita kertoja

   ☐ Kyllä – lievästi masentuneeksi silloin tällöin

   ☐ Ei – en ole kertaakaan tuntenut itseäni lainkaan masentuneeksi

4. Oletteko pystynyt HALLITSEMAAN KÄYTTÄYTYMISTÄNNE, AJATUKSIANNE, MIELIALOJANNE tai TUNTEITANNE viimeksi kuluneen viikon aikana?

   ☐ Kyllä, ehdottomasti

   ☐ Kyllä – useimmiten

   ☐ Yleensä

   ☐ En kovin hyvin

   ☐ En, ja se häiritsee minua jonkin verran

   ☐ En, ja se häiritsee minua kovasti

5. Onko Teitä vaivannut HERMOSTUNEISUUS tai LEVOTTOMUUS viimeksi kuluneen viikon aikana?

   ☐ Erittäin paljon, jopa niin, että en ole voinut tehdä työtä tai huolehtia asioista

   ☐ Hyvin paljon

   ☐ Melko paljon

   ☐ Jonkin verran, niin että se on vaivannut minua

   ☐ Vähän

   ☐ Ei lainkaan

6. Kuinka paljon TARMOA, PIRTEYTTÄ tai ELINVOIMAA Teillä on ollut viimeksi kuluneen viikon aikana?
   - ☐ Hyvin täynnä tarmoa – erittäin pirteä
   - ☐ Melko tarmokas suurimman osan ajasta
   - ☐ Tarmokkuuteni on vaihdellut melkoisesti
   - ☐ Yleensä vähän tarmoa tai pirteyttä
   - ☐ Hyvin vähän elinvoimaa tai tarmoa suurimman osan ajasta
   - ☐ Ei lainkaan tarmoa tai elinvoimaa – olen tuntenut itseni loppuun ajetuksi tai loppuun kuluneeksi

7. Olen tuntenut itseni ALAKULOISEKSI JA SYNKKÄMIELISEKSI viimeksi kuluneen viikon aikana?
   - ☐ En kertaakaan
   - ☐ Vähän tänä aikana
   - ☐ Jonkin verran tänä aikana
   - ☐ Melkoisen osan tästä ajasta
   - ☐ Suurimman osan tästä ajasta
   - ☐ Koko ajan

8. Oletteko yleisesti ollut KIREÄ tai tuntenut itsenne JÄNNITTYNEEKSI viimeksi kuluneen viikon aikana?
   - ☐ Kyllä, erittäin jännittyneeksi suurimman osan ajasta tai koko ajan
   - ☐ Kyllä, hyvin jännittyneeksi suurimman osan ajasta
   - ☐ En ole ollut koko ajan kireä, mutta olen tuntenut itseni melko jännittyneeksi useita kertoja
   - ☐ Olen tuntenut itseni vähän jännittyneeksi muutamia kertoja
   - ☐ En ole yleensä tuntenut itseäni jännittyneeksi
   - ☐ En ole lainkaan tuntenut itseäni jännittyneeksi

9. Kuinka ONNELLINEN, TYYTYVÄINEN tai MIELISSÄNNE olette ollut viimeksi kuluneen viikon aikana?

   ☐ Erittäin onnellinen, en olisi voinut olla tyytyväisempi tai enemmän mielissäni

   ☐ Hyvin onnellinen suurimman osan ajasta

   ☐ Yleensä tyytyväinen ja mielissäni

   ☐ Joskus melko onnellinen ja joskus melko onneton

   ☐ Yleensä tyytymätön ja onneton

   ☐ Hyvin tyytymätön tai onneton suurimman osan ajasta tai koko ajan

10. Oletteko tuntenut itsenne riittävän TERVEEKSI tekemään asioita, joita haluatte tehdä tai Teidän on ollut pakko tehdä viimeksi kuluneen viikon aikana?

    ☐ Kyllä, ehdottomasti

    ☐ Suurimman osan ajasta

    ☐ Terveysongelmat ovat merkittävästi rajoittaneet minua

    ☐ Olen ollut vain niin terve, että olen voinut huolehtia itsestäni

    ☐ Olen tarvinnut jonkin verran apua itseni huolehtimisessa

    ☐ Olen tarvinnut toista henkilöä auttamaan itseäni useimmissa tai kaikissa asioissa, joita minun on täytynyt tehdä

11. Oletteko tuntenut itsenne niin SURULLISEKSI, LANNISTUNEEKSI tai TOIVOTTOMAKSI, että olette miettinyt, onko millään mitään merkitystä viimeksi kuluneen viikon aikana?

    ☐ Erittäin paljon – niin paljon, että olen ollut valmis luovuttamaan

    ☐ Hyvin paljon

    ☐ Melko lailla

    ☐ Jonkin verran – sen verran, että se on vaivannut minua

    ☐ Vähän

    ☐ En lainkaan

12. Oletteko herännyt PIRTEÄNÄ ja LEVÄNNEENÄ viimeksi kuluneen viikon aikana?

- ☐ En kertaakaan
- ☐ Muutaman harvan kerran
- ☐ Joitakin kertoja
- ☐ Aika monta kertaa
- ☐ Useimmiten
- ☐ Joka kerta

13. Oletteko ollut HUOLISSANNE tai LEVOTON TERVEYDESTÄNNE viimeksi kuluneen viikon aikana?

- ☐ Erittäin paljon
- ☐ Hyvin paljon
- ☐ Melko paljon
- ☐ Jonkin verran, mutta en kovin paljon
- ☐ Käytännöllisesti katsoen en koskaan
- ☐ En lainkaan

14. Onko Teistä tuntunut siltä, että olisitte ”MENETTÄMÄSSÄ JÄRKENNE” tai KONTROLLINNE siitä, miten TOIMITTE, PUHUTTE, AJATTELETTE, TUNNETTE tai MITÄ MUISTATTE viimeksi kuluneen viikon aikana?

- ☐ Ei lainkaan
- ☐ Vain vähän
- ☐ Jonkin verran, mutta ei niin paljon, että olisin ollut huolissani tai levoton siitä
- ☐ Jonkin verran ja olen ollut vähän huolissani
- ☐ Jonkin verran ja olen ollut melko huolissani
- ☐ Kyllä, hyvin paljon ja olen ollut hyvin huolissani

15. Päivittäinen elämäni on ollut TÄYNNÄ minua KIINNOSTAVIA ASIOITA viimeksi kuluneen viikon aikana?

☐ Ei lainkaan tänä aikana

☐ Vain pienen osan tästä ajasta

☐ Joskus

☐ Melkoisen osan tästä ajasta

☐ Suurimman osan tästä ajasta

☐ Koko ajan

16. Oletteko tuntenut itsenne AKTIIVISEKSI/TARMOKKAAKSI tai TYLSÄKSI/VELTOKSI viimeksi kuluneen viikon aikana?

☐ Hyvin aktiiviseksi/tarmokkaaksi joka päivä

☐ Enimmäkseen aktiiviseksi/tarmokkaaksi – en koskaan tylsäksi/veltoksi

☐ Melko aktiiviseksi/tarmokkaaksi – harvoin tylsäksi/veltoksi

☐ Melko tylsäksi/veltoksi – harvoin aktiiviseksi/tarmokkaaksi

☐ Enimmäkseen tylsäksi/veltoksi – en koskaan aktiiviseksi/tarmokkaaksi

☐ Hyvin tylsäksi/veltoksi joka päivä

17. Oletteko ollut HUOLESTUNUT, HARMISSANNE tai AHDISTUNUT viimeksi kuluneen viikon aikana?

☐ Erittäin paljon – niin paljon, että olen tuntenut itseni melkein sairaaksi huolestuneisuudesta

☐ Hyvin paljon

☐ Melko lailla

☐ Jonkin verran – sen verran, että se on vaivannut minua

☐ Vähän

☐ En lainkaan

18. Olen tuntenut itseni TASAPAINOISEKSI ja VARMAKSI viimeksi kuluneen viikon aikana?

- ☐ En lainkaan tänä aikana
- ☐ Pienen osan tästä ajasta
- ☐ Joskus
- ☐ Huomattavan osan tästä ajasta
- ☐ Suurimman osan tästä ajasta
- ☐ Koko ajan

19. Oletteko tuntenut itsenne LEVOLLISEKSI/HUOJENTUNEEKSI vai PINGOTTUNEEKSI/KIREÄKSI viimeksi kuluneen viikon aikana?

- ☐ Olen tuntenut itseni levolliseksi ja huojentuneeksi koko viikon
- ☐ Olen tuntenut itseni levolliseksi ja huojentuneeksi suurimman osan ajasta
- ☐ Yleensä olen tuntenut itseni levolliseksi, mutta ajoittain olen tuntenut itseni melko pingottuneeksi
- ☐ Yleensä olen tuntenut itseni pingottuneeksi, mutta ajoittain olen tuntenut itseni melko levolliseksi
- ☐ Olen tuntenut itseni pingottuneeksi/kireäksi suurimman osan ajasta
- ☐ Olen tuntenut itseni hyvin pingottuneeksi/kireäksi koko ajan

20. Olen tuntenut itseni ILOISEKSI/HUOLETTOMAKSI viimeksi kuluneen viikon aikana?

- ☐ En lainkaan tänä aikana
- ☐ Pienen osan tästä ajasta
- ☐ Joskus
- ☐ Melkoisen osan tästä ajasta
- ☐ Suurimman osan tästä ajasta
- ☐ Koko ajan

21. Olen tuntenut itseni VÄSYNEEKSI ja LOPPUUN KULUNEEKSI viimeksi kuluneen viikon aikana?

- ☐ En lainkaan tänä aikana
- ☐ Pienen osan tästä ajasta
- ☐ Joskus
- ☐ Melkoisen osan tästä ajasta
- ☐ Suurimman osan tästä ajasta
- ☐ Koko ajan

22. Oletteko tuntenut itsenne ”STRESSAANTUNEEKSI”, RASITTUNEEKSI tai PAINEEN ALAISEKSI viimeksi kuluneen viikon aikana?

- ☐ Kyllä, melkein enemmän kuin voin sietää tai kestää
- ☐ Kyllä melko lailla
- ☐ Kyllä, jonkin verran – enemmän kuin tavallisesti
- ☐ Kyllä, jonkin verran – kuten tavallisesti
- ☐ Kyllä, vähän
- ☐ En lainkaan

TARKISTAKAA, ETTÄ OLETTE VASTANNUT KAIKKIIN KYSYMYKSIIN.

KIITOS HYVÄSTÄ YHTEISTYÖSTÄ.

# APPENDIX 3: QUESTIONNAIRE USED IN STUDY III

R_____

KYSELYKAAVAKE HENKILÖLLE, JOLLA ON KROONINEN MUNUAISTAUTI

Tutkimuksen tämä osa sisältää taustatietoja ja elintapoja selvittäviä kysymyksiä. Jokaisen kysymyksen osalta rastittakaa (X) se vaihtoehto, joka parhaiten sopii Teidän kohdallenne tai täyttäkää vastauksenne sille varatulle viivoitukselle.

1. Pituus (cm) _____ ja paino (kg) _____
2. Tuorein mittaamanne verenpainelukema (yläpaine/alapaine) _____
   (Jos Teillä on verenpainemittari helposti käytettävissä.)
3. Ammatti tai työtehtävä _____
4. Teillä todetut muut sairaudet

   ☐ verenpainetauti

   ☐ sepelvaltimotauti

   ☐ sydäninfarkti

   ☐ aivohalvaus tai muu aivoverenkiertohäiriö

   ☐ sydämen vajaatoiminta

   ☐ rytmihäiriösairaus

   ☐ astma tai keuhkoahtaumatauti

   ☐ diabetes

   ☐ kilpirauhassairaus

   ☐ haavainen paksusuolentulehdus (colitis ulcerosa)

   ☐ Crohnin tauti

   ☐ uniapnea

   ☐ keliakia

   ☐ reumasairaus

   ☐ masennus

   ☐ syöpä

   muu, mikä _____

   _____

5. Onko teille tehty suoliston alueen leikkausta?

   ☐ kyllä

   ☐ ei

Jos vastasitte kyllä, tarkentakaa mitä on leikattu, koska (arvio vuodesta riittää)

ja missä (esim. TAYS). _____

---

6. Oletteko viimeisen vuoden kuluessa käyttäneet antibioottikuurin?

   ☐ kyllä

   ☐ ei

7. Tupakoitteko?

   ☐ kyllä

   ☐ ei

*Jos vastasitte kyllä, vastatkaa myös kysymyksiin 8 ja 9, muuten voitte siirtyä kysymykseen 10.*

8. Kuinka pian (minuuteissa) herättyänne poltatte ensimmäisen savukkeen?

   ☐ alle 6

   ☐ 6-30

   ☐ 31-60

   ☐ yli 60

9. Kuinka monta savuketta poltatte päivittäin?

   ☐ 10 tai vähemmän

   ☐ 11-20

   ☐ 21-30

   ☐ yli 30

10. Kuinka usein juotte olutta, viiniä tai muita alkoholijuomia? Koettakaa ottaa mukaan myös ne kerrat, jolloin nautitte vain pieniä määriä, esim. pullon keskiolutta tai tilkan viiniä.

    ☐ ei koskaan

    ☐ noin kerran kuussa tai harvemmin

    ☐ 2-4 kertaa kuussa

    ☐ 2-3 kertaa viikossa

    ☐ 4 kertaa viikossa tai useammin

11. Kuinka monta annosta alkoholia yleensä olette ottanut niinä päivinä, jolloin käytitte alkoholia?

☐ 1-2 annosta

☐ 3-4 annosta

☐ 5-6 annosta

☐ 7-9 annosta

☐ 10 tai enemmän

12. Kuinka usein olette juonut kerralla kuusi tai useampia annoksia?

☐ en koskaan

☐ harvemmin kuin kerran kuussa

☐ kerran kuussa

☐ kerran viikossa

☐ päivittäin tai lähes päivittäin

13. Kuinka monta tuntia viikossa harrastatte liikuntaa vapaa-aikananne niin, että hengästytte tai hikoilette?

☐ en yhtään

☐ noin puoli tuntia

☐ noin tunnin

☐ noin 2-3 tuntia

☐ noin 4-6 tuntia

☐ seitsemän tuntia tai enemmän

14. Minkälaiseksi koette terveytenne nykyään?

☐ erinomainen

☐ erittäin hyvä

☐ hyvä

☐ kohtalainen

☐ huono

15. Koetteko munuaistautinne haittaavan päivittäistä elämäänne?

- ☐ ei lainkaan
- ☐ vähän
- ☐ kohtalaisesti
- ☐ merkittävästi
- ☐ erittäin paljon

16. Saako teihin olla yhteydessä mahdollisten jatkotutkimusten osalta?

- ☐ kyllä
- ☐ ei

KIITOS VASTAUKSESTANNE JA HYVÄSTÄ YHTEISTYÖSTÄ.

# PUBLICATIONS

# PUBLICATION I

## Inflammatory Bowel Disease in Patients Undergoing Renal Biopsies

Jussi Pohjonen, Rakel Nurmi, Martti Metso, Pia Oksanen, Heini Huhtala, Ilkka Pörsti, Jukka Mustonen, Katri Kaukinen, Satu Mäkelä

Clinical Kidney Journal. 2019;12(5):645-651.
doi:10.1093/ckj/sfz004

ckj OXFORD era edta LEADING EUROPEAN NEPHROLOGY

*Clinical Kidney Journal*, 2019, 1–7

**doi: 10.1093/ckj/sfz004**
Original Article

ORIGINAL ARTICLE

# Inflammatory bowel disease in patients undergoing renal biopsies

Jussi Pohjonen[1,2], Rakel Nurmi[1], Martti Metso[2], Pia Oksanen[3,4], Heini Huhtala[5], Ilkka Pörsti[2,4], Jukka Mustonen[2,4], Katri Kaukinen[1,2] and Satu Mäkelä[2,4]

[1]Celiac Disease Research Center, Faculty of Medicine and Life Sciences, Tampere University, Tampere, Finland, [2]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland, [3]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland, [4]Faculty of Medicine and Life Sciences, Tampere University, Tampere, Finland and [5]Faculty of Social Sciences, Tampere University, Tampere, Finland

Correspondence and offprint requests to: Jussi Pohjonen; E-mail: jussi.pohjonen@tuni.fi

## ABSTRACT

**Background.** There are no good data in the literature on the prevalence of inflammatory bowel disease (IBD) in patients with kidney disease and we do not know whether IBD affects the course of kidney disease or if the type of IBD is an influential factor. The aim of this study was to evaluate the prevalence of IBD among patients who have undergone renal biopsies due to clinical indications and to elucidate whether the presence of IBD influences renal and patient outcomes.

**Methods.** We collected retrospective data on concomitant diseases, especially IBD, from adult patients undergoing renal biopsy for any clinical indication between 2000 and 2012 at Tampere University Hospital, Tampere, Finland. Information was systematically collected on the activity of IBD, medication for IBD, surgery performed for IBD and markers of kidney function.

**Results.** Of the 819 patients biopsied, 35 (4.3%) had IBD. The prevalence of IBD was 13.3 and 4.6% in patients with tubulointerstitial nephritis (TIN) and immunoglobulin A nephropathy (IgAN), respectively. In comparison, the prevalence of IBD in the Finnish population is 0.6%. Ulcerative colitis and Crohn's disease were equally represented. The presence of IBD showed no impact on renal and patient outcomes.

**Conclusions.** IBD should not be overlooked in patients undergoing renal biopsies, especially those diagnosed with TIN or IgAN. The renal findings did not associate with the activity of intestinal inflammation. Whether a concomitant IBD truly affects the course of chronic kidney disease should be examined in further studies.

**Keywords:** chronic kidney failure, IgA glomerulonephritis, inflammatory bowel diseases, Interstitial nephritis, renal biopsy

*Received: 7.9.2018. Editorial decision: 3.1.2019*

## INTRODUCTION

Many publications have raised our awareness of the relationship between kidney diseases and increased intestinal permeability. Chronic kidney disease (CKD), and especially uraemia, alters the intestinal barrier and microbiome. The loss of the ability to prevent the influx of microbial toxins and other harmful products leads to local and systemic inflammation, which can further promote deterioration in kidney function [1–3]. This phenomenon probably promotes cardiovascular diseases as well, which are one of the leading causes of death in patients with end-stage renal disease (ESRD) [4]. Interestingly, intestinal permeability seems to be already increased in the earlier stages of CKD [5]. The linkage between the most common primary glomerulopathy [6], immunoglobulin A nephropathy (IgAN) and the mucosa is well known [7, 8]. Genome-wide association studies (GWASs) in patients with IgAN have identified risk loci in the genes involved in intestinal mucosa integrity and the immune network [9]. In one recent study, patients with IgAN who had persistent proteinuria were treated with targeted-release enteric budesonide, which resulted in a significant reduction in proteinuria [10].

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are increasingly common chronic inflammatory disorders of the gastrointestinal tract: the prevalence of IBD is currently 0.2–0.7% in Western countries [11–14]. Inflammation affects the large intestine and rectum in UC [15], whereas inflammation and progressive bowel damage can be present in any part of the intestine in CD [16]. A third entity is unclassified IBD (IBDU), in which inflammation of the intestine with chronic colitis is present but no characteristic histological signs of UC or CD are found [11]. IBD requires lifelong management. Renal damage in patients using 5-aminosalicylic acid (5-ASA) medication is a rare but well-documented complication [17–20]. IBD is not restricted to the gastrointestinal tract; 6–47% of sufferers also experience extraintestinal manifestations (EIMs) [21, 22]. The organs most commonly affected include the skin, eyes, joints and biliary tract [21]. The prevalence of renal or urinary manifestations can be as high as 20%, and they are largely explained by urological complications such as nephrolithiasis [23, 24]. Renal diseases in conjunction with IBD have been the subjects of primarily case reports [25, 26], and only a few register-based case series have been published [27, 28].

The aims of this study were to evaluate the prevalence of IBD among patients who have undergone renal biopsies due to clinical indications and to elucidate whether the presence of IBD has an influence on renal and patient outcomes.

## MATERIALS AND METHODS

### Patients and study design

The study cohort comprised 824 consecutive patients >16 years of age who had undergone a renal biopsy due to clinical indications at the Division of Nephrology at Tampere University Hospital (TAUH), Tampere, Finland, between January 2000 and December 2012. The data were missing in five patients, giving the study population of 819 patients. All patients included in the study provided written informed consent. If the same patient was biopsied twice during the study period, then the first diagnostic biopsy was included in the study. Renal biopsy specimens were taken and processed using standard methods as described earlier [29]. All specimens were studied with light and immunofluorescence microscopy by two renal pathologists. The indications for renal biopsies were classified into three groups: (i) abnormal urinary finding, including focal nephritic syndrome (haematuria and daily urinary protein excretion <1.5 g), diffuse nephritic syndrome (haematuria and daily urinary protein excretion >1.5 g), nephrotic syndrome (daily urinary protein excretion >3.5 g without haematuria), proteinuria (daily urinary protein excretion 0.3–3.5 g without haematuria) and haematuria (daily urinary protein excretion <0.3 g); (ii) renal insufficiency (elevated creatinine level) and (iii) any other indication. Based on the histopathological findings of the renal biopsy specimens, five groups were categorized: glomerular diseases, tubulointerstitial diseases, vascular diseases, other findings (e.g. cystic and congenital diseases) and no glomeruli (inadequate sample) [30]. Patients were divided into two groups based on whether they were diagnosed with IBD or not.

### Clinical data on kidney disease

The histories of all 819 patients were retrospectively collected from the medical records of TAUH between 2014 and 2016 [8]. Plasma creatinine concentration, quantitative 24-h urinary protein excretion and haematuria data were gathered from medical records at the time of the renal biopsy and the most recent follow-up. The urine dipstick test for haematuria was dichotomized as negative (values 0 or +) or positive (++ or +++). Estimated glomerular filtration rate (eGFR) was defined using the Chronic Kidney Disease Epidemiology Collaboration equation [30]. The annual change in eGFR was calculated by dividing the difference between the final and baseline values of eGFR by the number of years of follow-up. Only patients followed up for >1 year after the renal biopsy with preserved kidney function (no transplantation or chronic dialysis started during follow-up) were included in the calculations of kidney function at the most recent follow-up. Furthermore, data on chronic dialysis treatment or renal transplantation during follow-up were recorded and collectively called ESRD. The follow-up for individual patients was concluded at the last office visit or the last reliable set of laboratory results, whichever was closer to the time of data collection.

### Clinical data on IBD

Information regarding other diagnosed diseases, including IBD, was collected systematically. The EIMs comprised diseases of organs commonly accepted to be involved in IBD—diseases of the joints, eyes, skin, liver, biliary tract and urinary tract—as well as thrombotic events. Detailed data on IBD activity, medication, location, surgery and EIMs were collected. The immunomodulatory medications for IBD included azathioprine, methotrexate, glucocorticoids or tumour necrosis factor (TNF) inhibitors. IBD flare-up was defined as the need for systemic glucocorticoid medication equivalent to ≥30 mg of prednisolone. The site of IBD was determined by means of endoscopy or gastrointestinal imaging (e.g. enteric magnetic resonance imaging) reports and grouped into five different categories as follows: proctitis, left-sided colitis (including proctosigmoiditis), pancolitis/ileocolonic, small intestinal (no colonic affliction) and unknown. Abdominal surgery denoted any surgical procedure to the intestine (including appendectomy); operations on abdominal fistulas, strictures, hernias or abscesses and cholecystectomy.

### Statistical methods

The data are presented as medians and ranges for continuous variables and numbers and percentages for categorical

**Table 1. Basic characteristics of patients undergoing renal biopsy, indications for renal biopsies and renal biopsy findings**

| | Patients with IBD ($n = 35$) | | Patients without IBD ($n = 784$) | | P-value |
|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | |
| Male | 20 | 57.1 | 491 62.6 | 0.593 | |
| Age, median (range), years | 49 (18–76) | | 59 (16–85) | | 0.026 |
| Weight, median (range), kg[a] | 71 (46–112) | | 81 (23–150) | | 0.022 |
| Height, median (range), cm[b] | 172 (160–187) | | 173 (120–198) | | |
| Indications for renal biopsies | | | | | 0.285 |
| Abnormal urinary finding[c] | 22 | 62.9 | 586 | 74.7 | |
| Renal insufficiency | 12 | 34.3 | 185 | 23.6 | |
| Other causes | 1 | 2.9 | 13 | 1.7 | |
| Renal biopsy findings | | | | | 0.026 |
| Glomerular diseases | 17 | 48.6 | 556 | 70.9 | |
| Tubulointerstitial diseases | 10 | 28.6 | 98 | 12.5 | |
| Vascular diseases | 1 | 2.9 | 18 | 2.3 | |
| Other findings | 7 | 20.0 | 98 | 12.5 | |
| Inadequate sample | 0 | 0 | 14 | 1.8 | |
| Previous kidney transplantation | 2 | 5.7 | 56 | 7.1 | 0.747 |

Number of subjects available: [a]453, [b]639. [c]Focal nephritic syndrome, diffuse nephritic syndrome, nephrotic syndrome, proteinuria, haematuria.

variables. Groups were compared using the chi-square test, Fisher's exact test, independent $t$-test or Mann–Whitney U-test, as appropriate. Survival (ESRD as event) was determined using Kaplan–Meier curves and differences between IBD (yes/no) were compared by log-rank test. Univariate and multivariable analyses (adjusted for age, gender and presence of IBD) were performed using Cox proportional hazards regression. Hazard ratios and their 95% confidence intervals are given. All tests were two-sided and $P < 0.05$ was considered statistically significant. All statistical testing was performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

### Ethical consideration

The study protocol was approved by the Ethics Committee of Tampere University Hospital. All subjects gave written informed consent at the time of the renal biopsy.

## RESULTS

### Patient characteristics, renal biopsy findings and the prevalence of IBD

Twenty-eight (3.4%) of 819 patients had IBD at the time of renal biopsy and an additional 7 patients were diagnosed with IBD during the follow-up. Therefore a total of 35 (4.3%) patients had IBD (Table 1). The patients with IBD were younger than the patients without IBD. There were no differences in indications for renal biopsy between the patients with and without IBD (Table 1).

The most common renal biopsy finding in the patients with IBD was acute (four patients) or chronic (four patients) tubulointerstitial nephritis (TIN). Altogether, 22.9% of the patients with IBD presented with TIN, while 7 patients (20.0%) had IgAN. Ten patients had glomerular diseases other than IgAN, two patients had tubulointerstitial diseases other than TIN and eight patients had findings categorized as vascular diseases or other renal findings (Table 2). Tubulointerstitial diseases were more often found in the patients with IBD when compared with patients without IBD (28.6 versus 12.5%; $P = 0.017$) and glomerular diseases dominated in the patients without IBD when compared with patients with IBD (70.9 versus 48.6%; $P = 0.007$). Among the patients without IBD, TIN was diagnosed in 6.7% and IgAN in 18.4% of patients. Overall, the prevalence of IBD in the patients with TIN was 13.3%. Seven of 151 patients (4.6%) with IgAN had IBD compared with 8 of 308 patients (2.6%) with a glomerular disease other than IgAN ($P = 0.164$).

Patients with IBD and TIN were almost exclusively women (seven of eight patients), while no sex difference was found in patients with TIN and with no IBD (female 50.0%). Patients with a glomerular disease (including IgAN) and IBD were predominantly male [14/17 patients (82.4%)]. A preponderance of males was also found in patients with glomerular disease and no IBD [344/556 patients (61.9%)].

**Table 2. Renal biopsy findings in 35 patients with IBD**

| Diagnosis | $n$ |
|---|---|
| Glomerular diseases | |
| IgA GN | 7 |
| Membranous GN | 2 |
| IgM GN | 2 |
| Extracapillary GN | 1 |
| Mesangial, proliferative GN | 1 |
| Mesangial, sclerosing GN | 1 |
| Focal segmental glomerulosclerosis | 1 |
| Glomerulosclerosis, NOS | 1 |
| Amyloid nephropathy | 1 |
| Tubulointerstitial diseases | |
| Acute TIN | 4 |
| Chronic TIN | 4 |
| Myeloma cast nephropathy | 1 |
| Acute tubular necrosis | 1 |
| Vascular diseases | |
| Arteriosclerosis (hyalinic) | 1 |
| Other findings | |
| Normal finding | 3 |
| Morphologic description only | 2 |
| Chronic cellular graft rejection | 2 |

NOS, not otherwise specified.

**Table 3. Renal function at the time of renal biopsy and at the latest follow-up**

| | Patients with IBD ($n = 35$), median (range) | Patients without IBD ($n = 784$), median (range) | P-value |
|---|---|---|---|
| At renal biopsy | | | |
| Plasma creatinine (μmol/L) | 133 (56–671) | 123 (17–1776) | 0.921 |
| eGFR[a] (mL/min/1.73 $m^2$) | 44 (6–130) | 51 (2–172) | 0.711 |
| 24-h urinary protein excretion (g/day)[b] | 0.8 (0.1–6.4) | 1.5 (0.1–24.2) | 0.040 |
| Haematuria, *n* (%)[c] | 12 (37.5) | 346 (46.9) | 0.366 |
| At the latest follow-up | | | |
| Duration of follow-up (months) | 59 (0–178) | 66 (0–183) | 0.619 |
| Plasma creatinine (μmol/L)[d,e] | 90 (49–276) | 104 (11–1013) | 0.137 |
| eGFR (mL/min/1.73 $m^2$)[d,e] | 78 (19–117) | 57 (4–197) | 0.118 |
| Annual change of eGFR (mL/min/1.73 $m^2$/year)[d,f] | 0 (−11–35) | −1 (−84–70) | 0.086 |

[a]eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Number of subjects available:
[b]621;
[c]769;
[d]excluded if treated with dialysis, had received renal transplantation during the follow-up or the follow-up had lasted <12 months;
[e]567;
[f]552.

### Renal outcomes

The median follow-up time was 59 months in patients with IBD and 66 months in patients without IBD. There was no difference between the groups in eGFR at the time of renal biopsy or at the most recent follow-up. Patients with IBD had significantly lesser amounts of proteinuria at the time of renal biopsy (Table 3). The 24-h urinary protein excretion was quantitated in 26 of 35 patients with IBD. Of these, nine (34.6%) were using immunomodulatory medication at the time of renal biopsy. Yet the amount of proteinuria did not differ between those who were on immunomodulatory medication and those who were not (median of the 24-h excretion 0.8 and 0.9 g, respectively; $P = 0.833$). Two patients with IBD (5.7%) and 142 patients without IBD (18.1%) progressed to ESRD ($P = 0.068$). In Figure 1, a Kaplan–Meier curve shows the difference between patients with and without IBD and the occurrence of ESRD. We also performed Cox logistic regression analysis to determine the risk factors for ESRD (Table 4). Male gender was found to be a strong and independent predictor of ESRD, but the presence of IBD did not associate with the risk for ESRD.

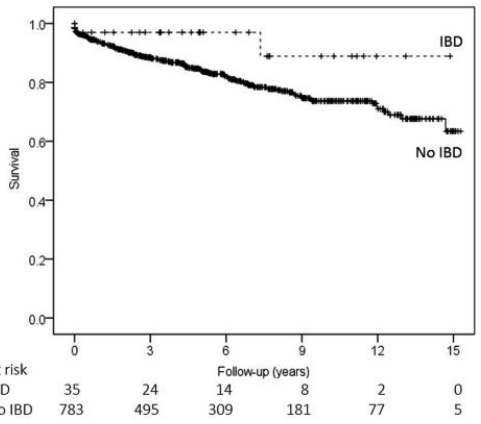


FIGURE 1: Kaplan–Meier survival curves for 35 patients with IBD and 783 patients with no IBD for progression to ESRD (log-rank $P = 0.086$).

### Phenotypes of IBD

Altogether, there were 14 cases of CD, 14 cases of UC and 7 cases of IBDU. Neither CD nor UC seemed to dominate in the different renal findings for TIN (three CD, four UC and one IBDU), IgAN (four CD and three UC) or other GD (four CD, four UC and two IBDU). All patients with TIN had a previous diagnosis of IBD and all of them used or had prior use of 5-ASA medication at the time of renal biopsy. Similarly, patients with glomerular diseases who had a diagnosis of IBD at the time of renal biopsy (13 patients) all had a history of 5-ASA medication. Altogether, 37.1% of the patients with IBD were taking either steroid or other immunomodulatory medication (azathioprine, methotrexate or TNF inhibitor) at the time of the renal biopsy. In terms of inflammatory activity, one-quarter (7/28) of the patients with previous IBD had a flare-up of IBD during the year preceding the renal biopsy.

Diffuse intestinal inflammation (pancolitis or ileocolonic) was the most common (54.2%) location of IBD, irrespective of the renal finding. Nine of 35 (25.7%) patients had undergone abdominal surgery. Most of the patients with IgAN and IBD had an EIM (71.4%), while just 12.5% of the patients with TIN and 20.0% of the patients with other glomerular diseases had an EIM.

## DISCUSSION

This study showed the prevalence of IBD among people undergoing renal biopsy to be as high as 3.4%; during the follow-up, the prevalence of diagnosed IBD was further elevated to 4.3%. As the pathogenesis of diseases can presumably take a variable number of years before clinical symptoms arise and the spectrum of symptoms of both renal diseases and IBD is wide, a clear determination cannot be made as to whether renal disease or IBD preceded the other in individual patients.

The prevalence of IBD in our study was large compared with that found (0.2%) in a previous study by Ambruzs *et al.* [27]. The major difference in the prevalence of IBD in these two studies is most likely explained by differences in study designs. Between 1986 and 2008, the prevalence of IBD has increased from 0.2 to 0.6% in Finland [11, 12]. There are few published prevalence

**Table 4. Univariate and multivariable Cox regression analysis of risk factors for ESRD among 819 patients who underwent renal biopsy due to clinical indication**

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age | 1.01 (1.00–1.02) | 0.010 | 1.01 (1.00–1.02) | 0.024 |
| Male gender | 1.71 (1.19–2.47) | 0.004 | 1.66 (1.15–2.40) | 0.007 |
| IBD | 0.31 (0.08–1.27) | 0.104 | 0.34 (0.08–1.36) | 0.126 |

rates of IBD globally, but they seem to vary from 0.2 to 0.7% [11, 13, 14]. Thus the prevalence of IBD in the present cohort of patients who had a clinical indication for the renal biopsy was approximately 7-fold compared with that in the general population.

The prevalences of IBD in patients with TIN and IgAN were as high as 13.3 and 4.6%, respectively. This is about 20- and 8-fold the IBD prevalence in the general population, respectively. In previous studies, the prevalence of IBD in IgAN patients has varied from 0.7 to 1.6% [27, 31, 32]. To our knowledge, the prevalence of IBD in patients with TIN has not been published before. There is no way to differentiate patients in this cohort for whom TIN was related to 5-ASA medication, as all the patients with TIN had an ongoing or previous history of 5-ASA use. Thus the high prevalence of IBD in patients with TIN might have been related to 5-ASA medication even though the correlation of 5-ASA to TIN has remained controversial in the literature [18, 20, 33]. In general, patients without IBD had greater amounts of proteinuria at the time of renal biopsy, a finding that most likely is explained by the dominance of glomerular diseases in patients without IBD. The preponderance of the female gender in patients with IBD and TIN was noteworthy, but the small number of patients with both IBD and TIN might have influenced the results. The finding of a male majority in patients with glomerulonephritis (GN) in general has been noted in earlier publications [34, 35] and recently in patients with IBD and GN as well [28]. Patient cases of TIN and IBD have not shown female dominance [33, 36, 37].

The connection between IgAN and intestinal inflammation is clearly recognized [7]. The HLA-DR1 allele for IgAN and the HLA-DR1/DQw5 allele for CD have led to a theory of a common genetic basis for both diseases [24]. GWASs in patients with IgAN have identified risk loci in genes involved in intestinal mucosal integrity and the immune network. Some of the risk alleles for IgAN are also associated with the risk for IBD [9]. The number of inflammatory cells in the intestinal mucosa increased in patients with GN [38–40]. However, no previous publication has shown such a high prevalence of IBD in patients with IgAN.

Previously, more than half of the patients with IgAN have presented with various other parallel diseases [31, 32]. No published data exist on the incidence of IBD and IgAN in association with a third disease entity, but patient cases of such triads have been published [41–43], as has one recent case series [28]. In our cohort, 71% of patients with IBD and IgAN had another EIM.

Male gender presented as a risk factor for ESRD. This finding is in line with previous publications [44, 45]. IBD was not related to an elevated risk for ESRD. The impression that the activity of IBD affects renal disease can arise when reading published patient cases [46–48]. Defining the activity of the disease in a retrospective manner is rather inaccurate. We can assume, based on the data shown, that the patients in the present study did not represent particularly difficult cases of colitis. Fewer than half of the patients with a previous diagnosis of IBD either had a flare-up during the preceding year before the kidney biopsy or were on an immunomodulatory medication at the time of the renal biopsy. Nevertheless, more than half had no clinical sign of active intestinal inflammation, and when the total population of 35 patients with IBD was evaluated, about one-third of the patients with IBD had intestinal inflammatory activity at the time of the renal biopsy. A quarter of the patients with IBD had undergone abdominal surgery at any given time point, either before or after the kidney biopsy. No clear difference was noticed in the concomitance of renal disease and IBD, as CD and UC were equally represented. In a recent letter published by Hungarian researchers, the few cases of GN found in patients with IBD were more often in conjunction with CD [28].

The renal biopsies in this study were taken at one centre and analysed by two renal pathologists. The unifying indications for renal biopsies as well as the interpretation of the renal samples are the strengths in the present study. Patients with renal diseases in our university hospital district are mostly followed up and treated in the nephrology unit of the university hospital. In a similar way, most of the patients with active IBD are followed-up by the university hospital. Thus we have been able to collect real-life data with long follow-up times. Due to the retrospective nature of the study, some of the information collected may be inaccurate or insufficient. Another obvious limitation is that some of the patients with no diagnosed IBD might have had clinically silent IBD, but the number of such patients presumably would be low and would not affect the results of the study.

To conclude, our study showed a remarkable prevalence of IBD in patients undergoing renal biopsy for any clinical indication. IBD should be kept in mind when the renal biopsy finding is either TIN or IgAN. A lack of obvious gastrointestinal symptoms does not necessarily indicate the absence of IBD, as more than half of the patients biopsied were asymptomatic at the time of biopsy. We do not yet know whether the coexistence of IBD and CKD results in one influencing the other. This cohort was too small to show either the benefit or disadvantage of IBD for CKD even though patients with IBD did well when compared with patients without IBD. Thus further studies are needed to examine the significance of concomitant IBD in patients with CKD.

## ACKNOWLEDGEMENTS

The authors are very grateful to Raija Hukkila and Marja-Leena Koskinen for their excellent technical assistance. The valuable work of Docent Ole Wirta (MD, PhD) is greatly appreciated.

## FUNDING

This study was supported by the Academy of Finland, the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (9U019, 9T018, 9S020, 9S059) and the Sigrid Juselius Foundation. The funding sources had no involvement in the study design; in the collection, analysis and interpretation of the data; in the writing of the report or in the decision to submit the article for publication.

## AUTHORS' CONTRIBUTIONS

All authors participated in the design of the study. J.P., R.N. and M.M. collected the data. J.P. and H.H. analysed and

interpreted the data. J.P. drafted the article. All authors read, revised and approved the final manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript contents have not been copyrighted or previously published, except in abstract form for the Annual Medical Congress arranged by the Finnish Medical Society Duodecim and the Medical Society of Tampere, Finland. We have no conflicts of interest to declare.

## REFERENCES


1. Vaziri ND, Wong J, Pahl M. Chronic kidney disease alters intestinal microbial flora. *Kidney Int* 2013; 83: 308–315
2. Vaziri ND, Yuan J, Nazertehrani S *et al.* Chronic kidney disease causes disruption of gastric and small intestinal epithelial tight junction. *Am J Nephrol* 2013; 38: 99–103
3. Vaziri ND, Zhao Y, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant* 2016; 31: 737–746
4. Anders H, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int* 2013; 83: 1010–1016
5. Rostoker G, Wirquin V, Terzidis H *et al.* Mucosal immunity in primary glomerulonephritis. III. Study of intestinal permeability. *Nephron* 1993; 63: 286–290
6. Geddes CC, Rauta V, Gronhagen-Riska C *et al.* A tricontinental view of IgA nephropathy. *Nephrol Dial Transplant* 2003; 18: 1541–1548
7. Coppo R. The intestine-renal connection in IgA nephropathy. *Nephrol Dial Transplant* 2015; 30: 360–366
8. Nurmi R, Metso M, Pörsti I *et al.* Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies. *Dig Liver Dis* 2018; 50: 27–31
9. Kiryluk K, Li Y, Scolari F*et al.* Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet* 2014; 46: 1187–1196
10. Fellström BC, Barratt J, Cook H *et al.* Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet* 2017; 389: 2117–2127
11. Manninen P, Karvonen A, Huhtala H *et al.* The epidemiology of inflammatory bowel diseases in Finland. *Scand J Gastroenterol* 2010; 45: 1063–1067
12. Jussila A, Virta LJ, Salomaa V *et al.* High and increasing prevalence of inflammatory bowel disease in Finland with a clear North-South difference. *J Crohns Colitis* 2013; 7: e262
13. Hein R, Köster I, Bollschweiler E *et al.* Prevalence of inflammatory bowel disease: estimates for 2010 and trends in Germany from a large insurance-based regional cohort. *Scand J Gastroenterol* 2014; 49: 1325–1335
14. Herrinton LJ, Liu L, Lafata JE *et al.* Estimation of the period prevalence of inflammatory bowel disease among nine health plans using computerized diagnoses and outpatient pharmacy dispensings. *Inflamm Bowel Dis* 2007; 13: 451–461
15. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105: 501–523
16. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017; 66: 2179–2187
17. Ransford RaJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; 51: 536–539
18. Gisbert JP, González-Lama Y, Maté J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2007; 13: 629–638
19. Patel H, Barr A, Jeejeebhoy KN. Renal effects of long-term treatment with 5-aminosalicylic acid. *Can J Gastroenterol* 2009; 23: 170–176
20. Van Staa TP, Travis S, Leufkens HGM *et al.* 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004; 126: 1733–1739
21. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol* 2006; 12: 4819–4831
22. Danese S, Semeraro S, Papa A. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol* 2005; 11: 7227–7236
23. Pardi DS, Tremaine WJ, Sandborn WJ *et al.* Renal and urologic complications of inflammatory bowel disease. *Am J Gastroenterol* 1998; 93: 504–514
24. Oikonomou K, Kapsoritakis A, Eleftheriadis T *et al.* Renal manifestations and complications of inflammatory bowel disease. *Inflamm Bowel Dis* 2011; 17: 1034–1045
25. Filiopoulos V, Trompouki S, Hadjiyannakos D *et al.* IgA nephropathy in association with Crohn's disease: a case report and brief review of the literature. *Ren Fail* 2010; 32: 523–527
26. Shaer AJ, Stewart LR, Cheek DE *et al.* IgA antiglomerular basement membrane nephritis associated with Crohn's disease: a case report and review of glomerulonephritis in inflammatory bowel disease. *Am J Kidney Dis* 2003; 41: 1097–1109
27. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol* 2014; 9: 265–270
28. Vegh Z, Macsai E, Lakatos L *et al.* The incidence of glomerulonephritis in a population-based inception cohort of patients with inflammatory bowel disease. *Dig Liver Dis* 2017; 49: 718–719
29. Wirta O, Mustonen J, Helin H *et al.* Incidence of biopsy-proven glomerulonephritis. *Nephrol Dial Transplant* 2008; 23: 193–200
30. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
31. Makdassy R, Beaufils M, Meyrier A *et al.* Pathologic conditions associated with IgA mesangial nephropathy: preliminary results. *Contrib Nephrol* 1984; 40: 292–295
32. Mustonen J, Pasternack A. Associated diseases in IgA nephropathy. In: Clarkson AR (ed). *IgA Nephropathy. Topics in Renal Medicine*, Vol. 2. Boston: Springer, 1987, 47–65
33. Izzedine H, Simon J, Piette A-M *et al.* Primary chronic interstitial nephritis in Crohn's disease. *Gastroenterology* 2002; 123: 1436–1440
34. Wilcox GM, Aretz HT, Roy MA *et al.* Glomerulonephritis associated with inflammatory bowel disease. Report of a patient

with chronic ulcerative colitis, sclerosing cholangitis, and acute glomerulonephritis. *Gastroenterology* 1990; 98: 786–791
35. Presti ME, Neuschwander-Tetri BA, Vogler CA *et al.* Sclerosing cholangitis, inflammatory bowel disease, and glomerulonephritis: a case report of a rare triad. *Dig Dis Sci* 1997; 42: 813–816
36. Thuluvath PJ, Ninkovic M, Calam J *et al.* Mesalazine induced interstitial nephritis. *Gut* 1994; 35: 1493–1496
37. Vuotila M, Ikaheimo R, Pietilainen T. Interstitial nephritis associated with mesalazine therapy. *Duodecim* 2003; 119: 1978–1982
38. Rantala I, Collin P, Holm K *et al.* Small bowel T cells, HLA class II antigen DR, and GroEL stress protein in IgA nephropathy. *Kidney Int* 1999; 55: 2274–2280
39. Honkanen T, Mustonen J, Kainulainen H *et al.* Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. *Kidney Int* 2005; 67: 2187–2195
40. Rostoker G, Delchier JC, Chaumette MT. Increased intestinal intra-epithelial T lymphocytes in primary glomerulonephritis: a role of oral tolerance breakdown in the pathophysiology of human primary glomerulonephritides? *Nephrol Dial Transplant* 2001; 16: 513–517
41. Peeters AJ, van den Wall Bake AW, Daha MR *et al.* Inflammatory bowel disease and ankylosing spondylitis associated with cutaneous vasculitis, glomerulonephritis, and circulating IgA immune complexes. *Ann Rheum Dis* 1990; 49: 638–640
42. de Moura CG, de Moura TG, de Souza SP *et al.* Inflammatory bowel disease, ankylosing spondylitis, and IgA nephropathy. *J Clin Rheumatol* 2006; 12: 106–107
43. Ku E, Ananthapanyasut W, Campese VM. IgA nephropathy in a patient with ulcerative colitis, Graves disease and positive myeloperoxidase ANCA. *Clin Nephrol* 2012; 77: 146–150
44. Kastarinen M, Juutilainen A, Kastarinen H *et al.* Risk factors for end-stage renal disease in a community-based population: 26-year follow-up of 25, 821 men and women in eastern Finland. *J Intern Med* 2010; 267: 612–620
45. Hsu C, Iribarren C, McCulloch CE *et al.* Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009; 169: 342–350
46. Forshaw MJ, Guirguis O, Hennigan TW. IgA nephropathy in association with Crohn's disease. *Int J Colorectal Dis* 2005; 20: 463–465
47. Choi J-Y, Yu CH, Jung H-Y *et al.* A case of rapidly progressive IgA nephropathy in a patient with exacerbation of Crohn's disease. *BMC Nephrol* 2012; 13: 84
48. Onime A, Agaba EI, Sun Y *et al.* Immunoglobulin A nephropathy complicating ulcerative colitis. *Int Urol Nephrol* 2006; 38: 349–353

# PUBLICATION II

## Prevalence of Inflammatory Bowel Disease and Celiac Disease in Patients With IgA Nephropathy Over Time

Rakel Nurmi, Jussi Pohjonen, Martti Metso, Ilkka Pörsti, Onni Niemelä, Heini Huhtala, Jukka Mustonen, Katri Kaukinen, Satu Mäkelä

Nephron. 2021;145(1):78-84.
doi:10.1159/000511555

Nephron

Clinical Practice: Research Article

Nephron 2021;145:78–84
DOI: 10.1159/000511555

Received: May 21, 2020
Accepted: September 9, 2020
Published online: December 3, 2020

# Prevalence of Inflammatory Bowel Disease and Celiac Disease in Patients with IgA Nephropathy over Time

Rakel Nurmi[a] Jussi Pohjonen[a, b] Martti Metso[b] Ilkka Pörsti[b, c] Onni Niemelä[c, d] Heini Huhtala[e] Jukka Mustonen[b, c] Katri Kaukinen[a, b] Satu Mäkelä[b, c]

[a]Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [b]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland; [c]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [d]Medical Research Unit, Seinäjoki Central Hospital, Seinäjoki, Finland; [e]Faculty of Social Sciences, Tampere University, Tampere, Finland



**Keywords**
IgA nephropathy · Inflammatory bowel disease · Celiac disease · Prevalence · Tissue transglutaminase antibodies

**Abstract**
***Introduction:*** IgA nephropathy (IgAN) has been connected with increased intestinal permeability and subclinical intestinal mucosal inflammation as well as with inflammatory bowel disease (IBD) and celiac disease – nevertheless, the results are controversial. The prevalence of bowel diseases has increased over time in Western populations. Whether similar trend is seen among IgAN patients remains obscure. Our aim was to study the prevalence of IBD and celiac disease in IgAN patients over time. ***Methods:*** The study cohort consisted of altogether 629 patients with newly diagnosed IgAN during years 1976–2012. Data on diagnosis of IBD and celiac disease were retrospectively collected from medical records. Further, to detect unrecognized celiac disease, IgA-class tissue transglutaminase antibodies (tTGA) were measured from serum samples taken at the time of kidney biopsy during years 1980–2012 (defined as screen-detected celiac disease autoimmunity). ***Results:*** The prevalence of IBD among IgAN patients increased over time from 0 to 4.4%, while the prevalence of clinically diagnosed celiac disease decreased from 2.6 to 0.6%. Moreover, the number of screen-detected tTGA-positive cases decreased from the 1980s to the 21st century (2.8–0.7%). ***Conclusion:*** The prevalence of IBD increased over time in IgAN patients, which exceeds the prevalence of 0.6% in Finnish general population. In parallel, the prevalence of celiac disease and screen-detected celiac disease autoimmunity decreased over time. The coexistence of IBD and IgAN is not negligible. Whether this finding is caused by the increase in the prevalence of IBD in the population or shared pathophysiology between IgAN and IBD remains a matter of further studies. 

## Introduction

IgA nephropathy (IgAN) is the most common primary chronic glomerular disease in the world. It is defined by the predominance of galactose-deficient IgA1 deposits in the mesangium of the glomeruli [1]. Abnormalities of the gastrointestinal mucosa have been sug-

karger@karger.com
www.karger.com/nef



Rakel Nurmi
Celiac Disease Research Center, Faculty of Medicine and Health Technology
Tampere University
FI–33014 Tampere (Finland)
rakel.nurmi@fimnet.fi

gested to play a role in the pathogenesis of IgAN [2, 3]. According to the literature, IgAN is associated with subclinical small bowel mucosal inflammation and intestinal hyperpermeability [4, 5]. This kind of hyperpermeability might lead to increased exposure to immunogenic dietary antigens and a breakdown of immune tolerance [2]. Current data suggest systemic response to an antigen challenge and dysregulation of IgA immune responses, which result in the appearance of pathogenic IgA1 in the serum and the formation of mesangial deposits in IgAN [2, 3, 6].

Some studies have suggested that IgAN could be connected with bowel diseases, including Crohn's disease, ulcerative colitis, and celiac disease – nevertheless, there is still a great deal of controversy in this field [2, 6, 7]. Crohn's disease and ulcerative colitis, defined as inflammatory bowel disease (IBD), are characterized by an immune-mediated inflammatory response in genetically predisposed individuals [8]. The incidence and prevalence of IBD have been increasing over time, and the current prevalence of IBD has been reported to be 0.6% in Finland [9, 10]. The studies concerning the association between IgAN and IBD have been mainly case reports and case series [11–14]. When IBD is associated with renal problems and a kidney biopsy is needed, surprisingly high proportion of patients with IBD are found to have concomitant IgAN [15]. Interestingly, some studies have also shown improvement of renal function after remission of bowel disease [11, 12].

Celiac disease is a chronic enteropathy in the small intestine which develops from an autoimmune response to dietary gluten in genetically predisposed individuals [16]. On exposure to gluten, small bowel plasma cells produce IgA-class antibodies for the tissue transglutaminase (tTGA) which are currently a hallmark of celiac disease [16, 17]. Application of these highly specific serological tests has led to increased recognition of celiac disease and enabled the estimation of the true prevalence of the disorder [18, 19]. According to screening studies, the true prevalence of celiac disease is around 1–2% in Europe, whereas the prevalence of clinically diagnosed cases remains around 0.7% at the most [18–20]. The incidence of celiac disease is increasing, as in IBD, due to the more effective detection of the disease and a true rise in prevalence [9, 19, 21]. Previous studies suggest that celiac disease is overrepresented in patients with IgAN even though the results have been inconclusive [22–25]. Of note, some of the reports have suggested that IgAN might improve on gluten-free diet, which is the gold standard treatment for celiac disease [17, 26, 27].

The increasing prevalence of IBD and celiac disease in the general population over time has been recognized [10, 19]. However it is not known whether a similar trend is seen in patients with IgAN. Therefore, we determined in a well-defined cohort whether the prevalence of clinically diagnosed IBD and celiac disease, as well as screen-detected celiac disease autoimmunity, has changed over the last decades in patients with IgAN.

## Materials and Methods

*Patients and Study Design*

The study cohort consisted of 629 patients with a new diagnosis of IgAN during the years 1976–2012. The study population was divided into groups according to the decade of the diagnosis of IgAN (years 1976–1979, 1980–1989, 1990–1999, and 2000–2012). There was no access to the medical records of 77 patients diagnosed from 1976 to 1979. However, the data on the diagnosis of IBD and celiac disease among these patients were available from our previous report [28]. Altogether 552 patients (age ≥16 years) were diagnosed between 1980 and 2012, the data of whom were collected systematically at Tampere University Hospital, Finland. Serum samples of the patients diagnosed from 1980 onwards were available for the analyses of the tTGA levels. Serum was separated by centrifugation at 1,500 *g* for 10 min and subsequently frozen and stored at −80°C until analyzed for tTGA. Positivity for tTGA was defined as having screen-detected celiac disease autoimmunity. Clinically detected celiac disease patients were not included in the group of patients with celiac disease autoimmunity.

The kidney biopsy specimens were taken and processed by standard methods, as earlier described [29]. The consent for the study and blood samples were taken at the time of kidney biopsy. If the same patient was biopsied twice during the study period, the 1st diagnostic biopsy was included in the study. Data on previous diagnoses of IBD and celiac disease were collected, and the prevalence rates of IBD, celiac disease, and screen-detected celiac disease autoimmunity in patients with IgAN were calculated and presented separately for each decade and compared to the general prevalence rates of bowel diseases in Finland [10, 19, 20].

*Clinical Data*

The clinical data of 552 IgAN patients diagnosed from 1980 to 2012 were systemically collected and analyzed from medical records with the same principles by 2 investigators during years 2014–2018 at Tampere University Hospital. Plasma creatinine, daily urinary protein excretion, and data on hematuria and proteinuria were gathered from patient records at the time of biopsy. Estimated glomerular filtration rate was defined using the Chronic Kidney Disease Epidemiology Collaboration equation [30]. Additionally, data on comorbidities including type 1 and 2 diabetes mellitus, hypertension, and hypercholesterolemia were collected.

The referral letters and the pathology reports of the kidney samples were reread and structurally categorized [25]. The indications for kidney biopsy were classified in a hierarchical order (1 > 2 > 3 > 4 > 5 > 6) as follows: (1) renal insufficiency: the pres-

**Table 1.** Main clinical characteristics of 552 patients with IgAN from 1980 to 2012 at the time of kidney biopsy

| | All, *n* = 552 | 1980–1989, *n* = 241 | 1990–1999, *n* = 150 | 2000–2012, *n* = 161 | *p* value |
|---|---|---|---|---|---|
| Indications for biopsy,[a] *n* (%) | | | | | <0.001 |
| Renal insufficiency | 23 (4.2) | 5 (2.1) | 7 (4.7) | 11 (6.8) | |
| Nephritic syndrome | 141 (25.5) | 34 (14.1) | 52 (34.7) | 55 (34.2) | |
| Proteinuria and hematuria | 233 (42.2) | 108 (44.8) | 59 (39.3) | 66 (41.0) | |
| Nephrotic syndrome | 21 (3.8) | 10 (4.1) | 6 (4.0) | 5 (3.1) | |
| Proteinuria | 46 (8.3) | 28 (11.6) | 8 (5.3) | 10 (6.2) | |
| Hematuria alone | 86 (15.6) | 54 (22.4) | 18 (12.0) | 14 (8.7) | |
| Other causes | 2 (0.4) | 2 (0.8) | 0 (0) | 0 (0) | |
| Female, *n* (%) | 186 (33.7) | 84 (34.9) | 51 (34.0) | 51 (31.7) | 0.801 |
| Age, median (range), years | 42 (16–80) | 41 (16–77) | 41 (17–79) | 45 (16–80) | 0.060 |
| P-creatinine, median (range), µmol/L | 97 (19–1,541) | 96 (62–880) | 94 (43–898) | 101 (19–1,541) | 0.916 |
| eGFR, median (range), mL/min/1.73 $m^2$ | 78 (3–138) | 79 (5–131) | 78 (3–133) | 73 (3–138) | 0.424 |
| Urinary protein excretion rate, median (range), g/day | 0.75 (0.02–18.0) | 0.59 (0.02–11.0) | 0.73 (0.05–18.0) | 1.2 (0.07–12.9) | <0.001 |
| Proteinuria, *n* (%) | | | | | <0.001 |
| 0/+ | 191 (61.0) | 59 (76.6) | 57 (66.3) | 75 (50.0) | |
| ++/+++ | 122 (39.0) | 18 (23.4) | 29 (33.7) | 75 (50.0) | |
| Hematuria, *n* (%) | | | | | <0.001 |
| 0/+ | 89 (29.6) | 44 (57.9) | 16 (21.3) | 29 (19.3) | |
| ++/+++ | 212 (70.4) | 32 (42.1) | 59 (78.7) | 121 (80.7) | |
| Duration of follow-up, median (range), years | 14 (0–37) | 24 (0–37) | 17 (0–27) | 8 (0–15) | <0.001 |

Variables from the available data. IgAN, IgA nephropathy. [a] More details in methods and in reference [29].

ence of renal insufficiency stated by the clinician as the cause of a biopsy irrespective of renal findings, (2) nephritic syndrome: proteinuria >1.5 g/24 h or dipstick urinary albumin ++/+++ and either red cell casts or urinary erythrocytes (dipstick ++ or +++), (3) proteinuria and hematuria: proteinuria <1.5 g/24 h or dipstick urinary albumin + and either red cell casts or urinary erythrocytes (dipstick +), (4) nephrotic syndrome: proteinuria >3.5 g/24 h or dipstick urinary albumin +++ and no hematuria, (5) proteinuria: proteinuria <3.5 g/24 h or dipstick urinary albumin +/++ and no hematuria, (6) hematuria alone: urinary erythrocytes either by dipstick test (+, ++, and +++) or microscopy.

*Defining Screen-Detected Celiac Disease Autoimmunity*

Available 484 stored serum samples were investigated for serum IgA-class tTGA by ELISA according to the manufacturer's instructions (Celikey®; Phadia, GmbH, Freiburg, Germany). All analyses were carried out blinded to the knowledge of the clinical information in an SFS-EN ISO 1589:2013 accredited clinical chemistry laboratory. Values >7.0 U were defined as screen-detected celiac disease autoimmunity. tTGA values from 3.1 to 7.0 U were regarded as low positive [31].

*Statistical Methods*

Quantitative data were expressed as medians and ranges. Statistical differences were evaluated by using the Kruskal-Wallis test and the $\chi^2$ test. A $p$ value <0.05 was considered statistically significant. All statistical testing was performed using SPSS version 23.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA).

## Results

Of the 629 IgAN patients, clinical characteristics were analyzed in altogether 552 patients who were biopsied in 1980 or after (34% female, median age 42 years, range 16–80 years) (Table 1). Additionally, type 1 and type 2 diabetes were reported in 0.4 and 17% of patients, respectively. Altogether 64% of patients suffered from hypertension and 33% from hyperlipidemia.

The most common indication for kidney biopsy was proteinuria and hematuria (42%) (Table 1). The indications for kidney biopsy changed over time. Hematuria alone was more often an indication for biopsy in the 1980s when compared with later decades (22.4, 12.0, and 8.7%, $p < 0.001$). The patients whose IgAN was diagnosed during years 2000–2012 had more proteinuria at the time of the kidney biopsy than the patients whose biopsy was taken in the earlier decades (Table 1).

None of the IgAN patients suffered from IBD in the 1970s (Table 2). The prevalence of IBD increased over time from 2.0 to 4.4% between years 1980 and 2012. The prevalence of IBD did not differ between the patients who had proteinuria (dipstick urinary albumin ++/+++) at the time of biopsy and who did not (data not shown). The prevalence of clinically detected celiac disease did not show significant changes during the decades 1970s and

**Table 2.** The prevalence rates of the bowel diseases[a] in patients with IgAN

| | IgAN, *n* | IBD, *n* (%) | | Celiac disease, *n* (%) | | Screen-detected celiac disease autoimmunity, *n* (%) | |
|---|---|---|---|---|---|---|---|
| | | prevalence in IgAN | prevalence in Finland[c] | prevalence in IgAN | prevalence in Finland[c] | prevalence in IgAN | prevalence in Finland[c] |
| 1976–79[b] | 77 | 0 (0) | No data | 2 (2.6) | (0.03) | No data | (1.0) |
| 1980–89 | 241 | 4/205 (2.0) | (0.2) | 6/208 (2.9) | No data | 6/215 (2.8) | No data |
| 1990–99 | 150 | 4/148 (2.7) | (0.4) | 1/148 (0.7) | (0.3) | 0/124 (0) | No data |
| 2000–12 | 161 | 7/160 (4.4) | (0.6) | 1/160 (0.6) | (0.5–0.7) | 1/145 (0.7) | (1.5) |

IgAN, IgA nephropathy; IBD, inflammatory bowel disease. [a] Bowel diseases include IBD, celiac disease, and screen-detected celiac disease autoimmunity. [b] Ref. [28]. [c] Reference data from [10, 19, 20, 51, 52].

1980s (2.6 and 2.9%, respectively); however, in the 1990s and afterward, the rates decreased to 0.6%. The prevalence of screen-detected celiac disease autoimmunity was 2.8% in the 1980s and decreased thereafter (0–0.7%) (Table 2). For comparison, the prevalence rates of the bowel diseases in the Finnish general population are presented in Table 2. Low positive tTGA values ranging from 3.1 to 7.0 U were found in 10 patients (4.7%) in the 1980s, in 1 patient (0.8%) in the 1990s, and in 10 patients (6.9%) during the years 2000–2012.

Among the 552 patients biopsied in 1980 or later, one of the patients was diagnosed with celiac disease before the kidney biopsy, 2 patients at the same episode of care, and 3 patients after the kidney biopsy (2, 8, and 2 years). The exact time of diagnosing celiac disease was not known in 2 patients. Respectively, 10 patients had been diagnosed for IBD before the kidney biopsy and 5 patients thereafter (10, 16, 17, 5, and 12 years).

## Discussion

The prevalence of IBD is increasing with time in populations of the Western countries [9]. The rising prevalence has been explained by modern lifestyle, dietary habits, widespread use of antibiotics, diminishing parasite infections, and improved diagnostics of IBD [32]. In the present study, the prevalence of IBD in patients with IgAN was 7-fold higher than that in the Finnish general population and 5.5-fold when compared with British nationwide rates [10, 33].

There were some changes over time in clinical practices regarding when to obtain a kidney biopsy: hematuria alone was more often an indication for biopsy in the 1980s when compared with later decades [29]. The higher urinary protein excretion rate during years 2000–2012 when compared with previous years reflects the same shift in the biopsy indications. In the present study cohort, however, no difference in the prevalence of IBD was found in patients who had proteinuria at the time of kidney biopsy compared to patients without proteinuria. Thus, the rising prevalence of IBD in patients with IgAN over time cannot be explained by the changes in biopsy indications.

The rising prevalence of IBD among IgAN patients can be logically explained by biological terms. Currently, the gut-kidney axis in IgAN is under active research. It seems that gut microbiota, dysregulated intestinal mucosal immunity, genetics, and dietary factors have an influence on inducing intestinal immune responses and favoring the development of IgAN [34]. Previous genome-wide association studies have suggested a shared genetic background of IgAN and IBD while genetic risk loci involved in IgAN have been shown to be associated with IBD [35]. Besides, a case-control association study by Shi et al. [36] discovered a shared susceptibility gene between IgAN and IBD, which may be linked with the predisposition to IgAN. Some studies have suggested that human leukocyte antigen (HLA)-DR1, abnormal T-helper lymphocytes, and cytokine IL-17 are common factors providing a link between IBD and IgAN [37–41]. However, the pathophysiological link between IBD and IgAN remains a matter of debate [37].

Like in the case of IBD, a real increase in the incidence and prevalence of celiac disease has been shown in Finland and globally [19, 42]. Surprisingly, in this study cohort, the prevalence of clinically detected celiac disease and screen-detected celiac disease autoimmunity decreased among patients with IgAN during the last decades. Intriguingly, the same phenomenon is seen in the

incidence and prevalence rates of dermatitis herpetiformis, one of the most well-known extraintestinal phenotypes of celiac disease [43, 44]. It has been hypothesized that dermatitis herpetiformis might be a consequence of undiagnosed and untreated celiac disease. Hence, screening and finding celiac disease earlier and starting the treatment in the early stage might prevent the skin manifestation of celiac disease from developing [43, 44]. This kind of theory might apply for the decreasing prevalence of celiac disease among IgAN patients – it has been previously suggested that when possible celiac disease is already treated with gluten-free diet, the clinical progression of IgAN might slow down and hence the association between these diseases could not be shown [26, 27].

Theoretically, the changing treatment protocols of IgAN in the 1980s, such as corticosteroids, might have had some effects on possible mucosal inflammation and its increased permeability and consequently influenced the condition of the bowel mucosa. However, this kind of theory should not only apply for celiac disease but also for IBD. As for the possible common mechanism between celiac disease and IgAN, the connection between gluten, transglutaminase 2, and transferrin receptor 1, dysfunction of the IgA system, and antibodies against gliadin might have a possible role in this association [2, 45–49].

As in many previously published prevalence studies, small bowel biopsy was not conducted to patients having positive tTGA levels. However, previous studies suggest that high positive tTGA values are connected with positive predictive value for celiac disease [50]. Further, positive serology has been used as a serological marker of celiac disease in many epidemiological studies [18, 19]. In addition, in the 1980s and in the beginning of the 21st century, there was a remarkable amount of IgAN patients with low positive tTGA values; nevertheless, the clinical meaning of this finding is not known.

There are many strengths in this unique study. The renal biopsies and serum samples were collected prospectively. The kidney biopsies were conducted in 1 hospital and interpreted by the same pathologists [25]. The follow-up data were extensive covering over 500 patients from 4 decades. The medical records were systematically analyzed by 2 investigators with the same criteria. Nevertheless, the data concerning the follow-up were retrospective. Furthermore, the clinical data of patients undergoing kidney biopsies during 1976–1979 were not available. Medical records of 39 patients biopsied afterward were lacking. Besides, we were not able to collect data on gluten-free diet and hence there was no possibility to evaluate the effect of the diet for renal function.

Several lines of evidence indicate that IBD and celiac disease may be linked with IgAN, even though the exact mechanisms remain unclear [2, 6, 11, 22–24]. Nevertheless, our data show that IBD is more common in patients with IgAN than in the general population [10, 51]. As far as we know, despite some suggested associations between bowel diseases and IgAN, no clinical guidelines for the systematic screening of bowel diseases in IgAN have been introduced. According to our study, the possibility of a coexisting IBD would be important to recognize when treating patients with IgAN.


## Acknowledgements

The valuable work of Dr. Ole Wirta (MD, PhD) is greatly appreciated.


## Statement of Ethics

The study protocol was approved by the Ethical Committee of Tampere University Hospital. All subjects gave written informed consent at the time of kidney biopsy.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

This study was supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (9T018, 9S020, and 9S059), the Academy of Finland, the Sigrid Jusélius Foundation, the Finnish Foundation for Cardiovascular Research, Seinäjoki Central Hospital (VTR16), the Finnish Celiac Society, Tampere University Doctoral School, and the Finnish Kidney and Liver Association. The funding sources had no involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.


## Author Contributions

All authors participated in the design of the study. R.N., J.P., M.M., and J.M. collected the data. R.N., H.H., and O.N. analyzed the data. R.N. drafted the article. All authors reviewed and edited the manuscript and approved the final draft.

## References


1 Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013 Jun;368(25):2402–14.
2 Floege J, Feehally J. The mucosa-kidney axis in IgA nephropathy. Nat Rev Nephrol. 2016 Mar;12(3):147–56.
3 Coppo R. The intestine-renal connection in IgA nephropathy. Nephrol Dial Transplant. 2015 Mar;30(3):360–6.
4 Honkanen T, Mustonen J, Kainulainen H, Myllymäki J, Collin P, Hurme M, et al. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. Kidney Int. 2005 Jun;67(6):2187–95.
5 Kovács T, Kun L, Schmelczer M, Wagner L, Davin JC, Nagy J. Do intestinal hyperpermeability and the related food antigens play a role in the progression of IgA nephropathy? I. Study of intestinal permeability. Am J Nephrol. 1996;16(6):500–5.
6 Pouria S, Barratt J. Secondary IgA nephropathy. Semin Nephrol. 2008 Jan;28(1):27–37.
7 Saha MK, Julian BA, Novak J, Rizk DV. Secondary IgA nephropathy. Kidney Int. 2018 Oct;94(4):674–81.
8 Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009 Nov;361(21):2066–78.
9 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46–e30.
10 Jussila A, Virta LJ, Salomaa V, Mäki J, Jula A, Färkkilä MA. High and increasing prevalence of inflammatory bowel disease in Finland with a clear North-South difference. J Crohns Colitis. 2013 Aug;7(7):e256–62.
11 Filiopoulos V, Trompouki S, Hadjiyannakos D, Paraskevakou H, Kamperoglou D, Vlassopoulos D. IgA nephropathy in association with Crohn's disease: a case report and brief review of the literature. Ren Fail. 2010 May;32(4):523–7.
12 Forshaw MJ, Guirguis O, Hennigan TW. IgA nephropathy in association with Crohn's disease. Int J Colorectal Dis. 2005 Sep;20(5):463–5.
13 Vegh Z, Macsai E, Lakatos L, Lakatos PL. The incidence of glomerulonephritis in a population-based inception cohort of patients with inflammatory bowel disease. Dig Liver Dis. 2017 Jun;49(6):718–9.
14 Pohjonen J, Nurmi R, Metso M, Oksanen P, Huhtala H, Pörsti I, et al. Inflammatory bowel disease in patients undergoing renal biopsies. Clin Kidney J. 2019 Feb;12(5):645–51.
15 Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol. 2014 Feb;9(2):265–70.
16 Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013 Jan;62(1):43–52.
17 Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014 Aug;63(8):1210–28.
18 Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010 Dec;42(8):587–95.
19 Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther. 2007 Sep;26(9):1217–25.
20 Ilus T, Kaukinen K, Virta LJ, Huhtala H, Mäki M, Kurppa K, et al. Refractory coeliac disease in a country with a high prevalence of clinically-diagnosed coeliac disease. Aliment Pharmacol Ther. 2014 Feb;39(4):418–25.
21 Ravikumara M, Tuthill DP, Jenkins HR. The changing clinical presentation of coeliac disease. Arch Dis Child. 2006 Dec;91(12):969–71.
22 Collin P, Syrjänen J, Partanen J, Pasternack A, Kaukinen K, Mustonen J. Celiac disease and HLA DQ in patients with IgA nephropathy. Am J Gastroenterol. 2002 Oct;97(10):2572–6.
23 Welander A, Sundelin B, Fored M, Ludvigsson JF. Increased risk of IgA nephropathy among individuals with celiac disease. J Clin Gastroenterol. 2013 Sep;47(8):678–83.
24 Moeller S, Canetta PA, Taylor AK, Arguelles-Grande C, Snyder H, Green PH, et al. Lack of serologic evidence to link IgA nephropathy with celiac disease or immune reactivity to gluten. PLoS One. 2014 Apr;9(4):e94677.
25 Nurmi R, Metso M, Pörsti I, Niemelä O, Huhtala H, Mustonen J, et al. Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies. Dig Liver Dis. 2018 Jan;50(1):27–31.
26 Coppo R, Amore A, Roccatello D. Dietary antigens and primary immunoglobulin A nephropathy. J Am Soc Nephrol. 1992 Apr;2(10 Suppl):S173-80.
27 Koivuviita N, Tertti R, Heiro M, Metsärinne K. A case report: a patient with IgA nephropathy and coeliac disease. Complete clinical remission following gluten-free diet. NDT Plus. 2009 Apr;2(2):161–3.
28 Mustonen J, Pasternack A. Associated diseases in IgA nephropathy. In: Clarkson AR, editor. IgA Nephropathy. Topics in Renal Medicine. Boston: Springer; 1987. Vol. 2; p. 47–65.
29 Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. Nephrol Dial Transplant. 2008 Jan;23(1):193–200.
30 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013 Jan;3(1):1–150.
31 Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012 Jan;54(1):136–60.
32 Yamamoto-Furusho JK, Sarmiento-Aguilar A, Toledo-Mauriño JJ, Bozada-Gutiérrez KE, Bosques-Padilla FJ, Martínez-Vázquez MA, et al. Incidence and prevalence of inflammatory bowel disease in Mexico from a nationwide cohort study in a period of 15 years (2000–2017). Medicine. 2019 Jul;98(27):e16291.
33 Jones GR, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, et al. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. Gut. 2019 Nov;68(11):1953–60.
34 Coppo R. The gut-kidney axis in IgA nephropathy: role of microbiota and diet on genetic predisposition. Pediatr Nephrol. 2018 Jan;33(1):53–61.
35 Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014 Nov;46(11):1187–96.
36 Shi D, Zhong Z, Wang M, Cai L, Fu D, Peng Y, et al. Identification of susceptibility locus shared by IgA nephropathy and inflammatory bowel disease in a Chinese Han population. J Hum Genet. 2020 Mar;65(3):241–9.
37 Choi JY, Yu CH, Jung HY, Jung MK, Kim YJ, Cho JH, et al. A case of rapidly progressive IgA nephropathy in a patient with exacerbation of Crohn's disease. BMC Nephrol. 2012 Aug;13(1):84.
38 Freedman BI, Spray BJ, Heise ER. HLA associations in IgA nephropathy and focal and segmental glomerulosclerosis. Am J Kidney Dis. 1994 Mar;23(3):352–7.
39 Toyoda H, Wang SJ, Yang HY, Redford A, Magalong D, Tyan D, et al. Distinct associations of HLA class II genes with inflammatory bowel disease. Gastroenterology. 1993 Mar;104(3):741–8.
40 Veny M, Esteller M, Ricart E, Piqué JM, Panés J, Salas A. Late Crohn's disease patients present an increase in peripheral Th17 cells and cytokine production compared with early patients. Aliment Pharmacol Ther. 2010 Mar;31(5):561–72.
41 Lin FJ, Jiang GR, Shan JP, Zhu C, Zou J, Wu XR. Imbalance of regulatory T cells to Th17 cells in IgA nephropathy. Scand J Clin Lab Invest. 2012 May;72(3):221–9.

42 Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ. Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. Clin Gastroenterol Hepatol. 2003 Jan;1(1):19–27.
43 Salmi TT, Hervonen K, Kautiainen H, Collin P, Reunala T. Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland. Br J Dermatol. 2011 Aug;165(2):354–9.
44 West J, Fleming KM, Tata LJ, Card TR, Crooks CJ. Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. Am J Gastroenterol. 2014 May;109(5):757–68.
45 Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Thamcharoen N, Pachariyanon P, Nakkala K, et al. Celiac disease and the risk of kidney diseases: A systematic review and meta-analysis. Dig Liver Dis. 2016 Dec;48(12):1418–24.
46 Smerud HK, Fellström B, Hällgren R, Osagie S, Venge P, Kristjánsson G. Gluten sensitivity in patients with IgA nephropathy. Nephrol Dial Transplant. 2009 Aug;24(8):2476–81.
47 Berthelot L, Papista C, Maciel TT, Biarnes-Pelicot M, Tissandie E, Wang PH, et al. Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. J Exp Med. 2012 Apr;209(4):793–806.
48 Papista C, Berthelot L, Monteiro RC. Dysfunctions of the Iga system: a common link between intestinal and renal diseases. Cell Mol Immunol. 2011 Mar;8(2):126–34.
49 Almroth G, Axelsson T, Müssener E, Grodzinsky E, Midhagen G, Olcén P. Increased prevalence of anti-gliadin IgA-antibodies with aberrant duodenal histopathological findings in patients with IgA-nephropathy and related disorders. Ups J Med Sci. 2006;111(3):339–52.
50 Fuchs V, Kurppa K, Huhtala H, Laurila K, Mäki M, Collin P, et al. Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. Aliment Pharmacol Ther. 2019 Feb;49(3):277–84.
51 Manninen P, Karvonen AL, Huhtala H, Rasmussen M, Collin P. The epidemiology of inflammatory bowel diseases in Finland. Scand J Gastroenterol. 2010 Sep;45(9):1063–7.
52 Collin P, Reunala T, Rasmussen M, Kyrönpalo S, Pehkonen E, Laippala P, et al. High incidence and prevalence of adult coeliac disease. Augmented diagnostic approach. Scand J Gastroenterol. 1997 Nov;32(11):1129–33.

# PUBLICATION III

## Presence of Gastrointestinal Symptoms in IgA Nephropathy: a Cross-Sectional Study

Jussi Pohjonen, Katri Kaukinen, Martti Metso, Rakel Nurmi, Heini Huhtala, Ilkka Pörsti, Jukka Mustonen, Satu Mäkelä

BMC Nephrology. 2022;23:395.
doi:10.1186/s12882-022-03019-8

Pohjonen *et al. BMC Nephrology (2022) 23:395*
https://doi.org/10.1186/s12882-022-03019-8

BMC Nephrology

**RESEARCH** **Open Access**

# Presence of gastrointestinal symptoms in IgA nephropathy: a cross-sectional study

Jussi T. Pohjonen[1,2*], Katri M. Kaukinen[1,2], Martti J. Metso[2], Rakel KK. Nurmi[1], Heini SA. Huhtala[3], Ilkka H. Pörsti[2,4], Jukka T. Mustonen[2,4] and Satu M. Mäkelä[2,4]

## Abstract

**Background:** Gastrointestinal (GI) symptoms are common in end-stage kidney disease. Mounting evidence indicates that the intestine plays an important role in the pathogenesis of IgA nephropathy (IgAN). However, no studies have addressed the obvious question; do IgAN patients suffer from GI symptoms?

**Methods:** Presence of GI symptoms and health-related quality of life were evaluated using the validated Gastrointestinal Symptom Rating Scale (GSRS) and Psychological General Well-Being (PGWB) questionnaires in 104 patients with kidney biopsy-verified IgAN and in 147 healthy controls. A person was regarded to experience 'increased GI symptoms' if the GSRS score exceeded plus 1 standard deviation of the mean of the corresponding score in the healthy controls.

**Results:** According to the GSRS total score, the IgAN patients had more GI symptoms than the healthy controls (2.0 vs. 1.7, $p < 0.001$). Female IgAN patients had higher GSRS total score than male patients (2.2 vs. 1.7, $p = 0.001$). More IgAN patients with preserved kidney function (eGFR > 60ml/min/1.73m$^2$) suffered from increased symptoms of diarrhoea (76 vs. 25%, $p = 0.028$), constipation (81 vs. 19%, $p = 0.046$) and reflux (85 vs. 15%, $p = 0.004$) than did IgAN patients with reduced kidney function (eGFR < 60ml/min/1.73m$^2$).

**Conclusions:** IgAN patients and especially female IgAN patients experienced more GI symptoms than healthy controls. More prevalent GI symptoms were already observed before kidney function was clearly reduced. Systematic enquiry of GI symptoms might increase the standard of care among IgAN patients. Moreover, GI symptoms may provide clues for future studies that examine the pathophysiology of IgAN.

**Keywords:** Chronic kidney disease (CKD), Gastrointestinal Symptom Rating Scale (GSRS), IgA nephropathy (IgAN), Psychological General Well-Being Index (PGWB)

## Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally and a notable cause of chronic kidney disease (CKD) and kidney failure [1]. Although the pathogenetic mechanisms of IgAN have not been fully determined, there is mounting evidence that abnormal mucosal immune responses, especially in the intestine, play a role in the disease process [2, 3].

An increased intestinal permeability is present in IgAN [4]. Subclinical small bowel mucosal inflammation has been demonstrated in IgAN patients [5, 6]. The finding of an abundance of intestinal intraepithelial T lymphocytes in IgAN has since been replicated [7]. Associations between IgAN and coeliac disease (CD) are convincing [8–12]. Kidney involvement in inflammatory bowel disease (IBD) is well documented [12–16]. Furthermore, therapy with enteric budesonide targeted at the intestine

*Correspondence: jussi.pohjonen@tuni.fi

[1] Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, FIN-33014 Tampere, Finland
Full list of author information is available at the end of the article

has reportedly reduced the amount of albuminuria in IgAN [17].

Gastrointestinal (GI) symptoms are common in patients with renal insufficiency [18–20]. The prevalence of GI symptoms has mostly been studied in patients with end-stage kidney disease (ESKD) or after kidney transplantation [21–27]. Only few studies have examined the presence of GI symptoms in patients with less advanced CKD [28, 29].

The aim of this study was to evaluate the presence of GI symptoms in IgAN patients with no diagnosed enteropathies and not progressed to ESKD, and to compare the results to those of healthy controls. Health-related quality of life was surveyed simultaneously. We also aimed to identify the predictors of the assumed GI complaints in IgAN.

## Materials and methods

### Design and study population

A single-centre cross-sectional study was carried out at the Tampere University Hospital (TAUH) and Tampere University, Finland. The TAUH district is an area with a high standard of living and a population of more than 500.000, nearly totally of Caucasian origin. About one hundred kidney biopsies are taken in TAUH annually due to clinical indications [30]. A total of 533 patients with biopsy-proven IgAN diagnosed between 1980 to 2018 were included. The definition of IgAN was based on clinical details and on the presence of glomerular IgA as the sole or predominant immunofluorescence finding [31].

The clinical histories of the 533 IgAN patients were collected from the medical records. Based on the following predefined exclusion criteria, 327 patients were excluded: death ($n=51$), progression to ESKD (defined as estimated glomerular filtration rate (eGFR) < 15/ml/min/1.73m$^2$, initiation of maintenance dialysis or kidney transplantation, $n=64$), age under 18 or over 80 at recruitment ($n=78$), known chronic enteropathy (CD or IBD, $n=16$) [12], moving to another hospital district ($n=79$), or other obvious reason for exclusion (major GI surgery performed, missing contact information, short life-expectancy for any reason, or a labile mental disorder, $n=39$). Study questionnaires were posted to the remaining 206 patients in August 2019. The patients were requested to return the questionnaires and the signed informed consent forms within one month. For those who did not return the forms, we verified the contact information and posted the forms in a similar manner once again.

The healthy controls were selected from a group originally comprising 160 people, who had participated in our earlier study [32]. As we restricted them to the same age (18 to 80) as the IgAN patients, the remaining number of available healthy controls was 147. The group was used for the comparison of gastrointestinal symptoms and quality of life. These subjects had no known intestinal diseases at the time of participation, nor did they have first-degree relatives with CD. No laboratory testing had been performed, thus no information, for example on actual kidney function, was available.

### Study questionnaires

For the systematic evaluation of current GI symptoms, all participants completed the self-administered, structured, and well-validated Gastrointestinal Symptom Rating Scale (GSRS) questionnaire [33–35]. The questionnaire evaluates five sub-dimensions of gastrointestinal symptoms: indigestion, diarrhoea, abdominal pain, reflux, and constipation. It comprises altogether 15 separate items. The scoring goes from 1 to 7 points, where 1 point signifies no symptoms, and 7 points signifies the most severe symptoms. The values for each of the five sub-dimension scores were calculated as a mean of the respective items and the total GSRS score as a mean of all 15 items. A person was deemed to suffer from 'increased GI symptoms' if the total GSRS score exceeded plus 1 standard deviation (SD) of the mean of the total score in the healthy controls [32]. The same principle was applied to the GSRS sub-scores: 'increased symptoms' were taken to be present if an individual's score exceeded plus 1 SD of the mean of the corresponding sub-score in the healthy controls.

All participants also completed the self-administered, validated questionnaire to measure health-related quality of life, the Psychological General Well-Being (PGWB) questionnaire [36–38]. The survey consists of 22 separate items covering six different sub-dimensions: anxiety, depression, wellbeing, self-control, general health, and vitality. The scoring goes from 1 to 6 points, higher score indicating better quality of life. The sub-dimension scores are calculated as a sum of the items in each sub-dimension and the total PGWB score as a sum of all 22 items.

For the IgAN patients, in addition, information about co-morbidities, and current height and weight was elicited. Tobacco and alcohol consumption were evaluated with standardized tools: The Fagerström Test for Nicotine Dependence and the Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire respectively [39, 40].

### Clinical data

The clinical data for IgAN patients was collected retrospectively from the medical records between 2019 and 2020. We collected data on medications used during the preceding year (antibiotics as courses of treatment), information on possible abdominal surgery and visits and

treatments at the nephrological outpatient clinic or ward. Follow-up at the nephrological unit was deemed active if a patient had made one visit during the preceding year and a control visit had been planned. Laboratory test results regarding kidney function were collected for no later than one year preceding the study recruitment.

Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [41]. eGFR > 60ml/min/1.73m$^2$ was regarded as preserved kidney function. Body mass index (BMI) was calculated according to numbers reported in the study questionnaire, by dividing the weight (kilograms) by the square of height (metres).

### Statistical methods

The data are presented as medians and interquartile ranges (IQR) for most of the continuous variables and as percentages for the categorical variables. If a patient failed to answer one or two items in the GSRS or PGWB questionnaires, the missing answer was replaced by the mean value of the other scores for the same subject. If more than two answers were missing, the questionnaire was rejected.

The groups were compared using the Chi-square test, Fisher's exact test or the Mann–Whitney *U*-test, as appropriate. Binary logistic regression analysis was applied to identify factors for increased GI symptoms. Three covariates were used to avoid overfitting the model. The associations are presented as odds ratios (OR) with 95% confidence intervals (CI).

All tests were two-sided, and *p*-values less than 0.05 were considered statistically significant. All statistical testing was performed using SPSS version 27.0 (IBM SPSS, NY, USA).

### Ethical considerations

The study protocol was approved by the Ethics Committee of the Tampere University Hospital (R18215). All study participants provided written informed consent.

## Results

### Clinical characteristics

Altogether 104 IgAN patients participated in the study. Median age was 55 years, 54% were males and median BMI was 29. Median time from the kidney biopsy was 11 years. Information about current kidney function was available from 82 patients and was preserved (eGFR > 60ml/min/1.73m$^2$) in 56% of them. Sixty-three per cent of the patients with preserved kidney function were females.

Female IgAN patients were younger, their BMI was slightly lower, they had better kidney function, and they more often reported concomitant thyroid diseases than male patients. IgAN patients' detailed characteristics are presented sex-based in Table 1.

There was a clear female preponderance (72%) among the healthy controls. The median age of the healthy controls was 54 years (42–68), so the groups did not differ in age ($p = 0.979$). Women were younger than men in the healthy controls, too ($p < 0.001$).

### Gastrointestinal symptoms and health-related quality of life

Compared to healthy controls, patients with IgAN reported more GI symptoms as determined by higher GSRS total score (2.0 vs. 1.7, $p < 0.001$). The GSRS subscores for diarrhoea, indigestion, reflux, and abdominal pain were also significantly higher among the patients than in controls (Table 2). Female IgAN patients had higher GSRS total score and sub-scores of indigestion, constipation and abdominal pain than male IgAN patients (Table 3). Total GSRS score did not differ between male IgAN patients and male controls (1.7 vs. 1.7, $p = 0.411$), but male IgAN patients had a higher sub-score for diarrhoea (1.7 vs. 1.3, $p = 0.025$). GSRS questionnaires were rejected for two participants among the healthy controls, and for one IgAN patient due to insufficient completion of the questionnaire.

PGWB total score as well as general health and vitality sub-scores were significantly inferior in patients with IgAN than those in healthy controls (Table 2). PGWB scores did not differ between female and male IgAN patients (Table 3). PGWB questionnaires of five participants among the healthy controls and one IgAN patient were rejected due to incomplete response to the questionnaire.

Prevalence of increased GI symptoms was more common in IgAN patients than among healthy controls (Fig. 1) and significantly more so when female IgAN patients were compared with healthy women (Fig. 2). No differences were observed in the prevalence of increased GI symptoms between male IgAN patients and healthy males (data not shown). IgAN patients with preserved kidney function reported increased GI symptoms more often than IgAN patients with reduced kidney function in the GSRS sub-scores for diarrhoea (76 vs. 25%, $p = 0.028$), constipation (81 vs. 19%, $p = 0.046$) and reflux (85 vs. 15%, $p = 0.004$). In a multivariable logistic regression analysis of risk factors for increased

**Table 1** Clinical characteristics of the 104 IgA nephropathy patients. Values are medians (interquartile range) unless otherwise indicated

| Patient characteristics | Females | Males | *p*-value |
|---|---|---|---|
| Number of subjects | 48 | 56 | |
| Current age, years | 52 (37–58) | 59 (51–70) | < 0.001 |
| Current body mass index, kg/m$^2$ | 27 (24–32) | 29 (27–33) | 0.048 |
| Current smoker, % | 19 | 7 | 0.135 |
| Risky alcohol use[a], % | 23 | 29 | 0.654 |
| Coexisting conditions, % | | | |
| Hypertension | 40 | 63 | 0.030 |
| Diabetes | 8 | 16 | 0.373 |
| Asthma or chronic obstructive pulmonary disease | 17 | 14 | 0.790 |
| Sleep apnoea | 10 | 10 | 1.000 |
| Rheumatic disease | 13 | 7 | 0.507 |
| Thyroid disease | 21 | 4 | 0.011 |
| Cancer; active or treated | 6 | 2 | 0.333 |
| Depression | 10 | 5 | 0.334 |
| Medication during the year before the study, % | | | |
| Blood pressure lowering | 69 | 84 | 0.101 |
| Lipid lowering | 31 | 43 | 0.310 |
| Glucose lowering | 9 | 13 | 0.750 |
| Immunosuppressive | 8 | 4 | 0.299 |
| Antibiotics | 50 | 43 | 0.555 |
| Proton pump inhibitor | 23 | 23 | 1.000 |
| Active follow-up at the nephrological unit, % | 21 | 23 | 0.816 |
| Time since diagnostic kidney biopsy, years | 10 (4–20) | 11 (6–20) | 0.150 |
| Current kidney function, data available from 41 female and 41 male patients | | | |
| Estimated glomerular filtration rate (eGFR), ml/min/1.73m$^2$ | 78 (54–93) | 54 (36–68) | < 0.001 |
| eGFR < 60 ml/min/1.73m$^2$, % | 29 | 59 | 0.014 |

[a] For women 5 or more points, for men 6 or more points in the Alcohol Use Disorders Identification Test (AUDIT−C)

GI symptoms among IgAN patients, female sex was positively and PGWB total score negatively associated with the higher points in the GSRS total score (Table 4).

## Discussion

IgAN patients had higher prevalence of GI symptoms than did healthy subjects, and especially female patients with IgAN were more symptomatic than males. An interesting finding was female IgAN patients experiencing increased GI symptoms more often compared to healthy women. Even though male IgAN patients had the same GSRS total score as healthy males, they had higher scores regarding diarrhoea. Interestingly, IgAN patients with preserved kidney function reported more often increased symptoms of diarrhoea, constipation, and reflux than patients with reduced kidney function. IgAN patients experienced poorer health-related quality of life than healthy controls, especially regarding general health and vitality. Furthermore, poorer quality of life associated with increased GI symptoms.

GI symptoms have not previously been evaluated in such a well-defined kidney disease population as in the present study. The fact that diagnosed intestinal diseases were excluded from the current study diminishes the possibility of the findings being biased by the presence of concomitant IBD or CD. In an earlier study where variable diseases had led to CKD stage 4 but dialysis was not yet required (eGFR < 25 ml/min/1.73m$^2$), the median of the GSRS total score was 1.84 and the median for the sub-scores were as follows: diarrhoea 1.67, indigestion 2.12, constipation 1.67, reflux 1.00 and abdominal pain 1.50 [21]. In the present study, all sub-scores, and thus also the total score, were at least as high among the IgAN patients. The GSRS total score of 2.0 (1.5–2.7) in IgAN patients in our study was close to the score of the peritoneal dialysis (PD) patients in the aforementioned study (2.07, 1.48–3.08) [21]. PD patients are well known to suffer from excess of GI symptoms [25, 26, 42].

**Table 2** Comparison of GSRS and PGWB scores (median and interquartile range) between IgA nephropathy (IgAN) patients and healthy controls

| | IgAN patients | Healthy controls | *p*-value |
|---|---|---|---|
| GSRS, number of subjects[a] | 103 | 145 | |
| Total score | 2.0 (1.5–2.7) | 1.7 (1.4–2.2) | < 0.001 |
| *Diarrhoea* | 1.7 (1.0-2.7) | 1.3 (1.0–2.0) | < 0.001 |
| *Indigestion* | 2.5 (2.0-3.3) | 2.3 (1.6–2.8) | 0.020 |
| *Constipation* | 1.7 (1.0-2.3) | 1.3 (1.0–2.0) | 0.093 |
| *Reflux* | 1.5 (1.0-2.5) | 1.0 (1.0-1.5) | < 0.001 |
| *Abdominal pain* | 1.7 (1.3–2.3) | 1.7 (1.0–2.0) | 0.006 |
| PGWB, number of subjects[b] | 103 | 142 | |
| Total score | 104 (95–113) | 109 (101–115) | 0.015 |
| *Anxiety* | 25 (22–27) | 25 (23–27) | 0.292 |
| *Depression* | 17 (16–18) | 17 (16–18) | 0.656 |
| *Wellbeing* | 17 (15–19) | 18 (16–19) | 0.585 |
| *Self-control* | 16 (15–17) | 16 (14–17) | 0.243 |
| *General health* | 13 (10–14) | 15 (13–16) | < 0.001 |
| *Vitality* | 17 (15–19) | 19 (17–21) | < 0.001 |

*GSRS* Gastrointestinal Symptom Rating Scale, *PGWB* Psychological General Well−being Index

[a] GSRS rejected for two healthy controls and one IgAN patient due to incomplete questionnaire

[b] PGWB disqualified for five healthy controls and one IgAN patient due to incomplete questionnaire

**Table 3** Sex-based comparison of GSRS and PGWB scores (median and interquartile range) in IgA nephropathy patients

| | Female | Male | *p*-value |
|---|---|---|---|
| GSRS, number of subjects[a] | 47 | 56 | |
| Total score | 2.2 (1.8–2.9) | 1.7 (1.5–2.3) | 0.001 |
| *Diarrhoea* | 1.7 (1.0-3.7) | 1.7 (1.3–2.3) | 0.767 |
| *Indigestion* | 3.0 (2.3–3.5) | 2.3 (1.8-3.0) | 0.005 |
| *Constipation* | 2.3 (1.3–3.7) | 1.3 (1.0–2.0) | < 0.001 |
| *Reflux* | 1.8 (1.0–3.0) | 1.5 (1.0–2.0) | 0.178 |
| *Abdominal pain* | 2.2 (1.7–2.7) | 1.7 (1.3-2.0) | < 0.001 |
| PGWB, number of subjects[b] | 48 | 55 | |
| Total score | 103 (90–112) | 105 (98–114) | 0.217 |
| *Anxiety* | 25 (20–27) | 25 (22–27) | 0.145 |
| *Depression* | 17 (15–18) | 17 (16–18) | 0.261 |
| *Wellbeing* | 18 (14–19) | 17 (16–19) | 0.576 |
| *Self-control* | 16 (14–17) | 16 (15–17) | 0.218 |
| *General health* | 13 (10–15) | 13 (11–14) | 0.223 |
| *Vitality* | 17 (15–20) | 17 (16–19) | 0.632 |

*GSRS* Gastrointestinal Symptom Rating Scale, *PGWB* Psychological General Well−Being Index

[a] GSRS rejected for one IgAN patient due to incomplete questionnaire

[b] PGWB disqualified for one IgAN patient due to incomplete questionnaire

Why did female IgAN patients suffer more often from GI symptoms than male IgAN patients? In general, irritable bowel syndrome (IBS) is more common in women than in men [43]. IBS was also more common among Turkish female than male dialysis patients [44]. Yet, no differences were found in the presence of GI symptoms between sexes in two studies evaluating ESKD patients [21, 42]. Among Australian kidney transplant patients, women again experienced more GI symptoms [27]. Thirty-nine percent of those patients had glomerulonephritis as the primary kidney disease. The sex disparity was speculated to be explained by e.g. hormonal levels, composition of gastrointestinal microbiota, and the finding of women reporting more GI symptoms to health care professionals when compared with men [27]. One explanation could be abdominal discomfort and pain related to the menstrual cycle in fertile-aged women. Still, despite any of the reasons speculated above, female controls in the current study experienced significantly less GI symptoms compared to female IgAN patients.

The present study was unique in focusing on patients with fairly well preserved kidney function; over 50% of the patients had eGFR above 60 ml/min/1.73m$^2$. Conventionally, the presence of GI symptoms has been studied in patients who have progressed to ESKD [25, 42]. To the best of our knowledge, only one study has so far evaluated the presence of GI symptoms with the GSRS questionnaire in CKD patients not on dialysis and before transplantation [21]. The other two studies that evaluated the presence of GI symptoms in patients who had not progressed to ESKD used a self-administered patient symptom form, which elicited GI symptoms originally presented in the Modification of Diet in Renal Disease (MDRD) study [28, 29] 'Abdominal bloating or gas' were among the most commonly reported symptoms in the MDRD study [28]. Moreover, the GI symptoms were reported to emerge long before ESKD, but still only after eGFR had fallen below 45 ml/min/1.73m$^2$ [28]. In the latter study, GI symptoms became more common as kidney function declined, the one exception being 'abdominal bloating or gas', which was equally common and frequently experienced with preserved kidney function [29]. So, why did IgAN patients with better kidney function report increased symptoms of diarrhoea, constipation, and reflux more often than those with reduced kidney function in our study? Etiology of GI symptoms is multifactorial, e.g. higher age diminishes the prevalence of IBS symptoms whereas increased IP and mucosal inflammation likely activate visceral pain in some IBS patients [43, 45]. If GI tract plays a role in the pathogenesis of IgAN, the possible mechanisms might differ between the early and the advanced stages of the disease.

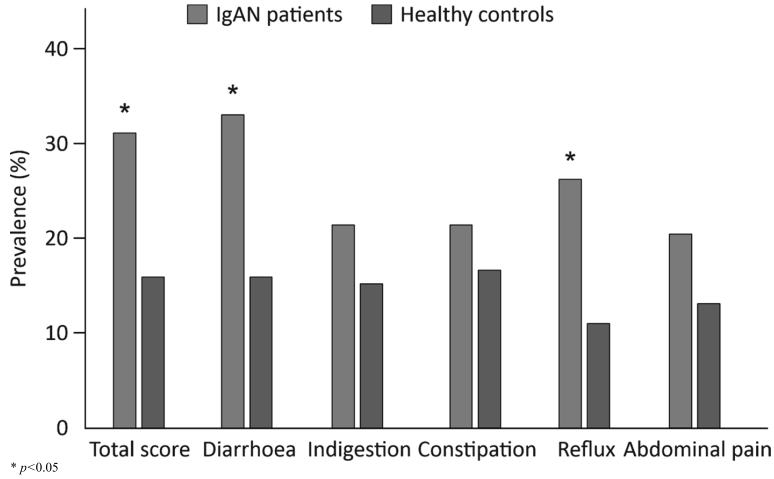


**Fig. 1** Prevalence of subjects with increased gastrointestinal symptoms in the study groups

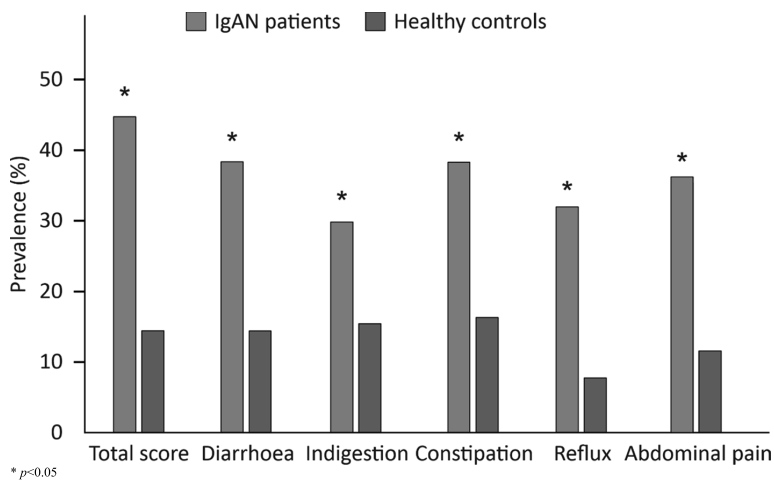


**Fig. 2** Prevalence of subjects with increased gastrointestinal symptoms in females

A well-defined and -sized group of patients with a definite diagnosis of IgAN is the strength of the current study. The male/female rate was similar as has been previously reported in IgAN and other glomerular diseases [30]. Exclusion of previously diagnosed intestinal diseases enabled us to focus on the study hypothesis of IgAN patients experiencing GI symptoms without clinically evident enteropathies. Information about kidney function was available in most cases and was most often regarded as normal, making our study population unique in abandoning the conventional idea of GI symptoms becoming prevalent first in advanced CKD.

Our study has some limitations. There was no control group with primary glomerulonephritides, which leaves it uncertain whether the patients experienced an excess of GI symptoms due to kidney disease in general or were the symptoms related with IgAN. The study was carried out in one centre, thus weakening the generalisability

**Table 4** Univariate and multivariable logistic regression analyses of risk factors for increased gastrointestinal symptoms among 103 IgA nephropathy patients

| | Univariate | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***p*-value** | **OR** | **95% CI** | ***p*-value** |
| Female sex | 3.30 | 1.38–7.93 | 0.007 | 2.80 | 1.08–7.29 | 0.035 |
| PGWB total score | 0.96 | 0.93–0.99 | 0.008 | 0.96 | 0.93–1.00 | 0.026 |
| Age | 0.98 | 0.95–1.01 | 0.202 | 1.00 | 0.97–1.03 | 0.958 |
| Antibiotic courses | 2.25 | 0.96–5.26 | 0.063 | | | |
| Smoking | 3.03 | 0.93–9.91 | 0.066 | | | |
| Risky alcohol use[a] | 2.24 | 0.90–5.59 | 0.084 | | | |
| Thyroid disease | 3.05 | 0.86–10.85 | 0.086 | | | |
| PPI medication | 1.85 | 0.72–4.78 | 0.204 | | | |
| eGFR > 60ml/min/1.73m$^2$ | 1.80 | 0.67–4.87 | 0.247 | | | |
| Body mass index | 0.97 | 0.90–1.04 | 0.359 | | | |

*PGWB* Psychological General Well−being Index, *eGFR* estimated glomerular filtration rate, *PPI* proton pump inhibitor

[a] For women 5 or more points, for men 6 or more points in the Alcohol Use Disorders Identification Test (AUDIT−C)

of the results. The two study groups had answered the questionnaires years apart. Yet, the results of the healthy controls were consistent with the controls in previous studies [21, 34]. The kidney function was regarded as current, despite the laboratory tests had in many cases been taken months before the study participation, and the information was not available for one fifth of the IgAN patients at all. Taking the most often slowly progressive or stable nature of IgAN into account, it's unlikely that a significant proportion of the study patients would have had a rapidly progressive disease. Symptomatic patients might have participated more eagerly than asymptomatic patients. This too seems unlikely, as more than one half of the participating IgAN patients were men and their GSRS total score was comparable to that in the healthy controls. Female IgAN patients reported more often thyroid diseases than males, which might explain some of the GI symptoms experienced by females. Thyroid dysfunction in general is more prevalent in women compared to men [46]. Usually GI symptoms in thyroid diseases resolve with treatment [47].

## Conclusions

IgAN patients and especially female IgAN patients suffered from excess GI symptoms even though kidney function was well preserved, and no enteropathies had been diagnosed. Male IgAN patients had also higher scores regarding the presence of diarrhoea than male controls. More prevalent GI symptoms were associated with poorer quality of life, a finding consistent with previous studies [21, 23, 27]. The present findings suggest that routine eliciting of IgAN patients' GI symptoms would be an appropriate clinical practice. Even though GI symptoms have multifactorial explanations and are not related to IgAN only, perhaps symptoms like presence of loose stools could guide future studies in revealing the complex pathophysiology of IgAN.

#### Abbreviations

BMI: body mass index; CD: coeliac disease; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; GI: gastrointestinal; GSRS: Gastrointestinal Symptom Rating Scale; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; IgAN: IgA nephropathy; IP: intestinal permeability; IQR: interquartile range; PD: peritoneal dialysis; PGWB: Psychological General Well-Being Index.

#### Acknowledgements

The valuable work of Dr. Ole Wirta M.D, Ph.D. is greatly appreciated.

#### Authors' contributions

All authors participated in the design of the study. J.P. and M.M. collected the data. J.P. and H.H. analysed and interpreted the data. J.P. and K.K. drafted the article. All authors provided intellectual content of critical importance to the study, and read, revised, and approved the final manuscript.

#### Funding

This study was supported by the Academy of Finland, the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (9AA026, 9AA052, 9AB025, 9T039, MK303), the Finnish Coeliac Society, the Finnish Society of Nephrology, and the Sigrid Jusélius Foundation. The funding sources were not involved in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit the article for publication.

#### Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study protocol complied with the Helsinki Declaration standards and was approved by the Ethics Committee of the Tampere University Hospital (R18215). All study participants provided written informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, FIN-33014 Tampere, Finland. [2]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland. [3]Faculty of Social Sciences, Tampere University, Tampere, Finland. [4]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.

Received: 11 May 2022 Accepted: 28 November 2022
Published online: 08 December 2022

**References**

1. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. Clin J Am Soc Nephrol. 2017;12(4):677–86.
2. Coppo R. The intestine-renal connection in IgA nephropathy. Nephrol Dial Transplant. 2015;30(3):360–6.
3. Floege J, Feehally J. The mucosa-kidney axis in IgA nephropathy. Nat Rev Nephrol. 2016;12(3):147–56.
4. Rostoker G, Wirquin V, Terzidis H, et al. Mucosal Immun Prim Glomerulonephritis Nephron. 1993;63(3):286–90.
5. Rantala I, Collin P, Holm K, Kainulainen H, Mustonen J, Mäki M. Small bowel T cells, HLA class II antigen DR, and GroEL stress protein in IgA nephropathy. Kidney Int. 1999;55(6):2274–80.
6. Honkanen T, Mustonen J, Kainulainen H, et al. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. Kidney Int. 2005;67(6):2187–95.
7. Rostoker G, Delchier JC, Chaumette MT. Increased intestinal intra-epithelial T lymphocytes in primary glomerulonephritis. A role of oral tolerance breakdown in the pathophysiology of human primary glomerulonephritides? Nephrol Dial Transplant. 2001;16(3):513–7.
8. Collin P, Syrjänen J, Partanen J, Pasternack A, Kaukinen K, Mustonen J. Celiac disease and HLA DQ in patients with IgA nephropathy. Am J Gastroenterol. 2002;97(10):2572–6.
9. Pierucci A, Fofi C, Bartoli B, et al. Antiendomysial antibodies in Berger's disease. Am J Kidney Dis. 2002;39(6):1176–82.
10. Welander A, Sundelin B, Fored M, Ludvigsson JF. Increased risk of IgA nephropathy among individuals with celiac disease. J Clin Gastroenterol. 2013;47(8):678–83.
11. Nurmi R, Metso M, Pörsti I, et al. Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies. Dig Liver Dis. 2018;50(1):27–31.
12. Nurmi R, Pohjonen J, Metso M, et al. Prevalence of Inflammatory Bowel Disease and Celiac Disease in Patients with IgA Nephropathy over Time. Nephron. 2021;145(1):78–84.
13. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol. 2014;9(2):265–70.
14. Corica D, Romano C. Renal involvement in inflammatory bowel diseases. J Crohns Colitis. 2015;10(2):1–10.
15. Pohjonen J, Nurmi R, Metso M, et al. Inflammatory bowel disease in patients undergoing renal biopsies. Clin Kidney J. 2019;12(5):645–51.
16. Rehnberg J, Symreng A, Ludvigsson JF, Emilsson L. Inflammatory Bowel Disease Is More Common in Patients with IgA Nephropathy and Predicts Progression of ESKD: A Swedish Population-Based Cohort Study. J Am Soc Nephrol. 2021 Feb;32(2):411–23.
17. Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. The Lancet. 2017;389(10084):2117–27.
18. Shirazian S, Radhakrishnan J. Gastrointestinal disorders and renal failure: Exploring the connection. Nat Rev Nephrol. 2010;6(8):480–92.
19. Costa-Moreira P, Vilas-Boas F, Teixeira Fraga A, Macedo G. Particular aspects of gastroenterological disorders in chronic kidney disease and end-stage renal disease patients: a clinically focused review. Scand J Gastroenterol. 2020;55(2):129–38.
20. Sumida K, Yamagata K, Kovesdy CP. Constipation in CKD. Kidney Int Rep. 2020;5(2):121–34.
21. Strid H, Simrén M, Johansson AC, Svedlund J, Samuelsson O, Björnsson ES. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being. Nephrol Dial Transplant. 2002;17(8):1434–9.
22. Cano AE, Neil AK, Kang JY, et al. Gastrointestinal symptoms in patients with end-stage renal disease undergoing treatment by hemodialysis or peritoneal dialysis. Am J Gastroenterol. 2007;102(9):1990–7.
23. Ponticelli C, Colombo D, Novara M, Basilisco G. Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are underrecognized by physicians. Transpl Int. 2010;23(11):1126–34.
24. Dong R, Guo ZY, Ding JR, Zhou YY, Wu H. Gastrointestinal symptoms: A comparison between patients undergoing peritoneal dialysis and hemodialysis. World J Gastroenterol. 2014;20(32):11370–5.
25. Zuvela J, Trimingham C, le Leu R, et al. Gastrointestinal symptoms in patients receiving dialysis: A systematic review. Nephrology. 2018;23(8):718–27.
26. Kosmadakis G, Albaret J, da Costa Correia E, Somda F, Aguilera D. Gastrointestinal Disorders in Peritoneal Dialysis Patients. Am J Nephrol. 2018;48(5):319–25.
27. Chan S, Cao C, Pascoe EM, et al. Patient-Reported Gastrointestinal Symptoms and the Association With Quality of Life Following Kidney Transplantation. Kidney Int Rep. 2021;6(1):138–45.
28. Rocco M, Gassman JJ, Wang S, Kaplan RM. Cross-Sectional Study of Quality of Life and Symptoms in Chronic Renal Disease Patients: The Modification of Diet in Renal Disease Study. Am J Kidney Dis. 1997;29(6):888–96.
29. Zhang X, Bansal N, Go AS, Hsu CY. Gastrointestinal symptoms, inflammation and hypoalbuminemia in chronic kidney disease patients: A cross-sectional study. BMC Nephrol. 2015;16(1):1–8.
30. Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. Nephrol Dial Transplant. 2008;23(1):193–200.
31. Mustonen J, Pasternack A, Helin H, Nikkilä M. Clinicopathologic correlations in a series of 143 patients with IgA glomerulonephritis. Am J Nephrol. 1985;5(3):150–7.
32. Laurikka P, Salmi T, Collin P, Huhtala H, Mäki M, Kaukinen K, et al. Gastrointestinal symptoms in celiac disease patients on a long-term gluten-free diet. Nutrients. 2016;8(7):1–11.
33. Dimenäs E, Glise H, Hallerbäck B, et al. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30(11):1046–52.
34. Dimenäs E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. Scand J Gastroenterol Suppl. 1996;31(221):8–13.
35. Kleinman L, Kilburg A, Machnicki G, Faull R, Walker R, Prasad R, et al. Using GI-specific patient outcome measures in renal transplant patients: Validation of the GSRS and GIQLI. Qual Life Res. 2006;15(7):1223–32.
36. Viljamaa M, Collin P, Huhtala H, Sievänen H, Mäki M, Kaukinen K. Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. Aliment Pharmacol Ther. 2005;22(4):317–24.
37. Roos S, Kärner A, Hallert C. Psychological well-being of adult coeliac patients treated for 10 years. Dig Liver Dis. 2006;38(3):177–80.
38. Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: A large cross-sectional study. BMC Gastroenterol. 2013;13:75.
39. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: A review of the Fagerstrom Tolerance Questionnaire. J Behav Med. 1989;12(2):159–82.

40. Higgins-Biddle JC, Babor TF. A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions. Am J Drug Alcohol Abuse. 2018;44(6):578–86.
41. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
42. Yi C, Wang X, Ye H, Lin J, Yang X. Patient-reported gastrointestinal symptoms in patients with peritoneal dialysis: the prevalence, influence factors and association with quality of life. BMC Nephrol. 2022;23(1):99.
43. Chang L, Toner BB, Fukudo S, et al. Gender, Age, Society, Culture, and the Patient's Perspective in the Functional Gastrointestinal Disorders. Gastroenterology. 2006;130(5):1435–46.
44. Kahvecioglu S, Akdag I, Kiyici M, et al. High prevalence of irritable bowel syndrome and upper gastrointestinal symptoms in patients with chronic renal failure. J Nephrol. 2005;18(1):61–6.
45. Camilleri M, Lasch K, Zhou W. Irritable Bowel Syndrome: Methods, Mechanisms, and Pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2012;303(7):775–85.
46. Madariaga AG, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: A meta-analysis. J Clin Endocrinol Metab. 2014;99(3):923–31.
47. Ebert EC. The thyroid and the gut. J Clin Gastroenterol. 2010;44(6):402–6.

## Publisher's Note

# PUBLICATION IV

## Indirect Markers of Intestinal Damage in IgA Nephropathy

Jussi Pohjonen, Katri Kaukinen, Heini Huhtala,
Ilkka Pörsti, Katri Lindfors, Jukka Mustonen, Satu Mäkelä

Submitted