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Insulin Resistance, Inflammatory Markers and Alcohol Consumption in IgA Glomerulonephritis

ACADEMIC DISSERTATION
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ABSTRACT

IgA glomerulonephritis (IgAGN) is one of the most common forms of primary glomerulonephritis worldwide, accounting for 25–50 % of all patients with primary glomerulopathy. The hallmark for diagnosis is the deposition of immunoglobulin A (IgA) in the glomerular mesangium, leading to histological damage of various degrees. A broad spectrum of clinical presentation and variable prognosis is typical for the disease and approximately 25–30 % of patients eventually develop end-stage renal disease (ESRD).

After the description of the disease in the late 1960s a considerable body of information has accumulated especially on the prognostic features and etiology of IgAGN. The classical risk factors for poorer prognosis comprise kidney insufficiency, urinary protein excretion above 1g/24 h, prevalence of hypertension and certain histopathological changes at the time of the biopsy. Novel risk factors include hyperuricemia, hypertriglyceridemia and several gene polymorphisms. The current understanding of the etiology relies on observed aberrant glycosylation in the IgA1 molecule, leading to subsequent accumulation in the mesangium.

Reports from population studies and kidney patients with varying degrees of renal insufficiency have shown insulin resistance and inflammatory parameters to be associated with renal function. Whether these cause kidney insufficiency or simply act as markers of reduced glomerular filtration rate (GFR) is not well established. Furthermore, some population studies have shown that moderate alcohol consumption can prevent kidney insufficiency. Previous studies with alcoholic patients have reported alcohol consumption to be linked with the development of secondary IgAGN, but no information is available on the impact of alcohol in established IgAGN.

The purpose of the present series was to further investigate the prognostic role of insulin resistance, inflammatory markers and alcohol consumption and to gather data on the use of the biomarkers available in evaluating alcohol consumption in patients with IgAGN.

The original study population consisted of 223 patients in whom IgAGN had been diagnosed. From this retrospective group a cohort were invited to attend physician's appointment twice. The median time from the diagnostic renal biopsy was 11 years on the first visit and the second took place approximately 6 years thereafter. ESRD had developed in 7 % of the patients by the time of the second visit and IgAGN was classified as progressive in 19.5 % as assessed by cystatin-C and 30.8 % as assessed

by GFR estimated by the MDRD equation eGFR(MDRD). Serum insulin level, homeostasis model assessment of insulin resistance (HOMA-IR), C-reactive protein (CRP), serum albumin and total leucocyte count (WBC) at the first visit showed significant associations with subsequent progression of IgAGN. The patients in the progressive group had higher insulin, HOMA-IR, CRP and WBC levels and lower serum albumin levels than stable subjects.

Detailed information on alcohol consumption was obtained at the first visit and biomarkers evaluating the use of alcohol were obtained simultaneously. ESRD patients were excluded from both alcohol studies. Both cross-sectional and longitudinal data were analysed in the alcohol consumption study and only a cross-sectional approach was utilized in the biomarker study. Moderate drinkers were found to have the best kidney function regardless of mode of measurement. Light drinkers among women and moderate drinkers among men evinced the best kidney function. In multivariate analyses of the whole population, adjusted by hypertension and 24-h urinary protein excretion, moderate alcohol consumption was a significant factor in better kidney function when analysed both cross-sectionally and longitudinally.

Serum carbohydrate-deficient transferrin (CDT), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), a combination marker mathematically derived from GGT and CDT (gamma-CDT) and a novel alcohol consumption marker IgA antibody against acetaldehyde-modified hemoglobin (anti-adduct IgA) were used to evaluate the use of alcohol and liver function. Serum levels of anti-adduct IgA were higher in IgAGN patients than in healthy controls and were elevated in 63 % of IgAGN patients. Moreover, the levels were not associated with alcohol consumption, as was the case in the male control population. CDT, MCV and gamma-CDT seemed to be the most useful consumption markers in the IgAGN population.

In conclusion, insulin resistance and inflammatory markers are associated with the progression of IgAGN and could be useful in establishing the prognosis. Whether they have an independent prognostic role remains to be elucidated in future prospective studies. Moderate alcohol consumption might be beneficial in protecting against kidney function decline and the protective level might vary according to gender. The most useful parameters for evaluating alcohol consumption in these patients seem to be markers other than anti-adduct IgA.

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitors
AGE	Advanced glycation end products
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
Anti-adduct IgA	IgA antibody against acetaldehyde-modified hemoglobin
ARB	Angiotensin II type 1 receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
C1q	Complement C1q
C3	Complement 3
Ccr	Creatinine clearance
CDT	Carbohydrate-deficient transferrin
CD3	CD3 positive cells
C3d	Complement C3d
CI	Confidence interval
CKD	Chronic kidney disease
Cl	Clearance
CRP	C-reactive protein
DBP	Diastolic blood pressure
eGFR(MDRD)	Estimated glomerular filtration rate by MDRD equation
eGFR(C-G)	Estimated glomerular filtration rate by Cockcroft-Gault equation
eNOS	Endothelial nitric oxide synthase
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
FSIVGT	Frequently sampled intravenous glucose tolerance test
Gamma-CDT	Combination marker derived from GGT and CDT
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
G/I	Glucose/insulin
CIGMA	Continuous infusion of glucose with model assessment
GMP-17	Granule membrane protein of 17 kDalton
HD	Hemodialysis
HDL	High density lipoprotein

HLA	Human leucocyte antigen
HOMA-IR	Homeostasis model assessment of insulin resistance
IF-γ	Interferon-γ
IgA	Immunoglobulin A
IgAGN	Immunoglobulin A glomerulonephritis
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
ITT	Insulin tolerance test
LDL	Low density lipoprotein
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MP-9	Metalloproteinase-9
OD	Optical density
OGTT	Oral glucose tolerance test
OR	Odds ratio
p	Probability value
PAF	Platelet activating factor
PD	Peritoneal dialysis
PTH	Parathyroid hormone
QUICKI	Quantitative insulin sensitivity check index
RAS	Renin-angiotensin system
rP	Pearson correlation coefficient
rS	Spearman correlation coefficient
SBP	Systolic blood pressure
SD	Standard deviation
SLE	Systemic lupus erythematosus
TG	Triglycerides
TLR-9	Toll-like receptor-9
TNF-α	Tumor necrosis factor-α
VEGF	Vascular endothelial growth factor
WBC	Blood leucocyte count

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their roman numerals (I–IV). In addition some unpublished data are presented.

I. K. Kaartinen, J. Syrjänen, I. Pörsti, A. Harmoinen, A. Pasternack, H. Huhtala, O. Niemelä and J. Mustonen: Insulin resistance and the progression of IgA glomerulonephritis. Nephrol Dial Transplant 2007; 22(3): 778–83

II. K. Kaartinen, J. Syrjänen, I. Pörsti, M. Hurme, A. Harmoinen, A. Pasternack, H. Huhtala and J. Mustonen: Inflammatory markers and the progression of IgA glomerulonephritis. Nephrol Dial Transplant 2008; 23(4): 1285–90

III. K. Kaartinen, O. Niemelä, J. Syrjänen, I. Pörsti, A. Harmoinen, A. Pasternack, H. Huhtala, and J. Mustonen: Alcohol consumption and kidney function in IgA glomerulonephritis.
Nephron Clin Pract 2009; 112: c86–93.

IV. K. Kaartinen, O. Niemelä, J. Syrjänen, P. Alatalo, I. Pörsti, A. Harmoinen, A. Pasternack, H. Huhtala, and J. Mustonen: IgA immune responses against acetaldehyde adducts and biomarkers of alcohol consumption in patients with IgA glomerulonephritis. Alcohol Clin Exp Res 2009; 33(7): 1231–37

1. INTRODUCTION

Since the 1960s, when IgA glomerulonephritis (IgAGN) was first described (Berger and Hinglais 1968), many attempts have been made to clarify its epidemiology, pathogenesis, prognostic factors and treatment. Despite a substantial body of literature covering different aspects of the disease, a considerable number of issues remain to be addressed (Glassock 2008).

IgAGN is currently the most common form of primary glomerular disease worldwide (Barratt and Feehally 2005). Most cases are sporadic, but familial forms have been described and are believed to account for up to 14 % of all cases (Scolari et al. 1999). IgAGN associated with liver disease is the commonest form of secondary IgAGN (Pouria and Feehally 1999), but dozens of other diseases and pathogens have been linked to the development of IgAGN (Pouria and Barratt 2008). The relatively high frequency of silent IgA deposits and subclinical IgAGN in supposedly healthy populations would imply that the chance of a clinical association between IgAGN and other conditions, related or unrelated, is also higher.

The prognosis and clinical spectrum of the disease are variable and approximately 25–30 % of patients eventually develop end-stage renal disease (ESRD) (Barratt and Feehally 2006). The condition is more common in males and can occur at any age, the usual clinical onset falling in the second and third decades of life (Chan and Trachtman 2006, Berthoux et al. 2008). The most common clinical course is a slow progression to renal insufficiency (D'Amico 2004), but resolution of all urinary abnormalities can take place in almost 10 % of all patients even without treatment (Barratt and Feehally 2006).

The search for prognostic determinants has been one of the most important investigative fields with different trends during recent years. Most of the focus in the past decade has been on histology and urinanalysis and to a greater extent on genotyping (Ballardie and Cowley 2008). However, the factors most consistently relevant to prognosis are apparently not specific to IgAGN, as proteinuria and hypertension are key determinants of outcome in the great majority of chronic renal diseases (Feehally 2001).

The purpose of the present series was to investigate certain novel prognostic determinants with a focus on insulin resistance, inflammatory markers and alcohol consumption, and to study alcohol consumption markers in IgAGN patients.

2. REVIEW OF THE LITERATURE

2.1. History and epidemiology of IgA glomerulonephritis

IgAGN was first described by French pathologists forty years ago characterizing a group of patients with diffuse mesangial IgA deposits (Berger and Hinglais 1968). The disease was originally named after the investigator who first identified it, "Berger´s disease", but has long been universally known as IgA glomerulonephritis or IgA nephropathy (Feehally and Barratt 2008).

IgAGN is the most common form of glomerulonephritis identified worldwide in places where renal biopsy is widely practised (Barratt and Feehally 2005). The true population incidences are unknown, as the diagnosis requires renal biopsy and policies governing the procedure vary from country to country and even within the same country (Hsu 2008). Worldwide biopsy practice is becoming increasingly uniform (Barratt and Feehally 2005) and one might therefore expect the latest incidence figures to be more reliable. Variability is clearly evident among recent European annual IgAGN incidence rates per population: in France 2.6/100 000 (Simon et al. 2004), in the Czech Republic 1.1/100 000 (Rychlik et al. 2004), in Spain 0.8/100 000 (Rivera et al. 2002) and in Finland 5/100 000 (Wirta et al. 2008). Differences between races also prevail, although this could be at least partly explained by the different biopsy policies. IgAGN has been reported to be uncommon in blacks living in the United States (Jennette et al. 1985, Hall et al. 2004), whereas in Japan it is the most common renal disease (Honma et al. 2008) with an incidence as high as 14.3/100 000 (Yamagata et al. 2002). Approximately 16 % of all renal donor allografts have silent mesangial IgA deposits, this reflecting their incidence in the general Japanese population (Suzuki et al. 2003). In Australia the annual incidence has likewise been reported to be as high as 10.5/100 000 (Briganti et al. 2001).

2.2. Etiology and pathogenesis of IgA glomerulonephritis

While the etiology has been a focus of intensive research, the cause of primary IgAGN remains unknown (Narita and Gejyo 2008). The initiating event in the pathogenesis of IgAGN is the mesangial deposit of IgA immunoglobulin, which constitutes predominantly polymeric IgA1. Co-deposits of other molecules (such as IgG and C3) are often identified, but

they are not essential to disease activity or progression, nor does their presence correlate with clinical outcome (Barratt et al. 2007b).

It has recently been demonstrated in a subset of IgAGN patients that mesangial polymeric IgA1 consists of secretory IgA, the dominant immunoglobulin in external mucosal secretions (Oortwijn et al. 2007). It has been reported that mesangial IgA deposits disappear after kidney transplantation from an IgAGN-positive donor into an IgAGN-negative recipient (Silva et al. 1982). After successful kidney transplantation, the recurrence of IgAGN leads to graft dysfunction in approximately 13 % and graft loss in 5 % of patients five years after the transplantation (Floege 2004). Together these observations would suggest that the fundamental abnormality lies within the IgA immune system rather than within the kidney itself.

A variety of factors seem to contribute to the development of IgAGN, among them the composition and nature of the IgA molecule, dysregulation of the IgA immune system and changes in the clearance of IgA from the circulation (Barratt et al. 2004). Based on different study techniques (lectin binding, mass spectrometry and chromatography) it has become evident that properties of the IgA molecule differ between normal subjects and IgAGN patients (Barratt et al. 2007b, Novak et al. 2008, Suzuki and Tomino 2008). IgAGN patients evince modestly increased serum IgA, anionic net IgA charge and sialylation as well as galactosylation defects (Barratt et al. 2007b, Suzuki and Tomino 2008). The principal O-glycosylation abnormality found is reduced galactosylation of the hinge-region O-glycans in the IgA1 molecule (Barratt et al. 2007a). However, only a small proportion of IgA1-producing B lymphocytes synthesize this abnormal IgA1 and a large portion of serum IgA1 is normally galactosylated even in patients with IgAGN (Hiki et al. 1998, Tarelli et al. 2004, Eijgenraam and van Kooten 2008). Patients with IgAGN have, however, increased serum levels of galactose-deficient IgA1 compared to healthy controls (Moldoveanu et al. 2007).

The IgA deposited in the mesangium has the same abnormal properties as serum IgA in patients with IgAGN, but mesangial IgA seems to be enriched in respect of these abnormalities (Barratt et al. 2007b). Whether the bone marrow or mucosal tissue is the origin of IgA1 in circulating immune complexes and in the mesangial deposits in IgAGN patients is a matter of controversy (Novak et al. 2008). On the basis of increasing evidence it has been proposed that displacement of IgA-secreting plasma cells from mucosal to systemic sites may reflect a mishoming of mucosally primed B cells to sites such as the bone marrow in IgAGN. These displaced cells then secrete their mucosal pIgA1 glycoforms into the systemic circulation and are eventually deposited in the mesangium (Barratt et al. 2007a, Smith et al. 2008). Recent articles have thoroughly covered the possible mechanisms whereby IgA deposits lead to immunological glomerular injury (Lai and Lai 2005, van der Boog et al. 2005, Novak et al. 2007, Moura et al. 2008).

In short, the process involves the interactions between the deposited IgA1 and mesangial IgA receptors, and disease progression via the combined action of mesangial and leucocyte cell activation, which in turn may involve several inflammatory pathways (Monteiro 2007, Moura et al. 2008). The final result is the glomerular injury of various stages characteristic of IgAGN.

The role of genetic factors in the development of IgAGN has been intensively investigated, but so far results have confirmed no single, uniform genetic defect. Studies have identified several IgAGN susceptibility loci for familial forms of the disease, but the contribution of genes to the development of sporadic forms of IgAGN has been less clearly defined (Gharavi et al. 2000, Takei et al. 2002, Obara et al. 2003, Lai and Lai 2005, Bisceglia et al. 2006, Beerman et al. 2007, Paterson et al. 2007) . Nonetheless, autosomal dominant inheritance with incomplete penetrance is a likely mode of transmission in families with IgAGN (Beerman et al. 2007). It has recently been reported that aberrant IgA1 galactosylation was inherited in both familial and sporadic forms of IgAGN, suggesting the presence of a major dominant gene on a polygenic background (Gharavi et al. 2008).

2.3. Diagnosis and clinical features of IgA glomerulonephritis

Despite efforts to devise non-invasive means of diagnosing IgAGN (Maeda et al. 2003, Haubitz et al. 2005), the diagnosis still requires renal biopsy (Donadio and Grande 2002, Julian and Novak 2004, Cook 2007). By definition IgAGN has a predominant deposition of IgA in the glomerular mesangium analysed on a semiquantitative scale (0, trace, 1+,2+,3+) under immunofluorescence. The deposits are granular, global and diffuse and co-deposits with other immunoglobulins or C3 can also be seen (Berthoux et al. 2008). IgA is the sole immunoglobulin in 26 % of biopsies, 25 % have IgA, IgG and IgM, and C3 is present in 95 %. C1q is present in only 12 % of biopsies and if prominent should raise suspicion of systemic lupus erythematosis (SLE) (Cook 2007). Light- microscopy findings can vary from minimal glomerular alterations to severe mesangial proliferation, sclerosis and crescents (Ferrario et al. 1999). No international consensus has been reached on the pathological or clinical classification of IgAGN, although a project is currently under way (Feehally et al. 2007).

A modest level of proteinuria with or without renal insufficiency is the most common presentation of clinical significance in IgAGN (Philibert et al. 2008). Proteinuria > 3g/24 h is seen in 1–33 % of patients (D'Amico 2004). Urinary abnormalities characterized by persistent microscopic hematuria associated with proteinuria can be the presenting clinical sign in up to 80 % of cases in some patients cohorts (Syrjänen et al. 2000), and microscopic

hematuria without proteinuria is seen in approximately 10–13 % (Syrjänen et al. 2000, D'Amico 2004). The typical acute presentation is macroscopic hematuria at the time of upper respiratory tract infection or gastroenteritis in 28–40 % of cases (Syrjänen et al. 2000, Lv et al. 2008), but different figures (20–78 %) have also been published (D'Amico 2004). Usually hematuria recurs with new infectious events (Berthoux et al. 2008). Impaired renal function of any stage at time of diagnosis is seen in 2–59 % of patients depending on the study (Woo et al. 1987, Syrjänen et al. 2000, Rauta et al. 2002, D'Amico 2004, Chacko et al. 2005). Nephrotic syndrome occurs in approximately 5 % of cases and acute renal failure may result from acute tubular necrosis as a consequence of macroscopic hematuria or superimposed crescentic nephritis in less than 5 % (Barratt and Feehally 2006).

The disease is more common in males, with a ratio of male to female ranging from 2:1 to 6:1 (Chan and Trachtman 2006). The prevalence of hypertension is between 6–53 % at the time of the renal biopsy (D'Amico 2004, Nagy et al. 2005). IgAGN occurs at all ages, the usual age at clinical onset being in the second and third decades of life (Donadio 2001, Berthoux et al. 2008).

2.4. Silent and secondary IgA glomerulonephritis

From necropsy studies it has become evident that silent mesangial IgA deposits without clinical renal findings are discovered in 4–5.6 % of subjects (Sinniah 1983, Varis et al. 1993). The histological population prevalence of IgAGN (those with mesangial IgA deposits **and** clinical renal findings **or** light microscopy changes) has been estimated to be 1.3 % (Varis et al. 1993). Furthermore, approximately 16 % of all renal donor allografts in the general Japanese population (both living donor and cadaveric) have silent mesangial IgA deposits (Suzuki et al. 2003). Such a relatively high frequency of silent IgA deposits and subclinical IgAGN in supposedly healthy populations would imply that the chance of a clinical association between IgAGN and other unrelated conditions is also higher (Pouria and Barratt 2008).

Henoch-Schönlein purpura is defined as a vasculitis of small vessels characterized by IgA immune deposits and it involves skin, gut, joints and glomeruli (Jennette et al. 1994). The glomerulonephritis here is indistinguishable from that in primary IgAGN and could therefore be a systemic form of the same disease, representing two variants of the same pathologic process (Waldo 1988, Donadio and Grande 2002). Features of the disease vary between different patients and renal involvement is encountered in some 60 % of cases (Rieu and Noël 1999).

Mesangial IgA deposits have been described as a secondary phenomenon in various conditions (Donadio and Grande 2002). IgAGN associated

with liver disease is the commonest form of secondary IgAGN (Pouria and Feehally 1999), but dozens of other different diseases and pathogens have been linked to the development of IgAGN, as described in a recent excellent review (Pouria and Barratt 2008). Forms of secondary IgAGN have been described in association with celiac disease (Collin et al. 2002), inflammatory bowel disease (de Moura et al. 2006) and different connective tissue disorders (Sato et al. 1988, de Moura et al. 2006, Corrado et al. 2007) as well as with neoplastic diseases (Mustonen 1984, Mustonen et al. 1984, Cherubini et al. 2001).

2.5. Treatment of IgA glomerulonephritis

2.5.1. Medication

As the pathogenesis of IgAGN is still unknown, specific treatment cannot be directed at the cause of the disease (Narita and Gejyo 2008). Some researchers encourage the use of immunosuppressive agents in cases of proteinuria and declining GFR (Ballardie 2007), while others reserve immunosuppressive medication for severe cases and those with failing supportive approach and progressive loss of renal function (Chan and Trachtman 2006, Floege and Eitner 2008).

According to some recent publications patients with recurrent macroscopic hematuria with preserved renal function or with microscopic hematuria and proteinuria < 1g/24 h require no treatment and those with nephrotic syndrome and minimal change seen on renal biopsy should be managed with steroids for which the earliest publication dates back to the beginning of 1980s (Mustonen et al. 1983). Those with crescentic glomerulonephritis in the absence of significant histologic injury should be managed similarly to renal small-vessel vasculitis with the exception of plasma exchange, for which evidence is lacking (Barratt and Feehally 2005, Barratt and Feehally 2006). Patients at greatest risk of progressive renal impairment (those with hypertension, proteinuria > 1g/24h and reduced GFR at diagnosis) should be treated up to a blood pressure of 125/75 mmHg with dual blockade of the renin-angiotensin system (RAS). Corticosteroids are to be considered in cases with strict blood pressure control (<125/75 mmHg) and maximal RAS blockade and nevertheless ongoing proteinuria > 1g/24h. For other treatment modalities the current knowledge is insufficient to encourage their use (Barratt and Feehally 2006).

In the future the response to angiotensin-converting enzyme (ACE) -inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) could possibly be predicted on the basis of urine proteome analysis (Rocchetti et al. 2008) or ACE genotyping (Narita et al. 2003, Woo et al. 2007). ACEI/ARB therapy should also be initiated for normotensive patients to reduce proteinuria < 0.5g/24h, but whether normotensive patients with

less proteinuria should be treated is not clear (Julian and Novak 2004). The therapy is apparently well tolerated and effective in terms of reducing proteinuria in normotensive patients (Shimizu et al. 2008). Opinions in opposition to treating minor proteinuria have also been published (Barratt and Feehally 2006).

A trial is under way to establish whether immunosuppression added to optimized supportive therapy confers any benefit in persistent proteinuria (Floege and Eitner 2008). According to a recent pilot study steroid treatment combined with ACEI therapy might be more effective than ACEI therapy alone in preventing kidney function decline (Lv et al. 2009).

A beneficial effect of intravenous immunoglobulin therapy in retarding kidney insufficiency and reducing proteinuria in IgAGN has recently been reported (Rasche et al. 2006). Meta-analysis of antiplatelet therapy has resulted in reduced proteinuria and protected renal function with an emphasis on dipyridamole (Taji et al. 2006). Tonsillectomy has been a popular therapy mode especially in Japan (Komatsu et al. 2008), but conflicting results have been published. Omega-3-fatty acids in patients with higher grades of proteinuria have been suggested in attempts to slow the progression of renal insufficiency (Tumlin et al. 2007).

2.5.2. Transplantation

IgAGN recurs in the transplanted kidney in some 50–60 % of cases 2–4 years after the transplantation (Berger et al. 1984, Berger 1988, Odum et al. 1994, Kiattisunthorn et al. 2008). If protocol biopsies are performed, some patients are found to have only histological recurrence (Floege 2004). Contemporary immunosuppressive regimens have not altered the recurrency rate and the suppression of RAS seems therefore tempting in the light of its well-established benefits in non-transplanted IgAGN patients (Julian and Novak 2004). The five-year graft survival in IgAGN appears comparable to that of other glomerulopathies, being around 81 % (Soler et al. 2005). Somewhat different figures have also been reported, graft dysfunction and loss occurring in approximately 13 % and 5 % of patients five years after the transplantation, respectively, (Floege 2004), 10-year graft survival being 51–75 % (Jeong et al. 2008).

2.6. Renal outcome

The most common clinical course is that of a slow progression to renal insufficiency, but a small percentage of cases may evince prolonged remission of all clinical signs of the disease even without treatment (D'Amico 2004). Resolution of all urinary abnormalities occurs in less than 10 % of all patients (Barratt and Feehally 2006). Previously it was thought that in spite of clinical remission, no concomitant spontaneous disappearance of

mesangial IgA deposits occurred (Costa et al. 1987, Alamartine et al. 1990, Ibels and Györy 1994), but histological regression along with complete disappearance of IgA deposits has since been reported (Hotta et al. 2002).

Three types of disease course have been described: a stable chronic course with constantly normal or minimally elevated serum creatinine lasting for years, a progressive course with continuously increasing serum creatinine, and an early acute course with a short-term increase in serum creatinine rapidly returning to normal range. A point of no return has been proposed after serum creatinine level exceed 265 μmol/l (3 mg/dl) (Schöll et al. 1999). Patients with macroscopic hematuria bouts and related acute tubular necrosis with renal insufficiency usually regain their original renal function, but in 25 % of cases this does not take place after the resolution of hematuria. Risk factors for incomplete recovery of renal function are the duration of macroscopic hematuria > 10 days, age > 50 years, decreased baseline GFR, absence of previous macroscopic hematuria bouts and the severity of tubular necrosis (Gutiérrez et al. 2007).

Approximately 25–30 % of any cohort develop ESRD within 20–25 years of presentation and 1.5 % of patients have been calculated to reach ESRD annually from the first symptoms of IgAGN (Barratt and Feehally 2005, Barratt and Feehally 2006). In a review of 21 publications actuarial 10-year renal survival rates were reported to vary between 57–94 % with a mean of 81 % (D'Amico 2004). Considerably worse figures have also been reported, with a 10-year cumulative probability of renal survival of 33 % (Chacko et al. 2005). One of the latest reports showed 77 % renal survival 10 years after biopsy (Lv et al. 2008). Ten-year renal survival rate from Finland has been 96 % (Geddes et al. 2003) and the latest figure of 89 % was obtained after a mean of 19 years from the clinical onset of the disease (Ronkainen et al. 2006).

When IgAGN patients with seemingly benign presentation (normal renal function, no hypertension and minimal proteinuria ≤ 0.4g/24h) have been evaluated, 38 % developed hypertension, 24 % developed renal insufficiency and 46 % had an increasing trend towards proteinuria in a follow-up of a mean period of 9 years (Shen et al. 2008). In another study with similar patient characteristics, proteinuria > 1g/24 h had developed in 33 %, hypertension in 26 %, impaired renal function in 7 % in a follow-up of a median of 7 years (Szeto et al. 2001). With only isolated microscopic hematuria at presentation, hypertension, renal insufficiency and proteinuria developed in 32 %, 20 % and 29 % of cases, respectively, in another follow-up of a mean of 8 years (Shen et al. 2007).

The reported rates of decline in GFR have varied between 0 and 7.1 ml/min/year (Rekola et al. 1991, Donadio et al. 1994, Bartosik et al. 2001, Geddes et al. 2003, Lemley et al. 2008).

2.7. Prognostic determinants

The search for prognostic determinants remains central and constitutes one of the most important investigative fields in IgAGN (Ballardie and Cowley 2008). In the course of time different trends in research topics have emerged, most of the focus being on histology and urinalysis, although interest in genotyping has increased in the past decade (Ballardie and Cowley 2008). The factors most consistently influential in prognosis are apparently not specific to IgAGN, as proteinuria and hypertension are generic features which are key determinants of outcome in the great majority of chronic renal diseases (Feehally 2001). Prognostic formulas using laboratory and clinical data have been proposed (Bartosik et al. 2001, Rauta et al. 2002, Magistroni et al. 2006, Wakai et al. 2006), but there is not yet sufficient consensus to recommend their use in clinical practice (Barratt and Feehally 2005).

The incidence of hypertension and impaired renal function continues to rise over time and life-long follow-up of IgAGN patients is therefore recommended (Szeto et al. 2001, Shen et al. 2007). The median time for progression from proteinuria to hypertension is 4 years and from proteinuria to renal impairment 7 years (Szeto et al. 2001). In the early phases of IgAGN the traditional clinical factors (hypertension and/or proteinuria) seem to predict the prognosis particularly powerfully (D'Amico 2004, Chacko et al. 2005), and hematuria and histological lesions seem also to play a role (Rauta et al. 2002, Manno et al. 2007, Shen et al. 2007, Shen et al. 2008).

Hypertension, severity of proteinuria and the presence of severe histological lesions in renal biopsies seem to be the most clearly established markers for poor prognosis moving towards chronic kidney disease (CKD) and ESRD (Berthoux et al. 2008). An approach incorporating sequential information on blood pressure and proteinuria can further refine estimates of the progression risk, although this only accounts for 30–33 % of overall risk (Bartosik et al. 2001, Barratt and Feehally 2005). A review of over 20 published studies has brought on three most prominent clinical variables contributing to poor prognosis: the aforementioned hypertension and proteinuria and elevated serum creatinine at diagnosis (D'Amico 2004).

2.7.1. Impaired renal function

One of the most commonly found parameters independently associated with the risk of ESRD is the degree of renal impairment at presentation (Bartosik et al. 2001, Coppo and D'Amico 2005). This does not however indicate the rate at which renal function has been lost, only its level at that point (Bartosik et al. 2001). Nevertheless, current serum creatinine is as good a predictor of ESRD as the previous-year creatinine trend (Donadio et al. 2002). Two recent reports have also confirmed the role of

renal impairment as a prognostic marker for poorer outcome (Lemley et al. 2008, Lv et al. 2008).

2.7.2. Hypertension

The occurrence of hypertension at any stage of the disease is an independent and strong risk factor for poor prognosis (Berthoux et al. 2008) and a recent study has also confirmed this finding (Lv et al. 2008). The target level of blood pressure is ≤ 130/80 mmHg and in patients with proteinuria > 1g/24 h even lower, ≤ 125/75 mmHg (Berthoux et al. 2008). IgAGN patients with optimal blood pressure also seem to have minimal histological damage compared to those with higher blood pressure (Osawa et al. 2001). Strict blood pressure control is justified on specific evidence as achieving a mean BP of 129/70 mmHg stabilized GFR in contrast to patients with a mean BP of 136/76 mmHg who showed a declining GFR of 13 ml/min in a follow-up of over 3 years (Kanno et al. 2000).

ACEI are now the agent of choice for the treatment of hypertensive IgAGN patients and ARBs are logical for subjects intolerant to ACEI (Praga et al. 2003, Julian and Novak 2004) and also as a first-line treatment (Li et al. 2006, Woo et al. 2008). Combination of the two agents confers additional benefit (Nakao et al. 2003, Dillon 2004). ACEI/ARB therapy has been shown to be effective in IgAGN patients at all levels of renal function in retarding progression towards ESRD (Woo et al. 2007) and the efficacy is not influenced by the degree of tubulointerstitial fibrosis at presentation (Kanno et al. 2005).

2.7.3. Proteinuria

The degree of proteinuria is a major risk factor for poor prognosis, both as a continuous and as a dichotomous variable with a commonly accepted cut-off level at 1g/24 h (Berthoux et al. 2008). A recent publication notes that in IgAGN patients with < 1g/24 h sustained proteinuria, the rate of decline in GFR is 90 % slower than the mean rate. Patients with sustained proteinuria > 3g/24 h lost their renal function 25-fold faster than those with < 1g/24h. Patients presenting with proteinuria ≥ 3g/24 h, but achieving a partial remission (<1g/24 h), had a course similar to those with ≤ 1g/24 h throughout in a follow-up of a mean 6.5 years. Achieving a level of < 1g/24 h thus yielded an excellent prognosis regardless of the initial level of proteinuria, highlighting the importance of proteinuria reduction by whatever means (blood pressure reduction, medication) (Reich et al. 2007). Judging from studies involving IgAGN patients with benign presentation, it would appear that even trace proteinuria (≤0.4g/24h) is an indicator of adverse outcomes (development of more severe proteinuria, hypertension or renal insufficiency) (Szeto et al. 2001, Shen et al. 2007). However, not all studies agree here, as one prognostic model has predicted zero risk of progression for normotensive patients with proteinuria < 0.2 g/24 h (Bartosik et al. 2001).

ACEI/ARB therapies are the cornerstones in reducing proteinuria and their initiation is recommended even for normotensive patients to reduce proteinuria < 0.5g/24h (Julian and Novak 2004, Glassock 2008). Addition of mineralocorticoid receptor blockers to ACEI or ARB therapy can further reduce proteinuria (Bomback et al. 2008). Immunosuppressive medication has likewise been shown to reduce proteinuria (Samuels et al. 2004, Rasche et al. 2007, Koike et al. 2008) and in combination with tonsillectomy (Komatsu et al. 2008). Antiplatelet therapy (Taji et al. 2006), intravenous immunoglobulin therapy (Rasche et al. 2006) and oral vitamin-D (Szeto et al. 2008) have been reported to result in reduced proteinuria in IgAGN patients.

2.7.4. Histological features

The presence of severe histological lesions such as hyalinosis and crescents on initial renal biopsy adumbrates a poor prognosis (Berthoux et al. 2008). Widespread global and/or segmental glomerular sclerosis, marked tubulointerstitial lesions and an elevated glomerular and/or tubulointerstitial score of lesions, and classes of highest severity of overall damage have been strong histological pointers to poor prognosis in multivariate analyses in the majority of older studies (D'Amico 2004), as also in recent publications (Lemley et al. 2008, Lv et al. 2008).

Numerous other histological markers for poorer outcome have been found, including granule membrane protein of 17 kDa (GMP-17)-positive cytotoxic T-lymphocytes in renal tubules and with B-lymphocytes in the interstitium (van Es et al. 2008), tubulointerstitial CD3 (Myllymäki et al. 2007), activation of the glomerular lectin pathway of complement (Roos et al. 2006), deposits of peritubular capillary C3d (Gherghiceanu et al. 2005) and the number of renal biopsy fibroblast-specific-protein-1 ≥ 20/high power field (Nishitani et al. 2005).

2.7.5. Sex and age

There are conflicting results as to whether sex has an impact on the progression of IgAGN. Sex is not generally regarded as a significant determinant (Barratt and Feehally 2005, Berthoux et al. 2008, Cattran et al. 2008), but not all agree (Frimat et al. 1997) and a meta-analysis on the topic (covering 25 studies) has shown that male gender is associated with poorer outcome in IgAGN (Neugarten et al. 2000). Older age at presentation has been linked with worse outcome (Ibels and Györy 1994, Barratt and Feehally 2005).

2.7.6. Hyperuricemia, hypertriglyceridemia and weight

Hyperuricemia at the time of renal biopsy has been associated with more rapid deterioration of renal function (Syrjänen et al. 2000, Ohno et al. 2001) and hypertriglyceridemia has had a similar association in IgAGN

(Syrjänen et al. 2000). Excessive body weight at the time of renal diagnosis has been linked with faster progression of IgAGN (Syrjänen et al. 2000, Bonnet et al. 2001, Barratt and Feehally 2005).

2.7.7. Genetic markers of progression

Over the past years, a great number of studies have sought to identify genes responsible both for disease susceptibility and for disease progression (D'Amico 2004). Genes linked with the progression of IgAGN have covered gene polymorphisms with RAS, human leucocyte antigen (HLA), T-cell receptor, endothelial nitric oxide synthase (eNOS), interleukin-1 (IL-1), interleukin-4 (IL-4), interferon-γ (IF-γ), uteroglobulin, adducin, megsin, mucin, chemokine receptor, monocyte chemoattractant protein-1, platelet activating factor (PAF), metalloproteinase-9 (MP-9) and α1 immunoglobulin gene 3' enhancer genes (Schmidt and Ritz 1999, Hsu et al. 2000, Tanaka et al. 2000, Galla 2001, Wada et al. 2003, D'Amico 2004, Chow et al. 2005, Coppo and D'Amico 2005, Julian et al. 2007).

2.7.8. Other markers of progression

Patients with a urinary IL-6/epidermal growth factor ratio > 1 have shown poorer prognosis compared to those with a level <1 (Ranieri et al. 1996). Urinary IL-8 levels above 2.5 ng/day at presentation have yielded an 8- fold risk of progression compared to those with levels < 1.0 ng/day (Harada et al. 2002). The occurrence of macroscopic hematuria bouts is associated with better prognosis (Ibels and György 1994, Barratt and Feehally 2005) and high serum IgA/C3 ratio (Komatsu et al. 2004) and high serum C4 binding protein level are indicative of worse outcome (Onda et al. 2007). Aberrant sialylation of serum IgA1 is associated with the prognosis; the lower the level of alpha 2,6 sialic acid, the poorer the renal survival rate (Ding et al. 2007). The urinary ratio of epidermal growth factor/monocyte chemotactic peptide-1 obtained at presentation predicts prognosis, those in the lowest tertile having a significant decline in renal survival, those in the highest tertile having excellent prognosis even after seven years (Torres et al. 2008).

2.8. Insulin resistance

2.8.1. Definition of insulin resistance

Insulin resistance is defined as a subnormal biologic response to a given concentration of insulin (Moller and Flier 1991). Insulin-resistant individuals with normal glucose tolerance are hyperinsulinemic when compared to insulin-sensitive individuals. The more insulin-resistant an individual is, the greater will be the degree of compensatory hyperinsulinemia, and significant fasting hyperglycemia occurs when

the state of hyperinsulinemia can no longer be sustained (Mak 2008). The development of hyperglycemia is the result of a complex interplay between muscle tissue, pancreatic β-cells, adipose tissue and liver (Reaven 1995). It has been argued that the two phenomena, insulin resistance and hyperinsulinemia, could exist in isolation, but one of the most recent publications has shown them to be closely linked in a nondiabetic population and can well be seen as a single entity (Kim and Reaven 2008). However, insulin resistance and metabolic syndrome do not necessarily coexist (Onat et al. 2006).

2.8.2. Assessment of insulin resistance

Insulin resistance can be assessed in a number of ways. The hyperinsulinemic euglycemic clamp is regarded as the gold standard in quantifying insulin sensitivity (Monzillo and Hamdy 2003, Shen et al. 2005), but other methods have been developed, some less laborious and hence more suitable in clinical practice. Fasting plasma insulin concentration, homeostasis model assessment (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), fasting plasma glucose-to-insulin ratio (G/I), continuous infusion of glucose with model assessment (CIGMA), the oral glucose tolerance test (OGTT), insulin sensitivity indices based on OGTT, the insulin tolerance test (ITT) and the frequent-sample intravenous glucose tolerance test (FSIVGT) and the minimal model are other possibilities (Monzillo and Hamdy 2003). HOMA-IR is said to be useful mostly in euglycemic individuals and in persons with mild diabetes. It may not, however, offer advantages over the fasting insulin concentration alone (Monzillo and Hamdy 2003). HOMA-IR and fasting insulin concentration are validated techniques in assessing insulin resistance even in renal failure patients (Shoji et al. 2001, Kanauchi et al. 2002).

2.8.3. Kidneys and glucose homeostasis

The kidneys are also involved in the glucose homeostasis. The renal cortex is capable of both degrading glucose via glycolysis and producing glucose via gluconeogenesis, while the medulla and papilla are only capable of degrading it (Adrogue 1992). Human podocytes, but not glomerular endothelial cells, are able to double glucose uptake under the influence of insulin stimulation (Coward et al. 2005). Only in the presence of sustained hypoglycemia are the kidneys thought to release significant amounts of glucose into the circulation (Adrogue 1992). Moreover, insulin is metabolized in proximal tubule cells (Adrogue 1992) and features of abnormal insulin metabolism in uremia include reduced degradation of insulin, reduced peripheral sensitivity to insulin action, hyperinsulinemia and normal, increased or decreased insulin secretion in response to glucose loads (Mak and DeFronzo 1992). The impaired insulin action commonly found in patients with renal failure is a consequence of peripheral insulin

resistance, and especially skeletal muscle is its primary site (DeFronzo et al. 1981, DeFronzo et al. 1983, Hager 1989, Alvestrand 1997, Mak 2008). Other CKD-related factors involved in the altered glucose homeostasis in uremia are accumulation of uremic toxins, metabolic acidosis, parathyroid hormone (PTH) excess, calcitriol deficiency and anemia (Procopio and Borretta 2003, Siew and Ikizler 2008).

The effects of insulin resistance on the kidneys are complex, consisting of both structural and functional alterations (El-Atat et al. 2004). Insulin resistance could lead to elevation of the glomerular filtration fraction and subsequent glomerular hyperfiltration and glomerulosclerosis, and it could activate RAS, cause oxidative stress and stimulate renal endothelial and mesangial cell proliferation, cause endothelial dysfunction and enhance extracellular matrix protein synthesis (Dengel et al. 1996, El-Atat et al. 2004, Whaley-Connell et al. 2006, Ritz 2008).

2.8.4. Effect of insulin resistance on renal function

Numerous both cross-sectional (Kubo et al. 1999, Chen et al. 2003, Chen et al. 2004a, Tanaka et al. 2006, Chen et al. 2007, Chonchol and Scragg 2007, Kronborg et al. 2007, Lee et al. 2007, Onat et al. 2007, Atamer et al. 2008) and follow-up studies from different populations including and excluding persons with glucose metabolism disorders have established a significant association between insulin resistance and risk of the development of CKD. Cross-sectional studies can only establish the relationship and follow-up studies are essential to explain the nature of the association (causality).

Most follow-up studies carry the same message in establishing insulin resistance as one of the independent risk factors for CKD. The most recent and thorough study used a combination of cross-sectional and longitudinal approaches. Higher insulin sensitivity at baseline was independently associated with a lower risk of impaired renal function in a community-based cohort of elderly men (Nerpin et al. 2008). Another study showed a marked association between the risk of CKD and increased fasting glucose (Lucove et al. 2008), this in contrast to an older Japanese study (Tozawa et al. 2007). Impaired fasting glucose alone was not associated with the development of CKD, unlike other components of the metabolic syndrome, but those in the highest HOMA-IR quintiles had a subsequent independent risk of developing CKD. The risk was significant above HOMA-IR level 1.8 (Kurella et al. 2005). In another analysis HOMA-IR was not linked with the development of CKD, but there the cut-off for HOMA-IR was set at the median value of the studied population, thus differing from what has been described as insulin-sensitive vs. insulin-resistant in different populations (Fox et al. 2005). Another study from Japan showed high vs. normal fasting plasma glucose to be an independent predictor of ESRD with the same magnitude as proteinuria vs. no proteinuria (Iseki et al. 2004). Detailed information on the follow-up studies is presented in **Table 1.**

Table 1. Summary of follow-up studies on the relationship between insulin resistance and risk of CKD of any magnitude. HOMA-IR = homeostasis model assessment of insulin resistance, OGTT = oral glucose tolerance test, eGFR(MDRD) = estimated glomerular filtration rate by MDRD equation, ESRD = end-stage renal disease.

Reference	Insulin resistance method	GFR method	Association with CKD	Follow-up time (years)	No of subjects
Iseki et al. 2004	Fasting glucose	ESRD yes/no	Significant	8 y	78 529
Kurella et al. 2005	HOMA-IR	eGFR(MDRD)	Significant	9 y	10 096
Fox et al. 2005	OGTT, HOMA-IR	eGFR(MDRD)	Insignificant	7 y	2398
Tozawa et al. 2007	Fasting glucose	eGFR(MDRD)	Insignificant	5 y	6371
Nerpin et al. 2008	Hyperinsulinemic euglycemic clamp	Cystatin-C-based GFR estimate	Significant	7 y	694
Lucove et al. 2008	Fasting glucose	eGFR(MDRD)	Significant	7 y	2420

Table 2. Summary of studies on the relationship between insulin resistance and kidney function in CKD patients excluding those with IgAGN. OGTT = oral glucose tolerance test, ITT = insulin tolerance test, HOMA-IR = homeostasis model assessment of insulin resistance, Ccr = creatinine clearance, eGFR(C-G) = estimated glomerular filtration rate by Cockcroft-Gault equation.

Reference	Insulin resistance method	GFR method	Association with kidney function	Setting	No of kidney patients
Dzurik et al. 1995	OGTT, fasting insulin	S-creatinine, Ccr	Insignificant	Cross-sectional	52
Eidemak et al. 1995	Hyperinsulinemic euglycemic clamp	51 Cr-EDTA-clearance	Insignificant	Cross-sectional	29
Vareesangthip et al. 1997	ITT	eGFR(C-G)	Insignificant	Cross-sectional	15
Šebeková et al. 2002	OGTT, fasting insulin	S-creatinine, eGFR(C-G)	Insignificant	Cross-sectional	61
Sechi et al. 2002	OGTT, Hyperinsulinemic euglycemic clamp	S-creatinine, ccr	Insignificant	Cross-sectional	321(116)
Kobayashi et al. 2005	Hyperinsulinemic euglycemic clamp, HOMA-IR	S-creatinine, ccr	Significant	Cross-sectional	29
Satirapoj et al. 2005	HOMA-IR, fasting insulin	Average of ccr and urea clearances	Insignificant	Cross-sectional	78
Becker et al. 2005	HOMA-IR	Iod-thalamate clearance	Insignificant	Cross-sectional	227
Fliser et al. 2005	HOMA-IR, fasting insulin	Iod-thalamate clearance	Insignificant	Follow-up 5 years	177
Sit et al. 2006	HOMA-IR	S-creatinine, ccr	Significant	Cross-sectional	89
Trirogoff et al. 2007	HOMA-IR	eGFR(MDRD)	Insignificant	Cross-sectional	95
Ikee et al. 2008	fasting glucose, HOMA-IR	S-creatinine	Significant/ Insignificant	Cross-sectional	23
Koch et al. 2008	HOMA-IR	Several	Significant	Cross-sectional	46

2.8.5. Insulin resistance in kidney diseases

A number of studies both cross-sectional and longitudinal from patient populations covering a wide variety of kidney diseases and various stages of kidney function have confirmed that a considerable proportion of these patients are insulin-resistant (Dzurik et al. 1995, Eidemak et al. 1995, Vareesangthip et al. 1997, Šebeková et al. 2002, Sechi et al. 2002, Becker et al. 2005, Fliser et al. 2005, Kobayashi et al. 2005, Satirapoj et al. 2005, Sit et al. 2006, Trirogoff et al. 2007, Ikee et al. 2008, Koch et al. 2008). However, not all studies have detected a significant relationship between kidney function and insulin resistance. Since detailed patient characteristics are not always reported, it is likely that IgAGN patients were also involved in some of them. More detailed information on the individual studies is given in **Table 2,** with the exclusion of those involving IgAGN patients.

Table 3. Summary of studies on the relationship between insulin resistance and kidney function in IgAGN patients. OGTT = oral glucose tolerance test, FSIVGT = frequent-sample intravenous glucose tolerance test, HOMA-IR = homeostasis model assessment of insulin resistance, Ccr = creatinine clearance.

Reference	Insulin resistance method	GFR method	Association with kidney function	Setting	No of IgAGN patients
Kaneshige et al. 1983	OGTT, fasting insulin	S-creatinine	Not reported	Cross-sectional	62
Stenvinkel et al. 1995	Hyperinsulinemic euglycemic clamp	Inulin clearance	Insignificant	Cross-sectional	8+1
Fliser et al. 1998	FSIVGT	Inulin clearance	Insignificant	Cross-sectional	29
Kato et al. 2000	Hyperinsulinemic euglycemic clamp	Para-aminohippurate clearance, ccr, s-creatinine	Significant/ insignificant	Cross-sectional	14
Kielstein et al. 2003	FSIVGT	Inulin clearance	Not reported	Cross-sectional	30
Eiro et al. 2003	HOMA-IR	S-creatinine, ccr	Insignificant	Cross-sectional	88

2.8.6. Insulin resistance in IgA glomerulonephritis

Studies involving IgAGN patients are summarized in **Table 3**. The earliest of them dates back to the beginning of the 1980s, covering a non-obese normal kidney function population. Seventy-three % of IgAGN patients had impaired glucose tolerance, but a possible relationship between kidney function and insulin resistance was not reported (Kaneshige et al. 1983). A small study of non-nephrotic IgAGN patients with well preserved renal function showed their metabolic clearance of glucose to be similar to that of healthy controls, indicating they were not insulin-resistant despite their significantly worse GFR. One more IgAGN patient was, however, in the

nephrotic syndrome group, which evinced a significantly lower metabolic clearance of glucose compared to healthy controls, indicating that this group were insulin-resistant (Stenvinkel et al. 1995). More than half of the population had IgAGN in a study where patients were subsequently categorized into three groups based on their GFR. The mean insulin sensitivity was lower in all kidney patients compared to matched healthy controls, but did not correlate with GFR (Fliser et al. 1998). In a Japanese study of non-nephrotic patients the majority had IgAGN. In a comparison between insulin-resistant and insulin-sensitive patients (divided by a mean M-value obtained from the clamp), GFR was notably lower in the insulin-resistant group, but no significant difference was found in serum creatinine values (Kato et al. 2000). In a study with solely IgAGN patients with well preserved renal function, insulin resistance was comparable to that previously described in nonobese subjects, indicating that this group of IgAGN patients were not particularly insulin-resistant. Whether insulin resistance was related to renal function was not reported (Kielstein et al. 2003). Another study of IgAGN patients with non-nephrotic proteinuria showed no significant difference in renal function between insulin- resistant and -sensitive groups, but insulin resistance was markedly associated with hypertension (Eiro et al. 2003).

In summary, most studies covering IgAGN patients do not establish insulin resistance as a prognostic indicator.

2.9. Inflammation

2.9.1. Definition of inflammation

At least 40 plasma proteins, including clotting proteins, complement factors, anti-proteases and transport proteins, are defined as acute-phase proteins based on changes in circulating concentration of at least 25 % after an inflammatory stimulus (Black et al. 2004). The state of inflammation can be evaluated by measuring any acute-phase protein, but serum CRP is the most commonly used (Lacson and Levin 2004). Serum levels of IL-6, albumin, fibrinogen, amyloid-A, WBC, erythrocyte sedimentation rate (ESR), ferritin, leptin, prealbumin, tumor necrosis factor-α (TNF-α) and other cytokines are also frequently utilized even in renal patients (Kalantar-Zadeh et al. 2003). There is currently no single best test to assess inflammation in CKD patients for diagnostic purposes (Kovesdy and Kalantar-Zadeh 2008).

Inflammation is a component in the major modifiable risk factors in renal disease (Vidt 2006). It has been suggested to be highly associated with insulin resistance (Festa et al. 2000, Chen et al. 2004b), another risk factor in renal patients. Many individuals have a minimal degree of tissue injury and subsequent low-grade inflammation known to be associated

with minor CRP elevation (between 3–10 mg/l), and a large number of medical conditions are also linked with minor CRP elevations (Kushner et al. 2006). These minor elevations predict undesirable outcomes both in healthy populations and in various medical conditions (Bassuk et al. 2004, Kushner et al. 2006).

2.9.2. Causes of inflammation in kidney diseases

CKD may lead to increased inflammatory responses through a number of mechanisms such as reduced renal clearance of cytokines, accumulation of advanced glycation end products (AGE) and other carbonyl stress substances, oxidative stress, deteriorating nutritional state, atherosclerosis per se, various inflammatory diseases, unrecognized persistent infections, volume overload, increased levels of endotoxins, decreased levels of antioxidants, genetic factors and several additional factors related to the dialysis procedure (Stenvinkel 2001, Stenvinkel 2002, Kalantar-Zadeh et al. 2003, Kovesdy and Kalantar-Zadeh 2008). CRP and inflammation have been linked with cardiovascular risk factors, cardiovascular disease, morbidity, mortality and nutritional status in patients with CKD, most notably in stage 5 (Stenvinkel 2001, Bassuk et al. 2004, Don and Kaysen 2004, Himmelfarb 2004, Lacson and Levin 2004, Vidt 2006).

2.9.3. Effect of inflammation on renal function

As a variety of inflammatory parameters have been studied, the focus of this literature review is on those reports which have used the same inflammatory variables as in this thesis.

Several population-based cross-sectional studies have established that high CRP is an independent predictor of renal function decline (Shlipak et al. 2003, Stuveling et al. 2003, Knight et al. 2004, Muntner et al. 2004, Lee et al. 2007). A significant relationship has not always been established (Stam et al. 2006, Onat et al. 2007,) or it has varied according to the renal function assessments used (Shlipak et al. 2005b, Gülcan et al. 2007, Keller et al. 2007, Singh et al. 2007, Keller et al. 2008). Elevated serum IL-6 has also been linked with reduced kidney function (Shlipak et al. 2003, Keller et al. 2008).

One follow-up study has confirmed an independent significant association between higher CRP and IL-6 and decline in kidney function, but WBC was not a significant determinant (Wannamethee et al. 2006). In another follow-up study of elderly individuals, higher CRP and WBC counts and lower serum albumin were independently associated with a rise in serum creatinine level (Fried et al. 2004).

2.9.4. Inflammation in kidney diseases

It has been estimated that some 20–65 % of ESRD and 30–50 % of predialysis and dialysis (both hemodialysis (HD) and peritoneal dialysis (PD)) patients

show evidence of an activated inflammatory response (Stenvinkel 2001, Stenvinkel 2002, Vidt 2006). In one large population study, 58 % of patients with a GFR between 15–29 ml/min had evidence of detectable levels of inflammation (Eustace et al. 2004).

A substantial body of papers have been published investigating different inflammatory variables in CKD populations with various levels of GFR and a summary of cross-sectional studies is presented in **Table 4**. In some of them CRP has been found to be significantly linked with worsening of renal function; however a multivariate analysis was not performed in all of them (Panichi et al. 2001, Panichi et al. 2002, Ates et al. 2005, Razeghi et al. 2008). In a cardiovascular morbidity-oriented follow-up study, the baseline GFR was significantly different in CKD patients divided into three groups based on their CRP tertile, but no other data regarding renal function and CRP was reported (Soriano et al. 2007).

In one recent study serum albumin differed significantly between healthy controls and CKD patients, but not between different CKD patients. The highest CRP levels were found in HD patients, then in PD patients and other CKD patients, the lowest levels being registered in healthy controls. However, no multivariate analysis was made in that study (Uzun et al. 2008). No independent association between CRP and GFR has been found in diabetic patients (Lin et al. 2006), nor with a group of subjects with CKD stage 2–4 (Stam et al. 2003) or in stage 3–5 (Annuk et al. 2005) or in a MDRD study (Menon et al. 2003), nor again in a Swedish study of predialysis patients (Stenvinkel et al. 1999).

Table 4. Summary of cross-sectional studies on the relationship between inflammatory markers and kidney function in CKD patients excluding those with IgAGN. CRP = C-reactive protein, IL-6 = interleukin-6, ccr = creatinine clearance, eGFR(C-G) = estimated glomerular filtration rate by Cockcroft-Gault equation, eGFR(MDRD) = estimated glomerular filtration rate by MDRD equation.

Reference	Serum inflammatory marker	GFR method	Association with kidney function	No of kidney patients
Stenvinkel et al. 1999	CRP	S-creatinine	Insignificant	109
Panichi et al. 2001	CRP, IL-6, albumin,	S-creatinine, ccr	Significant: CRP, IL-6	102
Panichi et al. 2002	CRP, IL-6, albumin	Ccr	Significant	103
Menon et al. 2003	CRP	Iothalamate clearance	Insignificant	801
Stam et al. 2003	CRP	eGFR(C-G)	Insignificant	65
Saraheimo et al. 2003	CRP, IL-6	S-creatinine, eGFR (MDRD and C-G)	Significant: IL-6	194
Pecoits-Filho et al. 2003	IL-6	Average of ccr and urea clearances	Significant	176
Landray et al. 2004	CRP, albumin	Cystatin-C	Significant: albumin	334
Oberg et al. 2004	CRP, IL-6	eGFR(MDRD)	Insignificant	60
Ates et al. 2005	CRP	Ccr	Significant	108
Annuk et al. 2005	CRP	eGFR(MDRD)	Insignificant	44
Lin et al. 2006	CRP	eGFR(MDRD and C-G)	Insignificant	732
Soriano et al. 2007	CRP	eGFR(C-G)	Significant	90
Razeghi et al. 2008	CRP	eGFR(C-G)	Significant	100
Uzun et al. 2008	CRP, albumin	S-creatinine	Significant:CRP	88

Both IL-6 and CRP have been seen to differ significantly between CKD patients and healthy subjects, but the association between GFR and inflammatory markers was not significant (Oberg et al. 2004). Significant correlations between IL-6 and all GFR estimates were found in a Finnish study of diabetic patients, but no significant correlations prevailed between CRP and GFR (Saraheimo et al. 2003). CRP, but not IL-6 or serum albumin, was significantly different in two groups of patients close to the start of dialysis divided by median GFR (cut-off 6.5 ml/min). However, only IL-6 was independently associated with residual GFR, while no similar analysis was reported on serum albumin or crp (Pecoits-Filho et al. 2003). Lower serum albumin was independently linked with more severe renal impairment in the CRIB study (Landray et al. 2004).

Follow-up studies of different duration have revealed that CRP levels were not associated with baseline kidney function in diabetic nephropathy. This particular study did not provide follow-up information in this aspect (Friedman et al. 2005). In another study of CKD patients higher baseline CRP was independently associated with faster loss of renal function (Tonelli et al. 2005). Two more studies with CKD patients found no significant

relationship between CRP and kidney function decline (Ortega et al. 2002, Sarnak et al. 2002). In HD patients a higher lymphocyte count was independently associated with higher creatinine, and a higher neutrophil count with lower creatinine, but no association was reported between creatinine and WBC (Reddan et al. 2003). Baseline CRP was inversely significantly correlated with baseline residual renal function in a follow-up cohort of PD patients, but no follow-up information was provided in this aspect (Wang et al. 2004). As these two studies involved ESRD patients it is difficult to extrapolate conclusions to other CKD patients. A summary of these studies is presented in **Table 5**.

Table 5. Summary of follow-up studies on the relationship between inflammatory markers and kidney function in CKD and ESRD patients. CRP = C-reactive protein, eGFR(MDRD) = estimated glomerular filtration rate by MDRD equation, WBC = white blood cell count, ccr = creatinine clearance.

Reference	Serum inflammatory marker	GFR method	Association with kidney function	Follow-up time (years)	No of kidney patients
Ortega et al. 2002	CRP	Ccr	Insignificant	1 y	66
Sarnak et al. 2002	CRP	Iothalamate clearance	Insignificant	2.2 y	585/255
Reddan et al. 2003	WBC	S-creatinine	Not reported	1 y	25661
Wang et al. 2004	CRP	Average of ccr and urea clearances	Significant at baseline	2.5 y	231
Friedman et al. 2005	CRP	S-creatinine	Insignificant at baseline	2.6 y	1560
Tonelli et al. 2005	CRP	eGFR(MDRD)	Significant	4.8 y	687

2.9.5. Inflammation in IgA glomerulonephritis

It is highly likely that some of the aforementioned studies also included IgAGN patients. However, as the diagnostic features are not reported in detail, conclusions concerning IgAGN are difficult to draw from them. A summary of studies on IgAGN patients is presented in **Table 6**.

Registry data from the United Kingdom (baseline medians of serum creatinine 97 μmol/l and proteinuria 1.2g/24h) revealed that serum albumin < 40g/l and creatinine > 120 μmol/l at presentation were the only variables independently predictive of poorer 10-year cumulative renal survival (Johnston et al. 1992). Another report similarly showed the prognostic significance of serum albumin and a model for estimating the strongest predictor showed serum creatinine to be the most important factor, followed by urinary albumin excretion and serum albumin (Bailey et al. 1994). In one Finnish study patients were divided into two groups

based on their initial GFR and then evaluated separately with respect to prognostic features obtained at presentation. Only in the better GFR group (≥ 85 ml/min) and in univariate analysis, was serum albumin a significant predictor. This was however explained by the significant correlation between serum albumin and urinary protein excretion (Rauta et al. 2002). Prognostic indicators have been studied in Chinese IgAGN patients and serum albumin at presentation was inversely significantly correlated with high histological grade, but no information on a direct linkage with kidney function was reported (Li et al. 2002).

Rostoker and coworkers divided IgAGN and Henoch Schönlein patients into two groups based on indicators of poor prognosis at presentation. After either high-dose or low-dose immunoglobulin therapy for nine months, serum levels of IL-6 were significantly reduced, but no correlation was noted between IL-6 and decline in GFR (Rostoker et al. 1998).

In an older study using no ultra- or highly sensitive CRP assays, no elevation was found in IgAGN patients compared to healthy controls or other glomerulonepritis, but CRP correlated significantly with serum creatinine in the whole study population consisting of IgAGN and other glomerulonephritis patients (Tencer et al. 1995). IgAGN patients had significantly higher CRP levels in comparison to healthy controls, but no significant difference was found when compared to hypertensive renal patients. Results from a follow-up substudy were also reported and those with progressive disease had a significantly higher CRP than those with stable disease. However, the level of CRP at presentation or the mean CRP during the first year and the subsequent slope of 1/creatinine were not significantly associated (Janssen et al. 2000). CRP at presentation was not a significant predictor of prognosis in a comparison of the two IgAGN groups divided by reaching the predetermined end-point (halving of creatinine clearance) in another study (Descamps-Latscha et al. 2004). Again CRP, ESR and WBC were significantly higher in IgAGN compared to healthy matched controls, but no significant association was observed between CRP and renal function and no information was given concerning the other systemic inflammatory variables (Nelson et al. 2005). In the most recent report CRP levels of IgAGN patients at presentation were not different compared to healthy matched controls and no difference was found between progressive and stable patients (Baek et al. 2008).

Table 6. Summary of studies on the relationship between inflammatory markers and kidney function in IgAGN patients. CRP = C-reactive protein, IL-6 = interleukin-6, cl = clearance, eGFR(C-G) = estimated glomerular filtration rate by Cockcroft-Gault equation, eGFR(MDRD) = estimated glomerular filtration rate by MDRD equation.

Reference	Serum inflammatory marker	GFR method	Association with kidney function	Setting	No of IgAGN patients
Johnston et al. 1992	Albumin	S-creatinine	Significant	Follow-up 10 y	253
Bailey et al. 1994	Albumin	S-creatinine	Significant	Follow-up 5.3 y	151
Rauta et al. 2002	Albumin	S-creatinine, eGFR(C-G)	Significant	Follow-up 9.1 y	259
Li et al. 2002	Albumin	S-creatinine	Not reported	Follow-up 7.4 y	168
Rostoker et al. 1998	IL-6	S-creatinine, eGFR(C-G), polyfructosan cl	Insignificant	Follow-up 0.75 y	29
Tencer et al. 1995	CRP	S-creatinine	Significant	Cross-sectional	38
Janssen et al. 2000	CRP	1/s-creatinine	Insignificant	Cross-sectional and follow-up 6.1 y	56+18
Descamps-Latscha et al. 2004	CRP	S-creatinine, eGFR(C-G)	Insignificant	Follow-up 5.4 y	120
Nelson et al. 2005	CRP	S-creatinine, eGFR(C-G), cystatin-C	Insignificant	Cross-sectional	51
Baek et al. 2008	CRP	eGFR(MDRD)	Insignificant	Follow-up 1 y	137

In summary, very few studies have been able to link inflammatory markers with progression of IgAGN, even though many have discovered that progressive patients seem to have higher levels of inflammation than stable patients or healthy controls.

2.10. Alcohol

Excess use of alcohol is known to have detrimental effects on health (Corrao et al. 2004, Di Castelnuovo et al. 2006) and its consequences in the kidneys are multiple, ranging from tubular disorders and glomerular damage to acute renal failure (De Marchi et al. 1993, Epstein 1997, Rodrigo et al. 1998, Vamvakas et al. 1998).

2.10.1. Alcohol consumption and cardiovascular diseases

Numerous studies have shown that light to moderate alcohol consumption has cardioprotective properties in terms of improved total and cardiovascular mortality and fewer cases of cardiovascular disease (Kloner and Rezkalla 2007, Tolstrup and Grønbaek 2007). The latest meta-analysis showed the lowest total mortality at approximately half a drink daily (corresponding to 6 g of alcohol), but up to four drinks daily in men and two drinks daily in women still conferred benefit (Di Castelnuovo et al. 2006). Analogously, in CKD patients nonuse of alcohol

has been linked independently with greater cardiovascular mortality vs. using > 2 drinks weekly (Shlipak et al. 2005a).

The beneficial effects of low alcohol consumption have been suggested to derive from its ability to increase antioxidant capacity, insulin sensitivity, HDL-cholesterol and fibrinolysis and its ability to reduce platelet aggregation and coagulation (de Lorgeril and Salen 1999, Rimm et al. 1999, Hines and Rimm 2001,Vasdev et al. 2006). There is no uniform evidence as to the type of beverage (wine, beer or liquors) which produces the putative benefits of alcohol (Mukamal et al. 2003, Bau et al. 2007).

Atherosclerosis and glomerulosclerosis have been suggested to have analogous pathobiologic mechanisms (Diamond 1991). One Japanese autopsy study has revealed that alcohol consumption is associated with less glomerular sclerosis and arteriosclerosis in an age-adjusted analysis in women. The result was similar in men, although not statistically significant (Kubo et al. 2003). Another autopsy study reported alcohol intake to be independently associated with less renal arteriolar hyalinization (marker of nephrosclerosis), which in turn seemed in that study to be a powerful marker of cerebral atherosclerosis (Burchfiel et al. 1997). It has been suggested that alcohol may beneficially affect renal function via mechanisms similar to those reported for cardiovascular disease (de Francisco et al. 2005). Especially wine has been thought to be of benefit due to its antioxidant properties (Rodrigo and Rivera 2002, Caimi et al. 2004, Presti et al. 2007).

2.10.2. Alcohol consumption and kidney function

Increasing evidence indicates that lifestyle factors have an impact on the risk of developing CKD and the risk of its progression (Ritz and Schwenger 2005). Smoking, obesity and salt and alcohol intake are among the factors individually modifiable. Several studies, both cross-sectional and longitudinal, have examined the relationship between alcohol consumption and the risk of CKD.

Based on cross-sectional studies alcohol consumption has been associated with either increased risk of CKD (Perneger et al. 1999, Shankar et al. 2006) or decreased risk (Savdie et al. 1984, Kubo et al. 1999, Chung et al. 2005, Noborisaka et al. 2007), or alcohol has had no impact (Vupputuri and Sandler 2003). Analysis of a population-based cohort both cross-sectionally and longitudinally has revealed that only heavy drinking (defined as consuming four or more alcoholic beverages daily) carries an independently increased risk of CKD. Amounts less than this appeared to be safe, although no statistically significant protective effect was found (Shankar et al. 2006).

Several follow-up studies on the same topic have been published in the last decade. Over six units of alcohol weekly was independently associated with an increase in GFR in men (Kronborg et al. 2008). Men consuming

≥ 21 drinks weekly at baseline were 48 % less likely to develop ESRD compared to abstainers even after multiple adjustments for confounding factors. Liquor especially was associated with a reduced risk vs. non-liquor products (Reynolds et al. 2008). Consumption of alcohol < 20 g daily vs. no alcohol independently reduced the risk of developing CKD stages 1 and 2 in men and the risk reduction for CKD stage 3 or worse was 8 % in male subjects and 9 % in female subjects, being significant in both genders (Yamagata et al. 2007). A prospective cohort study showed that those with baseline alcohol consumption ≥ 7 drinks weekly had the lowest risk of developing either elevated serum creatinine levels or reduced GFR even after multiple adjustments for confounding factors (Schaeffner et al. 2005). In another study neither baseline alcohol consumption nor the type of alcohol beverages was significantly related to a risk of CKD (Stengel et al. 2003). In a study involving only women alcohol consumption was insignificantly associated with less renal function decline, but in a subanalysis women with hypertension consuming alcohol in any quantity vs. abstainers had a significantly lower risk of ≥ 20 % GFR decline (Knight et al. 2003).

It may be concluded that the majority of longitudinal studies favor a significant protective effect of alcohol consumption against kidney function decline. The studies in question have covered follow-up times ranging from 7 to 14 years with a substantial number of subjects in each.

2.10.3. Alcohol consumption and IgA glomerulonephritis

The association between glomerulonephritis and liver cirrhosis has been known since the 1950s (Pouria and Feehally 1999). Along with the development of the immunofluorescence technique it has become evident that mesangial IgA deposits are the commonest finding in over 50 % of glomerulonephritis patients with liver cirrhosis (Newell 1987). IgA deposits are common in alcoholic liver disease (Smith and Hoy 1989), but they also occur in other forms of cirrhosis and chronic hepatitis (Endo et al. 1983, Pouria and Feehally 1999). Most IgAGN cases associated with chronic liver disease are asymptomatic (Nochy et al. 1984), but a small number of patients present with nephrotic syndrome and renal impairment (Pouria and Feehally 1999).

This notwithstanding, alcohol consumption has been suggested to have a protective effect against developing IgAGN in a case-control study from Japan (Wakai et al. 1999); the greater the alcohol consumption, the lesser the risk. In a subsequent study by the same group of investigators, the result no longer reached statistical significance (Wakai et al. 2002). Alcohol consumption among IgAGN patients was assessed by inquiries from the patients and their close relatives and compared to patients with other glomerulopathies. No differences in alcohol intake were observed between the kidney patients, either self-reported or as reported by relatives

(Garcia et al. 1995). There are no studies on the association between kidney function and alcohol consumption in patients with established IgAGN.

2.10.4. Evaluation and markers of alcohol consumption

There are several traditional methods to evaluate the use of alcohol, including direct measurement of blood, breath or urine ethanol, blood levels of gamma-glutamyltransferase (GGT), mean corpuscular volume (MCV), carbohydrate-deficient transferrin (CDT), GGT-CDT combination (gamma-CDT) and aminotransferases (aspartate aminotransferase AST and alanine aminotransferase ALT) (Hock et al. 2005, Hietala et al. 2006a, Niemelä 2007). CDT appears to be a highly specific marker of ethanol intake and a mathematically formulated combination from GGT and CDT (gamma-CDT) seems to improve sensitivity (Niemelä 2007).

Acetaldehyde is the first metabolite of alcohol (Riveros-Rosas et al. 1997) and autoantibodies against acetaldehyde adducts with different carrier proteins are among the newly emerging biomarkers in alcoholism (Worrall et al. 1994, Viitala et al. 1997, Worrall et al. 1998, Viitala et al. 2000, Niemelä 2001, Niemelä 2007). Virtually all proteins can bind with reactive acetaldehyde, but there would appear to be preferential targets in vivo, hemoglobin being one of them (Worrall et al. 1991, Niemelä and Israel 1992, Sillanaukee et al. 1992, Viitala et al. 1997, Takeshita and Morimoto 2000, Viitala et al. 2000, Niemelä 2001). Immune responses against acetaldehyde adducts consist primarily of IgA and to some extent IgG antibodies (Worrall et al. 1991, Clot et al. 1995, Viitala et al. 1997, Niemelä 2001). Titers of serum IgA autoantibody against acetaldehyde adducts may also provide a sensitive and specific marker of alcohol consumption (Worrall et al. 1998, Hietala et al. 2006b, Niemelä 2007).

In addition to laboratory analyses the most usual means of assessing alcohol consumption is that based on a questionnaire. Simple self-administered questionnaires seem to provide useful estimates of alcohol intake (Giovannucci et al. 1991). Depending on the study and the beverage type in question, a drink has usually been defined to contain 10–15 g of alcohol (Hines and Rimm 2001). What is regarded as the level of heavy drinking differs between men and women and Finland has national recommendations on this context (Aalto and Seppä 2007).

3. AIMS OF THE PRESENT RESEARCH

The purpose in the present series was to obtain information on the prognostic markers in IgAGN. The focus was set on insulin resistance, inflammatory markers and alcohol consumption with respect to progression (longitudinal analyses) and on alcohol consumption markers (cross-sectional analysis). The original publications covered these issues as follows:

1. The role of insulin resistance in the progression of IgAGN **(I)**
2. The role of inflammatory markers in the progression of IgAGN **(II)**
3. The impact of alcohol consumption on renal function and on the progression of IgAGN **(III)**
4. Use of alcohol consumption markers in IgAGN **(IV)**

4. SUBJECTS AND METHODS

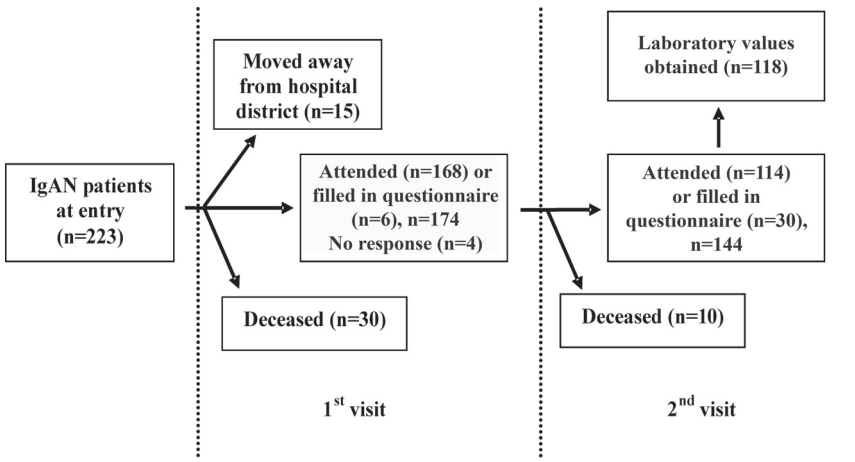
4.1. Subjects

4.1.1. Patients

The original population here consisted of patients living in the Pirkanmaa Health District in Finland (total population about 440 000) in whom IgAGN was diagnosed during a period of eleven years between January 1st 1980 and December 31st 1990 (223 patients). IgAGN was defined as glomerulonephritis with IgA as the sole or main glomerular immunofluorescence finding in renal biopsy. From this retrospective group a cohort was invited to attend a physician's appointment twice. Thirty patients had however died before the first visit and 15 had moved away from the district, whereby the remainder were invited to attend the first visit. The invitation for the second visit was sent approximately 6 years after the first.

For the first visit, a total of 174 patients (104 males) responded, of whom 168 (97 %) attended the appointment, while 6 (3 %) only filled in and returned a questionnaire. For the second visit, a total of 144 (82 males) patients responded. Ten more patients had died, 114 attended, 30 only returned the questionnaire, four of them also providing laboratory specimens. The study flow is depicted in **Figure 1** and the number of patients and gender distribution are presented in **Table 7**.

Figure 1. A description of the study flow.



The median patient age at the first visit was 48.5 years (range 17–85), the median time from renal biopsy 11 years (6–17). All patients had been diagnosed at least 5 years, 63 % at least 10 years and 26 % at least 15 years before the first visit. The median time from the first signs of IgAGN (episode of macroscopic hematuria, discovery of microscopic hematuria or proteinuria or renal insufficiency) was 14 years (7–57 years). Age at time of diagnosis was ≤ 40 years in 49 % of the patients and > 60 years only in 12 %. The median age at the second visit was 54 years (23–90) and the median time from biopsy was 16 years (11–24). A total of 100 % of the patients had been diagnosed at least 5 years, 97 % at least 10 years and 63 % at least 15 years before that visit. The median time from the first signs of IgAGN was 19 years (12–64 years).

One male was accidentally coded as a female and this was changed in study **IV**. After recalculation of the results from earlier studies, the results remained unaltered. Patients with diabetes mellitus were included in the published analyses and repetition of the statistics after their exclusion yielded similar results **(I)** (data not shown in this thesis). No patient was suffering a febrile infectious disease when laboratory values were obtained; no patient was thus subsequently excluded solely on the basis of CRP values. In both alcohol studies (**III**,**IV**) 10 ESRD patients (six of whom were on dialysis, four had undergone a kidney transplantation) were excluded to avoid the possible bias of terminal uremia leading to a reduction in alcohol consumption per se, and also six patients who only returned the questionnaire were excluded due to the lack of laboratory specimens.

Table 7. Number of patients and controls and distribution of gender in studies I–IV.

	Study I		**Study II**		**Study III**		**Study IV**	
No of visit	1st	2nd	1st	2nd	1st	2nd	1st	Controls
Men	104	82	104	82	95	76	96	99
Women	70	62	70	62	63	41	62	44
Altogether	174	144	174	144	158	117	158	143

4.1.2. Controls

In the alcohol marker study **(IV)** a healthy control population was gathered consisting of 143 individuals (99 men, 44 women), median age 46 years (19–84). They were either healthy abstainers or moderate or heavy drinkers evincing no clinical and laboratory signs of liver disease. Abstainers and moderate drinkers were hospital personnel or their acquaintances and heavy drinkers were individuals admitted for detoxification with a history of continuous ethanol consumption or binge drinking.

4.1.3. Clinical data

At the time of renal biopsy or during the follow-up there were no cases of SLE or liver cirrhosis. Two patients had celiac disease and six more developed it later in the follow-up. No cases of Crohn's disease were noted, but two patients had ulcerating colitis at the time of the renal diagnosis and one more was diagnosed during the follow-up. Twenty-six patients had a rheumatic disease of some kind (rheumatoid arthritis, polymyalgia rheumatica, psoriasis arthritis, gout, ankylosing spondylarthrosis or other rheumatic condition) and new rheumatic diseases were diagnosed in 46 during the follow-up, the majority of them with gout. One patient had a known malignancy at renal diagnosis and 22 developed malignancy in the follow-up. Twelve patients presented with some manifestations of Henoch-Schönlein purpura at renal diagnosis and one developed them later. Both primary and secondary IgAGN were thus included in this study. Clinical renal findings from both visits are presented in **Table 8**.

For the present analyses the criterion for hypertension was use of antihypertensive medication or systolic blood pressure (SPB) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg at the visits. The median values for SBP were 140 mmHg (104–190) at the first visit and 142 mmHg (90–224) at the second visit. DBP values were 89 mmHg (60–118) and 88 mmHg (52–120), respectively. The use of antihypertensive and lipid-lowering medications is presented in **Table 9**.

Table 8. Clinical renal findings from the visits. Proportion of patients (%).

Finding	1st visit (%)	2nd visit (%)
Macroscopic hematuria in history	29	42
Microscopic hematuria and proteinuria (≥ 0.08g/ 24h)	75	40
Microscopic hematuria alone	0	2
Proteinuria alone (≥0.08g/24h)	24	42
Proteinuria (≥1.0g/ 24h)	21	19
Proteinuria (≥3.0g / 24h)	4	6
Impaired renal function	13	22
ESRD	6	7
Transplantation once/twice	2/0	4/1

Table 9. Use of lipid-lowering and antihypertensive medications at the time of visits. Proportion of patients (%). ACEI= angiotensin-converting enzyme inhibitors, ARB= angiotensin II type 1 receptor blocker.

Medication	1st visit	2nd visit
Lipid-lowering agents	4	19
Statins	3	19
Fibrates	1	0
Antihypertensive medication	49	60
β-blockers	31	36
ACEI	25	29
ARB	0	10
Diuretics	14	22
Ca2+ entry blockers	20	28
Other	2	1

A patient was considered to have diabetes mellitus if the fasting venous blood glucose level was ≥ 7.1 mmol/l or the patient had previously been diagnosed the disease. Six patients had diabetes mellitus at the time of the renal biopsy and during the follow-up 19 new diabetic patients emerged. The number of diabetic subjects was thus 25 by the time of the second visit. Median body mass index (BMI) at the first visit was 26 kg/m^2 (18–45) and at the second visit 27 kg/m^2 (18–43), whereby the patients were slightly overweight and the tendency increased in the course of the time.

Thirteen per cent of the patients smoked at the time of the first visit, 16 % at the second. The percentages of ex-smokers were 33 % and 31 %, respectively. In the alcohol consumption study **(III)** there were 37 (23 %) abstainers, 80 (51 %) light drinkers, 25 (16 %) moderate drinkers and 16 (10 %) heavy drinkers. In the alcohol marker study **(IV)** the population was divided into three groups comprising 38 abstainers (24 %), 114 (72 %) moderate drinkers and 6 (4 %) heavy drinkers.

4.1.4. Ethical aspects

The study protocol was approved by the Ethics Committee of Tampere University Hospital, and the study was carried out according to the provisions of the Declaration of Helsinki.

4.2. Methods

4.2.1. Study protocols

The baseline clinical data on all the patients were collected from medical records. The follow-up involved two clinical visits separated by approximately six years. Data on medication, concurrent diseases, smoking and alcohol drinking habits as well as anthropometric measures, blood pressure and laboratory variables were recorded during the visits. Detailed information on the current amounts of alcohol consumption was obtained at the first visit by asking the quantities (a glass, a bottle, a can, a standard drink) as well as the types of alcoholic beverages consumed (beer, wine, or liquor) per week. The data were used to calculate total weekly intake of alcohol assuming that one regular drink contains 12 grams of alcohol. Apart from the laboratory variables analysed at the time of the visits, whole blood, serum, plasma and urine samples were frozen for subsequent additional analyses. Causes of death were confirmed from the patient files or from the death certificates kept by Statistics Finland. The follow-up ended at the second visit or at the latest available check obtained from the medical records or the questionnaires sent to patients who did not attend.

4.2.2. Laboratory determinations

4.2.2.1. GFR estimates

Different GFR estimates were used. Serum cystatin-C **(I,II,III)** was analysed using the immunoturbidometry method with Cobas Mira S (provided by F. Hoffmann–LaRoche, Basel, Switzerland) and values were considered normal if they were < 1.2 mg/l when the age was ≤ 50 years, or < 1.4 mg/l when the age was > 50 years. A six-variable eGFR(MDRD) (Levey et al. 1999) **(I,III)** was calculated and values were considered normal if they were ≥ 90 ml/min/1.73 m^2. The formula takes into account serum creatinine, urea and albumin as well as age, gender and race. Also eGFR(C-G) (Cockcroft and Gault 1976) **(III)** and creatinine clearance were determined, the latter using venous blood for s-creatinine and a 24-h urine collection and the following formula: creatinine clearance = (urine concentration of creatinine × 24 –h urine volume) / s-creatinine **(II)**.

4.2.2.2. Definition of progression of IgA glomerulonephritis

Progressive IgAGN at the second visit was defined as an elevation of serum cystatin-C above the normal level and over 20 % elevation from the value noted at the first visit, or if the patient had had a kidney transplant or was on dialysis **(I,II)**. No pre-emptive transplantations were carried out. In the alcohol consumption study **(III)** progression was defined as a reduction in eGFR(MDRD) below the normal level and an over 20 %

reduction from the value at the first visit. The 20 % rule was added in order to avoid misclassification of patients with elevated cystatin-C or reduced eGFR(MDRD) but nevertheless stable disease.

4.2.2.3. Insulin concentration and HOMA-IR

Serum insulin concentrations **(I)** were determined from overnight fasting samples, which were originally frozen at -70 °C. The analyses were simultaneously carried out for both visits using a human insulin-specific radioimmunoassay kit (Linco Research, Inc, St. Charles, MO, U.S.). The lowest detection level in the kit was 2 µU/ml in a 100-µl sample, the specificity for human insulin 100 % and for human proinsulin < 0.2 %, the means for within- and between-assay variations being 3.2 % and 3.88 %, respectively, and normal insulin concentrations being 5–15 µU/ml (all values as reported by the manufacturer). Homeostasis model assessment of insulin resistance (HOMA-IR) **(I)** was calculated according to the formula (Matthews et al. 1985): [plasma fasting insulin (µU/ml) x plasma fasting glucose (mmol/l) / 22.5].

4.2.2.4. Inflammatory markers

Serum highly sensitive CRP **(II)** values were analysed using an immunoturbidometry method with Cobas Integra 700 (provided by F. Hoffmann–LaRoche, Basel, Switzerland). The range of the measurements without dilutions was 0–160 mg/l. Serum albumin **(II)** was analysed by modified bromcresol green binding assay with Cobas Integra (F.Hoffmann-LaRoche, Basel, Switzerland), the range of measurements without dilutions being 0–60 g/l. The reference value for normal albumin was 36–50g/l. Serum IL-6 **(II)** was analysed by an enzyme immunoassay method using a commercial PeliKine compact human IL-6 Elisakit (Sanquin Reagents, Amsterdam, the Netherlands). WBC was analysed by in-house routine analytical methods in the laboratory of Tampere University Hospital.

4.2.2.5. Alcohol consumption markers and liver enzymes

Serum CDT **(III,IV)** was measured using automated immuno-nephelometric assays (N Latex CDT and N antiserum to human transferrin on a BN ProSpec analyzer, Dade Behring Marburg GmbH, Siemens Company, Marburg, Germany). The results were expressed as percentages of total transferrin. CDT was measured in an accredited (SFS-EN ISO/IEC 17025) laboratory at the Central Hospital of Seinäjoki, Seinäjoki, Finland. Serum urate, GGT, ALT, AST and ALP **(IV)** were measured by standard clinical chemical methods in the same laboratory in Seinäjoki. Gamma-CDT was determined using an equation based on GGT and CDT data as follows: 0.8 x ln(GGT) + 1.3 x ln(%CDT) (Hietala et al. 2006a) **(IV)**. The normal values for these variables were: CDT <2.0 %; GGT < 80 U/l (men), < 50 U/l (women); ALT < 50 U/l

(men), < 35 U/l (women); AST < 50 U/l (men), < 35 U/l (women); ALP 35–105 U/l; gamma-CDT < 4.0 (men) and < 3.5 (women). CDT values ≥ 2 % indicated heavy drinking.

IgA antibody against acetaldehyde-modified hemoglobin (anti-adduct IgA) **(IV)** was analysed in the laboratory of the Central Hospital of Seinäjoki by an ELISA technique. Microtiter plates (Nunc-Immuno Plate, Maxisorb™, InterMed, Denmark) were first coated with acetaldehyde-modified hemoglobin in PBS (3 µg protein in 100 µg well) and incubated for 1½ h at 37 °C. Nonspecific binding was blocked by incubation with 0.2 % gelatine in PBS (150 µl/well) for 1 h at 37 °C. The sample sera were diluted (1:40) in PBS containing 0.04 % Tween-20 (PBS-Tween). The serum dilutions were allowed to react with the coated protein for 1 h at 37 °C followed by extensive washing with PBS-Tween. Alkaline phosphatase-linked goat antihuman IgA (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, U.S.A.) was used to detect antibody-antigen complexes. The optical densities (OD) were read at 405 nm by an Anthos HT II microplate reader (Anthos Labtec Instruments, Salzburg, Austria). The values (OD 405) obtained in the reaction with the sample and unconjugated protein (background) were subtracted from the corresponding values measured from the reaction between the sample and the acetaldehyde-protein conjugate, and the values were expressed as U/l corresponding to OD 405 x 10E3.

4.2.2.6. Other laboratory variables

All blood samples were obtained after an overnight fast. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula providing that the triglyceride value was < 4.0 mmol/l (Friedewald et al. 1972). Other laboratory variables were analysed using the serum samples, spot and collection urine samples utilizing in-house routine analytical methods in the laboratory of Tampere University Hospital.

4.2.3. Definition of alcohol consumption

In the alcohol consumption study **(III)** the self-reported level of alcohol consumption and the result from CDT analysis were used to divide the study population into 4 categories: 0 g/week = abstainers, 0g –80g/week = light drinkers, 80g – 280 g/week (men) and 80g –190 g/week (women) = moderate drinkers and ≥ 280 g/week (men) and ≥ 190 g/week (women) = heavy drinkers, based on national recommendations for definition of heavy drinking (Aalto and Seppä 2007). Patients with a self-reported history of heavy drinking or positive alcohol biomarker (CDT≥ 2 %) data were classified as heavy drinkers. Thus 10 men who would otherwise have been classified as abstainers (1 patient), light (4 patients) or moderate (5 patients) users were all classified as heavy users instead. In the alcohol marker study **(IV)** the population was divided into 3 categories: 0 g/week = abstainers, >0 – 280 g/week (men) or >0 – 190 g/week (women) = moderate drinkers

and ≥ 280 g/week (men) or ≥ 190 g/week (women) = heavy drinkers. The division differed in the two alcohol studies as 4 categories were more appropriate to ascertain the level of protective and harmful consumption.

4.2.4. Statistical analyses

The SPSS for Windows 11.5 package was used for statistical analyses (SPSS Inc., Chigago, U.S.), and a two-sided p value < 0.05 was taken as the level for statistical significance. Correlations between two continuous variables were calculated using Pearson bivariate (r_P) correlations if both variables were normally distributed, and Spearman bivariate (r_S) correlations if one or both variables were non-normally distributed. Associations between categorical variables and continuous non-normally distributed variables were calculated using Mann-Whitney U-test or Kruskall-Wallis test depending on the number of categories. Associations between categorical variables and normally distributed variables were analysed by Student's t-test or one-way ANOVA depending on the number of categories. Relationships between categorical variables were analysed by $\chi 2$-test. Odds ratios and 95 % confidence intervals were computed using logistic regression analyses (enter method) with adjustments for the presence of hypertension (II) and both hypertension and proteinuria (III). In addition, some further adjustments were added in the results section.

5. RESULTS

5.1. Kidney function and progression of IgA glomerulonephritis

The median cystatin-C concentrations **(I,II)** at the first and second visits were 0.77 mg/l (range 0.44–5.70) and 1.06 mg/l (0.59–2.93), the medians for eGFR(MDRD) **(I)** were 77.3 ml/min/1.73m^2 (4.9–164.8) and 71.2 ml/min/1.73m^2 (11.9–127.5), for creatinine clearance **(II)** 1.76ml/s/1.73m^2 (0.01–3.68) and 1.55ml/s/1.73m^2 (0.01–2.98), respectively. After exclusion of ESRD patients and those lacking laboratory specimens **(III,IV)**, the medians for eGFR(MDRD), eGFR(C-G), creatinine clearance and cystatin-C on the 1st visit were 79.2 ml/min/1.73m^2 (18.3–164.8), 78.0 ml/min (19.8–208.2), 105.6 ml/min/1.73m^2 (30.0–220.8) and 0.76 mg/l (0.44–2.45), respectively. The values at the second visit were 71.9 ml/min/1.73m^2 (12.8–127.5), 70.2 ml/min (15–207), 94.2 ml/min/1.73m^2 (17.4–178.8) and 1.06 mg/l (0.71–2.93), respectively.

At the time of the first visit (I,II), 21/168 (13 %) patients had impaired kidney function, including 4 patients who had undergone kidney transplantation (with either normal or elevated cystatin-C values). At the second visit (I,II), 26/120 (22 %) patients presented with impaired kidney function, including 7 with kidney transplants. One of these patients had undergone two kidney transplantations. Altogether, ESRD had developed in 10/174 patients (6 %) by the time of the first visit, and in 13/174 patients (7 %) by the time of the second (I,II). All the transplanted patients were on dialysis before the procedure. At the second visit, IgAGN was classified as progressive in 23/118 (19.5 %) patients (I,II) and in 36/117 (30.8 %) patients (III) according to the definitions mentioned in the methods section.

5.2. Comparison between progressive and stable patients (I,II)

Those patients classified as progressive at the second visit were characterized by higher age, higher prevalence of hypertension, increased urate concentration values, and higher levels of proteinuria as well as poorer renal function at the first visit. There was no statistical difference in BMI, waist circumference, gender distribution, smoking habits or plasma lipid profiles between the groups. The comparisons are presented in detail in **Table 10**.

Table 10. Comparison of clinical and laboratory variables at the 1st visit between patients with progressive and stable disease at the 2nd visit (n=118). Data are presented as median values and range (in parenthesis).

1st visit	Stable disease (n=95)	Progressive disease (n=23)	P-value
Age (years)	45 (23–74)	56 (33–82)	0.007
Hypertension (% of patients)	61 %	96 %	0.001
BMI (kg/m2)	26 (19–41)	27 (18–45)	0.364
Waist circumference (cm)	89 (59–128)	93 (71–121)	0.154
Male sex (% of patients)	64 %	65 %	1.0
Smoking (% of patients)			0.317
Never	50 %	52 %	
Current	16 %	4 %	
Ex-smokers	34 %	44 %	
Cystatin-C (mg/l)	0.70 (0.44–2.45)	1.12 (0.62–4.72)	0.0001
MDRD (ml/min/1.73m2)	90 (18–165)	50 (5–91)	0.0001
Creatinine clearance (ml/s/1.73m2)	1.88 (0.50–3.68)	1.23 (0.03–2.10)	0.0001
Urate (mmol/l)	0.38 (0.15–0.66)	0.47 (0.27–0.71)	0.0001
Proteinuria (g/24 h)	0.3 (0.1–2.5)	0.9 (0.1–5.4)	0.009
Cholesterol (mmol/l)	5.3 (3.7–7.2)	5.3 (3.9–9.5)	0.187
HDL-cholesterol (mmol/l)	1.21 (0.62–2.46)	1.14 (0.68–2.03)	0.329
Triglycerides (mmol/l)	1.29 (0.42–7.50)	1.54 (0.78–6.54)	0.308
LDL- cholesterol (mmol/l)	3.4 (1.9–5.2)	3.4 (1.5–7.4)	0.100

5.3. Insulin resistance in IgA glomerulonephritis (I)

Serum insulin concentrations measured at the first visit showed a significant association with the progression of IgAGN during the follow-up (**Figure 2**). The patients in the progressive group had higher insulin concentrations than the stable patients (19 μU/ml vs. 14 μU/ml, p=0.02). Also the HOMA-IR at the first visit showed a significant association with progression, and analogously the progressive patients had a higher index when compared to the stable group (4.43 vs. 2.79, p=0.005). When insulin and HOMA-IR were adjusted by either proteinuria or the presence of hypertension, the results were no longer significant in either insulin resistance marker.

If kidney function at the second visit was estimated by cystatin-C and eGFR(MDRD), the insulin recorded at the first visit had the following correlations with them, respectively: r_S =0.291, p=0.002 and r_S =-0.132, p=0.154. HOMA-IR at the first visit showed the same correlations as follows: r_S =0.340, p<0.001 and r_S =-0.179, p=0.054. Two patients who had undergone a kidney transplantation between the visits were excluded from these correlation analyses.

5.4. Inflammatory markers in IgA glomerulonephritis (II)

CRP and WBC at the first visit were associated with progression, those with progressive disease having higher CRP and WBC values than the stable group (p=0.014 and p=0.023, respectively). Serum albumin was significantly associated with progression (p=0.0001), the progressive patients yielding lower levels. Serum IL-6 was not a significant determinant (p=0.091) (**Table 11**). When the inflammatory variables were adjusted for the presence of hypertension at the first visit, the associations for CRP (OR=1.1, 95% CI 0.99–1.2, p=0.07), WBC (OR=1.4, 95% CI 0.99–1.9, p=0.05) and IL-6 (OR=1.1, 95% CI 0.9–1.3, p=0.2) were not significant. However, the association with albumin was still highly significant (OR=0.7, 95% CI 0.6–0.9, p=0.001). When the inflammatory variables were adjusted by creatinine clearance noted at the first visit, only albumin was significant (OR=0.74, 95% CI 0.6–0.9, p=0.004), although CRP and WBC approached significance. Serum albumin was a significant factor even after adjustment for 24-h urinary protein excretion with the following results: serum albumin (OR 0.78, 95% CI 0.66–0.92, p=0.003) and 24-h urinary protein excretion (OR 1.98, 95% CI 1.08–3.69, p=0.027).

There were significant correlations between inflammatory variables noted at the first visit and kidney function at the second visit: CRP and cystatin-C (r_S =0.227, p=0.014), albumin and cystatin-C (r_S=−0.327, p=0.0001) and WBC and cystatin-C (r_S=0.236, p=0.011), but no significant correlation emerged between IL-6 and cystatin-C (r_S=0.155, p=0.096). If kidney function was estimated by creatinine clearance, the correlations with the inflammatory variables were as follows: CRP (r_S=−0.207, p=0.026), albumin (r_P=0.335, p=0.0001), IL-6 (r_S=−0.033, p=0.727) and WBC (r_P =−0.117, p=0.211). Two patients who had undergone kidney transplantation between the visits were excluded from these correlation analyses.

Figure 2. Plasma insulin concentration (panel A) and Homa-IR (panel B) at the 1st visit and the progression of IgAGN. Results are depicted as median (line inside the box), 25th persentile and 75th persentile (box), and range (whiskers).

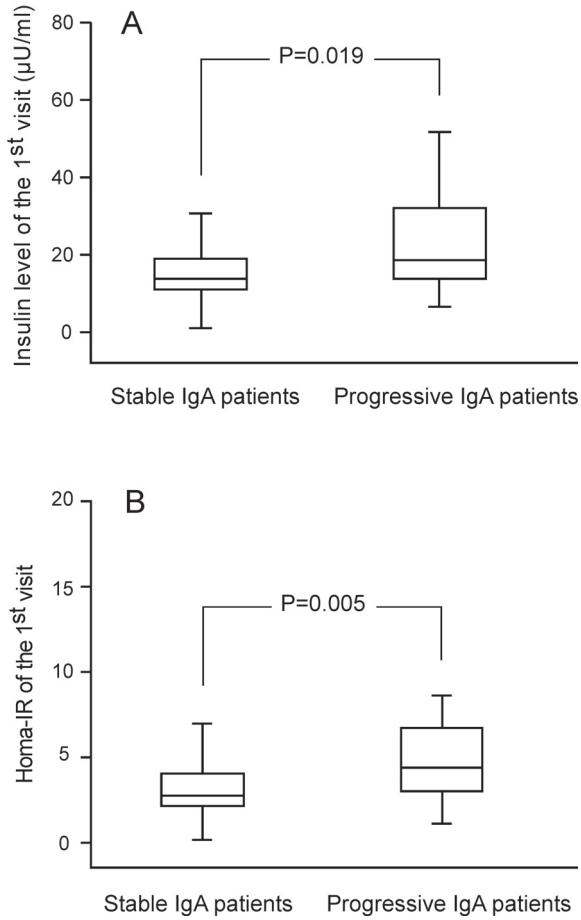


Table 11. Comparison of inflammatory variables at the 1st visit between patients with progressive and stable disease (n=118). The data are expressed as median values and range (in parenthesis).

1st visit	Stable disease n=95	Progressive disease n=23	P-value
CRP (mg/l)	1.8 (0.1–21.1)	2.9 (0.3–64.8)	0.014
IL-6 (pg/ml)	1.6 (0–14.3)	2.6 (0.7–17.0)	0.091
Albumin (g/l)	42 (31–50)	39 (26–45)	0.0001
WBC (10E9/l)	5.4 (3.0–11.6)	6.4 (3.8–8.8)	0.023

5.5. Alcohol consumption in IgA glomerulonephritis (III)

The median amount of self-reported weekly alcohol use was 12 (0–500) grams. Abstainers consumed no alcohol, light drinkers consumed 12 (1–75), moderate drinkers 120 (80–170) and heavy drinkers 338 (300–500) grams on a weekly basis. Women were found to use significantly less alcohol than men ($p<0.001$) and no women reported heavy use.

5.5.1. Clinical and laboratory variables in different alcohol consumption groups

CDT differed significantly between the alcohol consumption groups ($p<0.001$). Abstainers had the lowest value, 1.17 % (0.8–1.68), light drinkers 1.22 % (0.8–1.74), moderate drinkers 1.32 % (0.83–1.98) and the highest value 2.57 % (1.56–4.28) was observed in heavy drinkers. No significant difference prevailed between abstainers vs. light or moderate users. Age ($p<0.001$), gender distribution ($p<0.001$), the prevalence of hypertension ($p=0.016$), HDL-cholesterol levels ($p=0.014$) and 24-h urinary protein excretion ($p=0.02$) were found to differ significantly between the alcohol consumption groups. However, BMI, SBP and DBP values, cholesterol, triglycerides, serum albumin, urate, insulin and CRP were not statistically significantly different.

5.5.2. Alcohol consumption and kidney function

In the subgroups with different levels of alcohol intake, moderate drinkers were found to have the best kidney function independent of the GFR variable used (**Table 12**). However, when cystatin-C values were compared between light and moderate drinkers, the difference was not statistically significant ($p=0.167$), in contrast to the other GFR estimates (creatinine clearance $p=0.01$, eGFR(C-G) $p=0.005$ and eGFR(MDRD) $p=0.016$). The amount of reported alcohol intake correlated significantly with the GFR variables (all values are from the first visit): cystatin-C $r_S=-0.160$, $p=0.045$; creatinine clearance $r_S=0.246$, $p=0.002$; eGFR(C-G) $r_S=0.272$, $p=0.001$ and eGFR(MDRD) $r_S=0.216$, $p=0.007$. The corresponding figures between the reported alcohol intake at the first visit and GFR variables at the second visit were as follows: $r_S=-0.163$, $p=0.084$; $r_S=0.214$, $p=0.024$; $r_S=0.249$, $p=0.007$ and $r_S=0.235$, $p=0.011$.

Light drinkers were found to have the best kidney function among women and moderate drinkers among men independently of the GFR estimate used (**Table 12**). In women, abstainers vs. light drinkers yielded significant results with all the GFR estimates ($p<0.05$ for all comparisons), but no significant difference emerged between light vs. moderate drinkers in any of the GFR estimates. In men, abstainers vs. moderate drinkers, light vs. moderate drinkers and moderate vs. heavy drinkers showed significant differences in all GFR estimates ($p<0.05$ for all comparisons).

The correlations between the amount of reported weekly alcohol intake and kidney function (all values from the first visit) were stronger in women, with the following correlation coefficients and p-values for cystatin-C, creatinine clearance, eGFR(C-G) and eGFR(MDRD): r_S=–0.430, p<0.001; r_S=0.464, p<0.001; r_S=0.373, p=0.003; r_S=0.436, p=<0.001, respectively. The corresponding values for men were: r_S=–0.125, p=0.229; r_S=0.190, p=0.065; r_S=0.272, p=0.008; r_S=0.174, p=0.093, respectively. No significant difference emerged in GFR estimates between the genders (p=0.77 for creatinine clearance, p=0.73 for eGFR(C-G) and p=0.453 eGFR(MDRD)), although cystatin-C was almost significant (p=0.08).

5.5.3. Alcohol consumption and kidney function in univariate and multivariate analyses

The data on cross-sectional and longitudinal univariate and multivariate analyses between kidney function, as estimated by eGFR(MDRD), alcohol intake and other study variables are summarized in **Table 13.** In multivariate analyses alcohol consumption was adjusted for hypertension and 24-h urinary protein excretion, the traditional risk factors for a progressive course of IgAGN. Whether examined using the univariate or multivariate approach, moderate alcohol consumption emerged as a protective factor against kidney function decline in both cross-sectional and longitudinal analyses. Light alcohol consumption was a protective factor only in cross-sectional univariate and in longitudinal multivariate analysis.

Table 12. Kidney function and reported weekly alcohol consumption combined with CDT in different alcohol consumption groups and divided by gender. All values are from the 1st visit. The values are expressed as medians and range (in parenthesis).

All	**Abstainers (n=37)**	**Light drinkers (n=80)**	**Moderate drinkers (n=25)**	**Heavy drinkers (n=16)**	**p-value between the groups**
Cystatin-C (mg/l)	0.84 (0.55–1.73)	0.74 (0.44–1.88)	0.69 (0.44–1.13)	0.97 (0.45–2.45)	<0.001
Creatinine clearance (ml/min/1.73 m2)	87 (34–140)	108 (38–205)	124 (68–221)	93 (30–133)	<0.001
Cockcroft–Gault (ml/min)	68 (20–106)	77 (25–186)	97 (43–208)	67 (22–112)	<0.001
MDRD (ml/min/1.73 m2)	73 (22–111)	83 (26–164)	97 (46–165)	62 (18–129)	<0.001

Women	**Abstainers (n=20)**	**Light drinkers (n=40)**	**Moderate drinkers (n=3)**	**Heavy drinkers (n=0)**	**p-value between the groups**
Cystatin-C (mg/l)	0.93 (0.55–1.73)	0.67 (0.44–1.25)	0.74 (0.67–0.93)	n.a	<0.001
Creatinine clearance (ml/min/1.73 m2)	74 (34–131)	114 (71–175)	109 (97–165)	n.a	0.002
Cockcroft–Gault (ml/min)	65 (20–95)	84 (50–154)	79 (71–82)	n.a	0.006
MDRD (ml/min/1.73 m2)	66 (22–108)	92 (46–164)	82 (63–132)	n.a	<0.001

Men	**Abstainers (n=17)**	**Light drinkers (n=40)**	**Moderate drinkers (n=22)**	**Heavy drinkers (n=16)**	**p-value between the groups**
Cystatin-C (mg/l)	0.78 (0.55–1.65)	0.78 (0.53–1.88)	0.68 (0.44–1.13)	0.97 (0.45–2.45)	0.002
Creatinine clearance (ml/min/1.73 m2)	91 (40–140)	102 (38–205)	125 (68–221)	93 (30–133)	0.003
Cockcroft–Gault (ml/min)	74 (32–106)	74 (25–186)	99 (43–208)	67 (22–112)	0.001
MDRD (ml/min/1.73 m2)	76 (45–111)	77 (26–156)	99 (46–165)	62 (18–129)	0.001

n.a = not available

Table 13. Cross-sectional and longitudinal univariate and multivariate analyses (adjusted for hypertension and 24-h protein excretion) for the different variables with respect to kidney function (measured by eGFR(MDRD)) in the whole study population. All variables are continuous unless otherwise indicated.

	MDRD, cross-sectional, n=156-158, cut-off 90 ml/min						**MDRD, longitudinal, n=117, GFR < 90ml/min and reduction > 20 % during follow-up**					
Variable	**Univariate**			**Multivariate**			**Univariate**			**Multivariate**		
	OR	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**
Age	1.1	1.06–1.1	<0.001				1.04	1.0–1.1	0.024			
Hypertension												
No	ref			ref			ref			ref		
Yes	5.0	2.4–10.1	<0.001	4.6	2.1–10.0	<0.001	2.7	1.1–6.9	0.038	1.8	0.6–5.2	0.279
Gender												
Male	ref						ref					
Female	0.8	0.4–1.5	0.435				0.5	0.2–1.2	0.132			
Use of alcohol												
Abstainers	ref			ref			ref			ref		
Light drinkers	0.4	0.2–0.97	0.042	0.5	0.2–1.2	0.126	0.4	0.2–1.1	0.069	0.3	0.1–0.9	0.024
Moderate drinkers	0.2	0.1–0.6	0.005	0.1	0.04–0.5	0.002	0.1	0.01–0.5	0.01	0.03	0.003–0.3	0.002
Heavy drinkers	0.8	0.2–3.3	0.787	0.5	0.1–2.3	0.389	2.3	0.6–9.7	0.244	1.7	0.4–7.6	0.492
24-h urinary protein excretion	1.9	1.1–3.3	0.027	1.7	0.9–3.1	0.093	2.4	1.4–4.3	0.002	3.1	1.5–6.2	0.002
HDL-cholesterol	0.8	0.3–1.8	0.536				0.5	0.2–1.6	0.249			

When analyses were carried out separately for genders, light alcohol consumption vs. abstinence in women was a protective factor when assessed cross-sectionally (OR 0.1, 95 % CI 0.04–0.57, p=0.006), but not longitudinally. Male moderate drinkers vs. abstainers yielded almost significant results cross-sectionally (OR 0.26, 95 % CI 0.1–1.004, p=0.051) and significant results longitudinally (OR 0.04, 95 % CI 0.004–0.34, p=0.004). The use of multivariate analyses was not possible due to the low number of outcomes.

5.6. Alcohol consumption markers in IgA glomerulonephritis (IV)

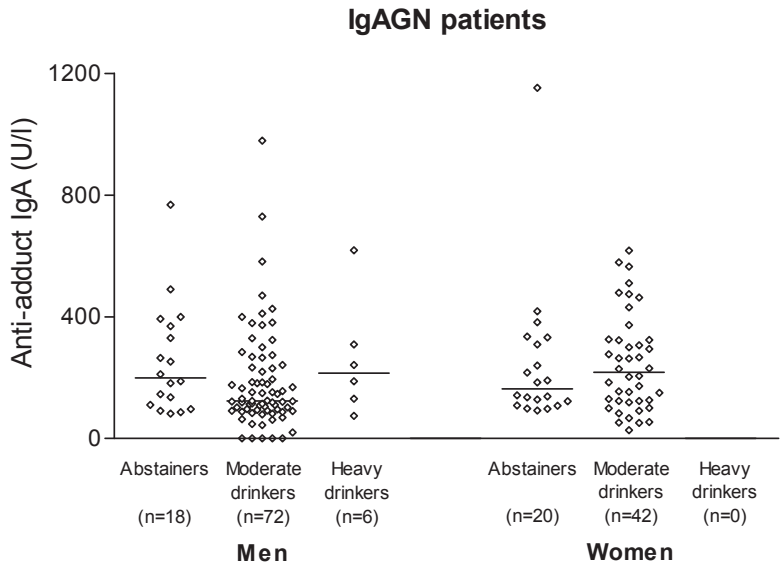
In the marker study the population was trichotomized on the basis of reported alcohol consumption; abstainers reported not consuming any alcohol, moderate drinkers consumed 24 (1–170) and heavy drinkers 338 (300–500) grams per week. Men used significantly more alcohol than women ($p<0.001$) and all heavy drinkers were men.

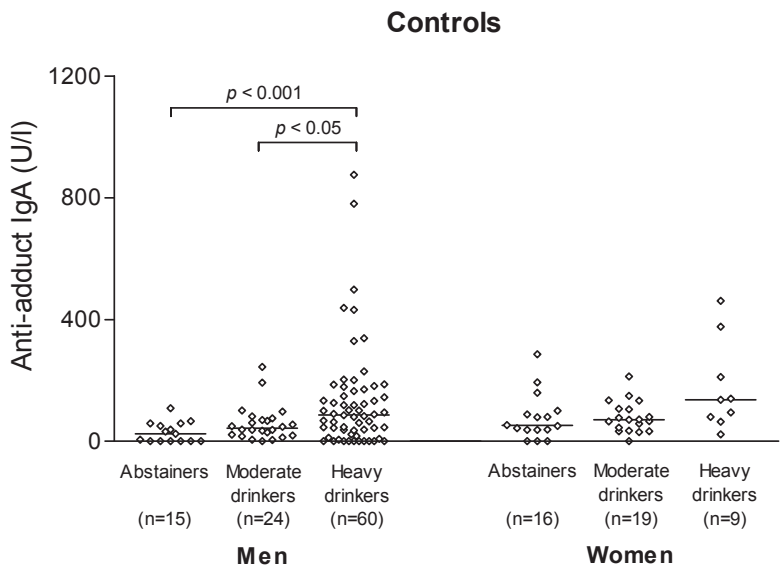
The results from the various biochemical methods for evaluating alcohol consumption and liver function in the subgroups classified according to self-reported alcohol consumption showed that in male IgAGN patients, drinking status was found to be significantly associated with MCV ($p < 0.001$), CDT ($p < 0.01$) and gamma-CDT ($p < 0.05$), but not with any other laboratory variable. In female IgAGN patients none of the tested variables was associated with alcohol consumption **(Table 14)**. In IgAGN patients the levels of anti-adduct IgA were significantly higher than those in the healthy controls both in men ($p < 0.001$) and in women ($p < 0.001$) and were elevated in 63 % of patients. However, the titers were not found to be associated with drinking status **(Figure 3)**. In the control population, all biomarkers and anti-adduct IgA levels were found to vary according to drinking status in men and all other variables except ALT (p=0.090) and anti-adduct IgA (p=0.099) also in women.

Table 14. Clinical and laboratory characteristics of patients with IgAGN and controls divided into subgroups according to gender and self-reported alcohol consumption. The values are expressed as medians and range (in parenthesis). MCV=mean corpuscular volume, GGT= gamma-glutamyl transferase, AST= aspartate aminotransferase, ALT= alanine aminotransferase, ALP= alkaline phosphatase, CDT= carbohydrate-deficient transferrin, Gamma-CDT= combination marker derived from GGT and CDT.

	Men					Women			
	Abstainers	**Moderate drinkers**	**Heavy drinkers**	**p-value**		**Abstainers**	**Moderate drinkers**	**Heavy drinkers**	**p-value**
MCV (fl)									
IgAGN patients	90 (85–95)	91 (85–101)	99 (91–107)	< 0.001		91 (84–97)	91 (71–102)	–	0.683
Controls	91 (85–97)	93 (85–103)	96 (86–107)	< 0.001		91 (83–94)	91 (83–97)	94 (87–101)	< 0.05
GGT (U/l)									
IgAGN patients	32 (15–71)	31 (9–223)	47 (19–2000)	0.358		22 (9–98)	21 (9–81)	–	0.833
Controls	26 (14–47)	24 (15–80)	92 (21–2078)	< 0.001		18 (11–33)	16 (11–42)	58 (31–607)	< 0.001
AST (U/l)									
IgAGN patients	22 (10–36)	22 (9–88)	29 (17–126)	0.240		18 (11–33)	16 (9–41)	–	0.242
Controls	24 (20–42)	27 (17–56)	51 (19–213)	< 0.001		23 (16–36)	21 (16–28)	43 (25–152)	< 0.001
ALT (U/l)									
IgAGN patients	14 (11–14)	16 (10–86)	22 (21–22)	0.272		12 (10–13)	16 (13–21)	–	0.223
Controls	22 (14–52)	28 (15–63)	53 (11–275)	< 0.001		21 (13–40)	19 (11–38)	32 (13–128)	0.090
ALP (U/l)									
IgAGN patients	64 (47–130)	65 (6–119)	64 (38–105)	0.955		56 (23–137)	51 (7–113)	–	0.474
Controls	60 (48–87)	58 (37–103)	76 (22–201)	< 0.001		56 (40–86)	45 (33–76)	88 (46–167)	< 0.001
CDT (%)									
IgAGN patients	1.2 (1.0–2.0)	1.3 (0.9–4.3)	2.3 (1.6–3.1)	< 0.01		1.2 (0.8–1.7)	1.2 (0.8–1.7)	–	0.676
Controls	1.3 (1.2–1.9)	1.5 (1.2–1.9)	2.5 (0.9–11.2)	< 0.001		1.5 (1.4–1.8)	1.5 (1.2–1.9)	3.8 (1.3–6.3)	< 0.01
Gamma-CDT									
IgAGN patients	3.0 (2.2–3.8)	3.2 (2.1–6.1)	4.0 (3.4–7.0)	< 0.05		2.7 (1.7–4.3)	2.6 (1.9–3.8)	–	0.430
Controls	2.9 (2.4–3.9)	3.2 (2.5–3.9)	4.9 (3.1–7.5)	< 0.001		2.8 (2.4–3.3)	2.8 (2.5–3.3)	5.0 (3.3–7.5)	< 0.001
IgA (g/l)									
IgAGN patients	3.7 (2.2–6.3)	3.4 (0.9–7.7)	4.9 (3.6–8.3)	< 0.05		3.3 (1.6–6.6)	2.6 (1.2–5.4)	–	< 0.05
Controls	2.3 (1.2–5.5)	2.1 (1.0–3.2)	2.8 (1.4–5.7)	< 0.05		1.7 (0.9–3.7)	1.9 (0.6–3.3)	2.9 (1.6–6.5)	< 0.01
Anti-adduct IgA (U/l)									
IgAGN patients	200 (82–768)	124 (0–979)	215 (74–618)	0.127		163 (92–1153)	218 (27–618)	–	0.673
Controls	24 (0–108)	43 (0–244)	87 (0–875)	< 0.01		52 (0–286)	70 (0–213)	136 (23–461)	0.099

Figure 3. IgA titers of antibodies against acetaldehyde adduct in IgAGN patients and healthy controls classified into subgroups according to gender and drinking status. In male healthy controls the titers were significantly higher in heavy drinkers than in moderate drinkers and abstainers. When comparing only moderate drinkers and abstainers, the difference was nearly significant (p=0.054). The comparisons between healthy females as well as between IgAGN patients were not significant. Lines indicate medians and significant comparisons are marked with p-value.





6. DISCUSSION

6.1 Patient characteristics

The population described here comprised IgAGN patients with conditions ranging from normal kidney function to severe kidney dysfunction, including ESRD. Of the original population 63 % were men and IgAGN is reported to have male predominance (Chan and Trachtman 2006). IgAGN occurs at any age with the usual clinical onset before the fourth decade of life (Donadio 2001, Berthoux et al. 2008) and in this cohort almost half of the patients had been diagnosed before that age.

6.2. Estimates of kidney function

Serum cystatin-C is considered a more reliable indicator of kidney function than serum creatinine and the estimates of glomerular filtration derived from it (Dharnidharka et al. 2002, Laterza et al. 2002). To enhance the credibility of the results several GFR estimates were used, including creatinine clearance, eGFR(MDRD) and eGFR(C-G). Creatinine clearance is regarded as more sensitive than serum creatinine measurement in detecting renal dysfunction, but it requires timed urine collection and is thus more laborious and sometimes inaccurate (Lamb et al. 2005). As eGFR(MDRD) is now widely used in clinical practice (Lamb et al. 2005), it was also included in this series as well and the original six-variable equation was chosen as serum albumin and urea were available. There have also been doubts that the plasma level of cystatin-C is influenced by factors other than renal function, and one study has suggested that CRP may be independently associated with cystatin-C level even after adjusting for creatinine clearance (Knight et al. 2004). Kidney function was therefore also assessed using creatinine clearance in the inflammation study **(II)**.

6.2.1. Definition of progression and rate of progression

The definition of progression was based on changes in serum cystatin-C levels **(I,II)** and eGFR(MDRD) levels **(III)**. Progressive IgAGN was defined as an elevation of serum cystatin-C above the normal level and > 20% elevation of the serum cystatin-C concentration during the follow-up **(I,II)**. The 20 % addition was implemented in order to avoid misclassification of patients with elevated cystatin-C values but nevertheless stable disease.

Analogously, progressive IgAGN was defined as eGFR(MDRD) < 90 ml/min/1.73 m^2 and > 20% reduction in eGFR(MDRD) during the follow-up **(III)**. Both 60 and 90 ml/min/1.73 m^2 cut-off values are used in publications, 60 ml/min/1.73 m^2 mostly with population studies (Sechi et al. 2002, Fox et al. 2005, Kurella et al. 2005, Satirapoj et al. 2005). What is to be considered a change in GFR sufficient to be regarded as progressive may be a matter of debate. However, in other publications the same level (20 %) has been used (Syrjänen et al. 2000, Rauta et al. 2002).

The median time from the diagnostic renal biopsy was 16 years at the second visit and almost all had been diagnosed at least 10 years prior to that visit. ESRD had developed in 7 % and impaired renal function of some magnitude in 22 % by that time. The number of progressive patients varied according to the GFR estimate used, being 19.5 % and 30.8 % with cystatin-C and eGFR(MDRD), respectively. In another Finnish study slightly worse figures have been noted, as ESRD developed in 9.7 % of the patients after a mean follow-up of 9.1 years. However, the proportion of progressive patients was 31 %, which is approximately the same as in this series (Rauta et al. 2002). ESRD is described as developing in 25–30 % of patients within 20–25 years from presentation (Barratt and Feehally 2006) and 10-year renal survival varies between 57–94 % (D'Amico 2004), thus the patient cohort in this thesis had reasonably well preserved renal function.

6.3. Insulin resistance in IgA glomerulonephritis

Various techniques have previously been utilized to assess insulin resistance and glucose tolerance in studies involving IgAGN patients (Kaneshige et al. 1983, Stenvinkel et al. 1995, Fliser et al. 1998, Kato et al. 2000, Eiro et al. 2003, Kielstein et al. 2003). There is considerable variation regarding the cut-off point for patients to be defined either as insulin-resistant or insulin-sensitive using the HOMA-IR method (Monzillo and Hamdy 2003), for which reason this was examined as a continuous variable in the present study. As glucose tolerance test or clamp were not feasible in the present study design, the fasting insulin values and HOMA-IR were used to assess insulin resistance.

Most earlier studies on insulin resistance in mild to moderate renal insufficiency have included patients with a variety of kidney diseases, and the number of IgAGN patients in many of the reports is rather low (Kaneshige et al. 1983, Stenvinkel et al. 1995, Fliser et al. 1998, Kato et al. 2000, Eiro et al. 2003, Kielstein et al. 2003). None of the previous studies provides follow-up information concerning the progression of IgAGN in relation to insulin levels. A recent Japanese report covering solely IgAGN patients found no relationship between insulin resistance and renal function (measured using ccl and serum creatinine), but showed an association between insulin resistance and hypertension (Eiro et al. 2003). In the study in question

insulin resistance was assessed using HOMA-IR, and insulin values were also reported as continuous variables. However, the study design was a cross-sectional, which may well explain the discrepancy when compared to the present results. It is possible that the influence of insulin resistance on the progression of IgAGN only becomes evident in the course of the time, and is easily hidden beneath other stronger variables (hypertension, proteinuria, age). However, it must be noted that a thorough multivariate analysis was not possible here due to the low number of outcomes, and when insulin resistance markers were adjusted for the presence of hypertension or proteinuria, the result was no longer significant.

BMI was not associated with the progression of IgAGN and the BMIs of the progressive and stable groups in the present series were similar. Two previous studies report that BMI at the time of diagnosis was significantly higher in the progressive group (Syrjänen et al. 2000, Bonnet et al. 2001). The differences in the results may be explained by the different time scales involved, as the patients in the present study were not assessed at diagnosis but approximately 11 and 16 years after the renal biopsy.

The characteristic components of the metabolic syndrome correlated significantly with insulin values also in the present IgAGN cohort. The risk of atherosclerosis is known to be increased in both patients with the metabolic syndrome and patients with impaired kidney function, while hyperinsulinemia itself has been implicated as an independent risk factor for cardiovascular disease (Stout 1985). It has also been postulated that similar mechanisms lie beneath the development of atherosclerosis and glomerulosclerosis, thus linking these two phenomena (Diamond 1991). As a significant association was found between elevated insulin as well as HOMA-IR values and the progression of IgAGN, one possible mechanism could be the analogous underlying pathophysiology in atherosclerosis and glomerulosclerosis.

In conclusion, the results here show that insulin resistance may be associated with the progression of IgAGN. Insulin might be used as an additive tool when evaluating the metabolic profile in these patients. It may well be that the findings are not limited to patients with IgAGN but can more likely be applied to a variety of proteinuric kidney diseases. However, further studies are needed to confirm whether an independent relationship exists between insulin resistance and progression of IgAGN.

6.4. Inflammatory markers

6.4.1. CRP in IgA glomerulonephritis

So far only five reports have been published on CRP in IgAGN, with follow-up times ranging from one to seven years. The majority of the studies in question do not favor a significant relationship between CRP and kidney

function or progression of IgAGN, although progressive patients seem to have higher levels of inflammation compared to stable patients or healthy control populations. The oldest report has no ultra- or high sensitive CRP assay (Tencer et al. 1995), in contrast to the other publications.

CRP was significantly linked with the progression of IgAGN in this series, whether kidney function was assessed using cystatin-C or creatinine clearance. The discrepancy over against other publications might partly be explained by the different estimates of GFR and follow-up times as well as the number of patients involved. Also several components of the metabolic syndrome (SBP, BMI, waist circumference, HDL, TG, insulin, urate) correlated with CRP, thus confirming previous observations from a non-renal population in the IRAS study (Festa et al. 2000) and observations in IgAGN patients (Nelson et al. 2005). However, whether the observed minor elevations of CRP signify only inflammation remains unclear. A recent review suggests that the presence of distressed cells rather than inflammation might be the stimulus for C-reactive protein production in several medical conditions (Kushner et al. 2006). Distressed renal cells could perhaps act in the same way, causing minor elevations of serum CRP.

6.4.2. Serum albumin in IgA glomerulonephritis

Serum albumin along with kidney function at presentation is a strong predictor of renal survival in IgAGN and this cannot be explained solely as a consequence of urinary protein excretion, as both serum albumin and proteinuria seem to have an independent role (Johnston et al. 1992, Bailey et al. 1994). The results in the present study also show that serum albumin was a significant predictor even after adjustment for daily proteinuria, and it is of note that the patients were also not heavily proteinuric. Serum albumin and urinary 24-h protein excretion did not even significantly correlate, although a significant inverse correlation between serum albumin and overnight urinary albumin excretion was found. Since serum albumin is also a negative acute-phase reactant (Kalantar-Zadeh et al. 2003, Black et al. 2004), it could have dual actions as a progression marker.

One Finnish study has shown that among patients in the better GFR group (≥ 85 ml/min) at presentation, serum albumin was a significant predictor of renal survival in univariate analysis; this finding was however explained by the significant correlation between serum albumin and urinary protein excretion (Rauta et al. 2002).

6.4.3. Serum IL-6 in IgA glomerulonephritis

There are more reports assessing urinary than serum IL-6 levels with respect to the prognosis of IgAGN. A French group has reported serum cytokines as having no correlation with the decline in GFR, although serum IL-6 levels were higher in IgAGN compared to healthy controls and decreased significantly after immunoglobulin therapy (Rostoker et al.

1998). The present findings support these results, as serum IL-6 was the only inflammatory variable studied which was not significantly associated with progression.

6.4.4. WBC in IgA glomerulonephritis

In the present study WBC was significantly associated with IgAGN progression, although adjustments for other variables weakened the significance. In another report, WBC was significantly higher in IgAGN compared to healthy matched controls, but no other information concerning this variable was given (Nelson et al. 2005).

In conclusion, the results presented in this study show that several inflammatory variables, serum albumin, CRP and WBC, were associated with the progression in IgAGN. Whether they have an independent role remains unclear, since due to the low number of outcomes an extensive multivariate assessment was not possible. IL-6 seemed to be an insignificant factor with respect to progression.

6.5. Effect of alcohol consumption in IgA glomerulonephritis

The results presented here constitute the first report on the link between alcohol consumption and kidney function in established IgAGN. The present data indicated the best kidney function in those with moderate alcohol consumption, while abstainers and heavy drinkers showed somewhat lower GFR. In multivariate analyses moderate alcohol consumption seemed to be a significant factor for better GFR when adjusted for hypertension and proteinuria. The follow-up data confirmed the finding from the cross-sectional approach and revealed that both light and moderate alcohol consumption are associated with a possible beneficial influence on the progression of IgAGN. The present data are also in accord with previous findings from cross-sectional studies (Kubo et al. 1999, Chung et al. 2005, Noborisaka et al. 2007) and with observations from follow-up studies (Knight et al. 2003, Schaeffner et al. 2005, Yamagata et al. 2007, Kronborg et al. 2008, Reynolds et al. 2008).

In the present study kidney function was assessed using four different methods. In a previous study from Taiwan very different results were obtained with different kidney filtration estimates. With serum creatinine, no significant differences were to be found between alcohol consumption groups, whereas with the other estimates (eGFR(C-G) and eGFR(MDRD)) significant changes were noted (Chung et al. 2005).

Taken together, the present data showed a significant association between moderate alcohol intake and better preserved GFR in IgAGN. Future studies appear warranted to examine the pathogenic and prognostic

implications of such findings. Even if future prospective trials were to show a similar beneficial effect of moderate alcohol consumption, there still remains the question of the safe level of use, which might even be different for various kidney diseases and for men and women.

6.6. Assessments of alcohol consumption in IgA glomerulonephritis

Most studies on alcohol drinking habits are based on self-reported levels of consumption. In study **IV** here, the majority of IgAGN patients were either abstainers or moderate drinkers, and their ethanol consumption profiles therefore differed markedly from typical alcoholic or general populations, which have previously been addressed in studies on alcohol biomarkers. The prevalence of abstainers (23 % in **III** and 24 % in **IV**) was markedly higher than that in the general Finnish population (10 %) of corresponding age and sex (Halme et al. 2008). Similarly, the prevalence of individuals exceeding the levels of hazardous drinking (10 % in **III** and 4 % in **IV**) was lower than expected from the population in general (15 %).

A wide variety of well-established biomarkers of alcohol abuse were analysed to increase the credibility of the results in the alcohol consumption study **(III)** and to gather information on the most useful methods for assessing alcohol consumption in IgAGN **(IV)**. Ten male IgAGN patients were found (one in the abstainer, four in the light and five in the moderate consumption group) in whom CDT was above the upper normal limit, possibly indicating underreporting of alcohol consumption. Underreporting alcohol intake is particularly common in health care settings, especially among women (Seppä et al. 1994, Lappalainen-Lehto et al. 2005). With this in mind a combination of CDT measurements together with the reported amounts of consumed alcohol was used in the analyses **(III)**. The advantage of CDT over other markers of alcohol abuse is its high specificity and false-positive results are rare (Stibler et al. 1988, Stibler 1991, Niemelä 2007).

The alcohol marker study in this series **(IV)** is the first publication on the association between alcohol consumption and IgA immune response to ethanol metabolites in patients with IgAGN. Studies on specific IgA responses appear particularly interesting, since IgAGN is known to involve specific derangements in the IgA system (Barratt et al. 2007b). Interestingly, the levels of anti-adduct IgA in this population were substantially higher than those in healthy controls. It is possible that among IgAGN patients there is an enhanced individual susceptibility to the firing of an IgA immune response even at fairly low levels of alcohol intake, and analogously, previous studies on immune responses to oral polio vaccine show that IgAGN patients respond to vaccination with an augmented IgA

antibody increase (Leinikki et al. 1987). Besides alcohol consumption, there may also be endogenous acetaldehyde and endotoxin production by gastrointestinal bacterial flora which might contribute to acetaldehyde levels, adduct formation and mucosal immune responses (Riveros-Rosas et al. 1997, Homann et al. 2000, Stickel et al. 2002, Latvala et al. 2005).

It is not clear whether these immune responses represent protective or harmful mechanisms. In the light of previous data on the sequence of events leading from excessive ethanol intake to advanced liver disease, it is argued that the early-phase antibody responses to ethanol-induced antigens could reflect regulation of tissue damage and immune protection mechanisms (Latvala et al. 2005). Anti-adduct IgA antibodies may contribute to the exclusion and neutralization of antigens resulting from the chemical modifications of proteins (Koskinas et al. 1992, Klassen et al. 1995). Anti-adduct IgA levels normalize at an average rate of 3 % per day after alcohol ingestion has ceased, the mean time required for normalization being approximately one month (Hietala et al. 2006b).

The amount of alcohol consumed prior to IgAGN diagnosis was unknown in the studied population. Studies with experimental animals have indicated that six weeks' chronic ethanol intake leads to the development of experimental IgAGN, characterized by mesangial expansion and intense IgA deposition in approximately 60 % of the population (Smith et al. 1990, Amore et al. 1994).

6.7. Influence of gender on alcohol studies in IgA glomerulonephritis

Gender is known to be a significant confounding factor in studies on immunological responses, although the specific underlying mechanisms involved have remained unclear. It is postulated that sex hormones play a role in the regulation of the immune responses and that inflammatory and immune responses are stronger in females than in males (Kovacs and Messingham 2002). In the alcohol marker study **(IV)** the immune response to protein adduct gave higher values in women, whereas no significant difference was found between genders in the estimates of kidney function. Based on the present data **(III)** it also appeared that sex may be a significant determinant in the effects of alcohol on GFR. Women showed stronger correlations between alcohol consumption and GFR, despite the fact that they consumed lower actual amounts of alcohol than men. Women seemed to report the amount of consumed alcohol more reliably, as was evident from the results from alcohol biomarker measurements. As seen in patients with cardiovascular diseases (Tolstrup and Grønbaek 2007), the safe and possibly protective levels of alcohol intake in respect of kidney function may also differ between men and women.

To conclude, the results showed high levels of anti-adduct IgAs in IgAGN patients, which, however, were not associated with the levels of self-reported alcohol consumption. Other markers (CDT, MCV and gamma-CDT) should therefore be used in the evaluation of alcohol consumption in such a patient population. Future studies are warranted to establish the significance of anti-adduct IgA immune response and its possible relationship with the aberrant protein glycosylation profiles described in IgAGN patients.

7. SUMMARY AND CONCLUSIONS

The summary of and conclusions to be drawn from the main findings in the present series are as follows:

1. In addition to the previously known risk factors, insulin resistance was associated with the progression of IgAGN. Insulin resistance could be used as an additive tool in evaluating the metabolic profile in these patients. The characteristic components of the metabolic syndrome correlated significantly with insulin values in the present cohort. It is, however, unclear whether insulin resistance has an independent role in the progression of IgAGN.

2. Increased values of C-reactive protein and total blood leucocyte count and lower values of serum albumin were associated with progression of IgAGN. Whether these constitute independent predictors for prognosis awaits larger studies with more thorough multivariate analyses. Serum IL-6 seemed to be irrelevant with respect to prognosis.

3. A significant association was noted between moderate alcohol intake and better preserved GFR. Light alcohol consumption in women and moderate consumption in men were associated with improved indices of GFR estimates. In this cohort women seemed to show stronger correlations between alcohol consumption and GFR, despite consuming lower actual amounts of alcohol than men. Whether moderate alcohol consumption has an independent role for prognosis remains to be elucidated in future studies.

4. Several markers of alcohol consumption (CDT, MCV, gamma-CDT) could be used in its evaluation in IgAGN patients. High levels of anti-adduct IgAs were found in IgAGN compared to healthy controls, but the levels were not associated with alcohol consumption, in contrast to the male control population.

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