Tampere University

ELINA PELTOLA

Long-term Prognosis of Patients with an Insulinoma

Tampere University Dissertations 454

Tampere University Dissertations 454

ELINA PELTOLA

Long-term Prognosis of Patients with an Insulinoma

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F115
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 17 September 2021, at 12 o'clock.

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

Supervisor and Custos	Professor Pia Jaatinen Tampere University Finland	
Supervisor	M.D., Ph.D. Päivi Hannula Tampere University Finland	
Pre-examiners	Docent Niina Matikainen University of Helsinki Finland	Docent Saila Kauhanen University of Turku Finland
Opponent	Docent Leo Niskanen University of Eastern Finland Finland	

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-2061-4 (print)
ISBN 978-952-03-2062-1 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2062-1

PunaMusta Oy – Yliopistopaino
Joensuu 2021

To my children.

ACKNOWLEDGEMENTS

This dissertation was carried out at the Faculty of Medicine and Health Technology of Tampere University, at the Division of Internal Medicine in Seinäjoki Central Hospital, at the Department of Internal Medicine in Tampere University Hospital, and in close collaboration with the University Hospitals of Helsinki, Kuopio, Oulu and Turku.

First of all, I owe my deepest gratitude to my excellent thesis supervisors, professor Pia Jaatinen and Päivi Hannula. They have been there for me around the clock, encouraging me to aim high and excel myself, and supporting me in my professional and scientific growth. I am most thankful for their detailed practical help, mental support and insightful opinions. This support has been inexpressibly meaningful to me. I admire my supervisors for their engagement in this project and scientific work in general.

My warmest thanks belong to Heini Huhtala, for her expert help with the statistics. I admire her expertise and ability to focus on the essentials. I am truly grateful to docent Saara Metso and docent Juhani Sand, the members of my official follow-up group, for their encouragement and belief in me in those moments, when this project has felt endless to me. I am also thankful to all my other co-authors, professor Johanna Arola, docent Tapani Ebeling, Hanna Hämäläinen, Ulla Kiviniemi, docent David Laaksonen, professor Johanna Laukkarinen, docent Leena Moilanen, professor Markus Mäkinen, professor Pirjo Nuutila, Antti Piiroinen, Elina Pirinen, docent Pasi Salmela, docent Camilla Schalin-Jäntti, professor (emeritus) Harri Sintonen, Jukka Sirén, Minna Soinio, Fia Sundelin, docent Mirva Söderström, Mirja Tiikkainen and Martine Vornanen, as well as for their contribution during the collection, analysis and interpretetation of the data, and for the insightful discussions during the past ten years. I am very grateful to Karri Helin, Matti Kotila, Tapani Salonen and docent Jaakko Antonen, the physicians in chief, for enabling me to carry out this project alongside my clinical work at Seinäjoki Central Hospital and Tampere University Hospital.

My humble gratitude goes to the reviewers of this thesis, docent Niina Matikainen and docent Saila Kauhanen, for helping me to improve my work. I am also most

grateful to Esko J. Väyrynen for the revision of the English language in the original publications and this thesis.

My most heartfelt thanks belong to all of my friends from the different phases of life. Especially I am thankful for Maija, Emmi, Saara, Hanna and Emma for our long-lasting friendship. I am so happy to have You in my life. My dear friends and colleagues, Hanna and Maarit, it is hard to even imagine the time in medical school and after that without Your relaxing, inspiring and joyful company.

I am grateful for my loving family and in-laws. I wish to thank my parents, Leena and Ari, for their belief in me, and their endless support and concrete help during the past few years. My sisters Johanna and Maria, I am thankful for the happy moments spent together with our children. These moments have offered me a welcome rest from the scientific work. I am always thankful to my parents-in-law, Kaija and Reijo, for their help and support in the life of our family, and for providing me a home while I was living in Seinäjoki.

My most loving thanks belong to my dear husband Pekka, for all his concrete help and support during this project, and to our lovable daughter Emilia, who is the light of our life.

This thesis was financially supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, the Medical Research Fund of Seinäjoki Central Hospital and the Cities of Seinäjoki and Tampere, Tampere University Research Funds, and the Finnish Medical Foundation.

Tampere, August 2021

Elina Peltola

ABSTRACT

Insulinomas are rare pancreatic insulin-producing neuroendocrine neoplasms (NENs), with an incidence of 1–4 per million persons per year. The incidence of all NENs has increased during the past few decades, at least partly due to the improved imaging studies and clinical awareness. In insulinomas, the excessive insulin secreted by the tumour leads to repeated episodes of hypoglycaemia, especially in the fasting state. This appears as neuroglycopenic symptoms (such as confusion, visual disturbances and loss of consciousness) caused by the brain's deprivation of glucose, and autonomic symptoms (such as palpitations and diaphoresis) caused by activation of the autonomic nervous system due to hypoglycaemia. Because of the diverse symptoms and the rarity of the disease, the delay from the beginning of the symptoms to the diagnosis of insulinoma is often long. Insulinomas are usually non-metastatic and considered cured after a surgical removal of the tumour, but little is known about the long-term prognosis of insulinoma patients. For patients with a metastatic insulinoma (<10% of all insulinoma patients), the overall survival is known to be significantly impaired, with a median survival of less than 2 years.

The aim of this study was to assess the incidence, clinical characteristics, diagnostics and treatment of insulinoma in Finland, and to study the long-term morbidity, mortality and quality of life (QoL) of insulinoma patients compared to the general population.

This retrospective study included all the adult patients diagnosed with an insulinoma in Finland during 1980–2010 (n=79). Firstly, clinical data related to patient and tumour characteristics, diagnostics, and treatment of insulinomas were gathered from the patient records in Tampere, Helsinki, Kuopio, Oulu and Turku University Hospitals. The incidence, diagnostic delay, success rates of preoperative localization and applied surgical methods were compared between patients diagnosed in the 1980s, 1990s and 2000s.

Secondly, the health-related quality of life (HRQoL) of insulinoma patients was assessed by a validated 15D questionnaire and a questionnaire on current health. The results of the 15D questionnaire were compared to those of an age- and gender-adjusted reference population from the National Finrisk 2011 Study.

Thirdly, four controls matched for age, gender and the place of residence were obtained for each patient from the National Population Registry. Endocrine, cardiovascular, gastrointestinal and psychiatric diagnoses of the patients and the controls between 1980 and 2015 were obtained from the National Hospital Discharge Register, and cancer diagnoses from the Finnish Cancer Registry (FCR). The incidences of these diseases in the patients versus controls were compared by calculating the incidence rate ratios with 95% confidence intervals using the Mantel-Haenszel method.

The main results of this study were that the incidence of insulinomas increased in Finland almost two-fold during the study period from 1980 to 2010, but despite the improved diagnostic options the diagnostic delay remained the same, with a median of 13 months. Long-term morbidity due to atrial fibrillation, intestinal obstruction and breast and kidney cancers was increased in insulinoma patients compared to controls. Despite the increased long-term morbidity, the overall survival (OS) of patients with a non-metastatic insulinoma was similar to that of the general population. In patients with a metastatic insulinoma, the OS was significantly impaired, with a median survival of 3.4 years. In patients participating in the HRQoL survey, the mean total 15D score, indicating the overall HRQoL, as well as scores on the dimensions of mobility, usual activities and eating, were significantly better than in the controls.

In conclusion, the incidence of insulinomas has increased during the past few decades, but the diagnostic delay has remained unchanged. Despite the excellent OS and long-term HRQoL in patients with a non-metastatic insulinoma, the prognosis of insulinoma patients is negatively affected by the increased morbidity due to atrial fibrillation, intestinal obstruction and possibly breast and kidney cancer. In the future, larger studies are needed to confirm these results and to specify factors associated with the increased morbidity, enabling appropriate strategies for the early diagnosis, treatment, and long-term follow-up of patients previously treated for an insulinoma.

TIIVISTELMÄ

Insulinoomat ovat harvinaisia insuliinia tuottavia haiman neuroendokriinisia kasvaimia. Ilmaantuvuus on yhdestä neljään miljoonaa henkilöä kohti vuodessa. Kaikkien neuroendokriinisten kasvainten ilmaantuvuus on kasvanut viime vuosikymmenten aikana, johtuen ainakin osin parantuneista kuvantamismenetelmistä ja lisääntyneestä tietoisuudesta neuroendokriinisten kasvainten suhteen. Insulinoomien liiallinen insuliinineritys johtaa toistuvasti veren glukoosipitoisuuden laskuun etenkin paastotilassa, aiheuttaen keskushermoston glukoosinpuutteesta johtuvia oireita, kuten sekavuutta, näköhäiriöitä ja tajunnan alenemista, sekä autonomisen hermoston aktivoitumisesta johtuvia oireita, kuten hikoilua ja rytmihäiriöitä. Oireiden moninaisuudesta ja kasvainten harvinaisuudesta johtuen insulinooman toteaminen usein viivästyy. Insulinoomat eivät yleensä lähetä etäpesäkkeitä ja ne ovat useimmiten parannettavissa leikkauksella. Insulinoomapotilaiden pitkän aikavälin ennusteesta ei kuitenkaan ole juurikaan aiempaa tietoa. Pahanlaatuiset, etäpesäkkeitä lähettäneet insulinoomat ovat harvinaisia, mutta niitä sairastavilla potilailla keskimääräinen elossaoloaika diagnoosin jälkeen on alle kaksi vuotta.

Tutkimuksen tarkoituksena oli tutkia insulinooman ilmaantuvuutta, oirekuvaa, diagnostiikkaa ja hoitotuloksia Suomessa, sekä selvittää insulinoomapotilaiden pitkäaikaissairastuvuutta, kuolleisuutta ja terveyteen liittyvää elämänlaatua taustaväestöön verrattuna.

Tutkimukseen otettiin mukaan kaikki yli 18-vuotiaat henkilöt, joilla todettiin insulinooma Suomessa vuosina 1980–2010. Kliiniset tiedot potilaiden oireista, insulinoomien diagnostiikasta ja hoidosta ja kasvainten piirteistä kerättiin Tampereen, Helsingin, Kuopion, Oulun ja Turun yliopistollisten sairaaloiden potilastietojärjestelmistä. Insulinoomien ilmaantuvuutta, diagnoosin viivästymistä, kuvantamismenetelmien osuvuutta ja käytettyjä leikkausmenetelmiä verrattiin 1980-, 1990- ja 2000-luvulla diagnosoitujen potilaiden välillä.

Toisessa vaiheessa insulinoomapotilaiden terveyteen liittyvää elämänlaatua tutkittiin validoidulla 15D-elämänlaatukyselyllä ja sitä taustoittavalla terveystietokyselyllä. Elämänlaatukyselyn tuloksia verrattiin Finriski 2011-tutkimuksen iän ja sukupuolen mukaan kaltaistettuun verrokkiväestöön.

Kolmanneksi jokaiselle insulinoomapotilaalle poimittiin Väestörekisteristä neljä iän, sukupuolen ja asuinpaikan mukaan kaltaistettua verrokkia. Tiedot potilaiden ja verrokkien tautidiagnooseista (umpieritysrauhasten taudit, sydän- ja verisuonitaudit, vatsan alueen taudit sekä mielenterveyden ja käyttäytymisen häiriöt) haettiin Terveydenhuollon hoitoilmoitusrekisteristä ja tiedot syöpädiagnooseista haettiin Syöpärekisteristä vuosilta 1980–2015. Tautien ilmaantuvuutta potilailla insulinoomadiagnoosin jälkeen verrattiin verrokkien vastaavaan ilmaantuvuuteen laskemalla ilmaantuvuuksien suhteet 95 %:n luottamusväleineen Mantel-Haenszel -tilastomenetelmällä.

Tutkimuksen tulosten perusteella insulinooman ilmaantuvuus kasvoi miltei kaksinkertaiseksi 1980-luvulta 2000-luvulle tultaessa, mutta parantuneista kuvantamismenetelmistä huolimatta viive oireista diagnoosiin pysyi pitkänä, ollen keskimäärin 13 kuukautta. Pitkäaikaisseurannassa insulinoomapotilaiden sairastuvuus sydämen eteisvärinään, suolitukoksiin ja rinta- ja munuaissyöpiin oli merkitsevästi yleisempää kuin taustaväestöllä. Lisääntyneestä sairastuvuudesta huolimatta etäpesäkkeettömän insulinooman sairastaneiden potilaiden kokonaiselossaoloaika ei merkitsevästi eronnut taustaväestöstä. Sen sijaan niillä potilailla, joilla todettiin insulinooman etäpesäkkeitä, keskimääräinen elossaoloaika insulinoomadiagnoosin jälkeen oli vain 3.4 vuotta. Elämänlaatututkimukseen osallistuneilla potilailla yleistä terveyteen liittyvää elämänlaatua kuvastava keskimääräinen 15D-luku sekä elämänlaadun tasoarvot liikkuvuuden, tavanomaisten toimintojen ja syömisen ulottuvuuksilla olivat merkitsevästi parempia kuin iän ja sukupuolen mukaan kaltaistetuilla verrokeilla.

Johtopäätöksenä on, että insulinooman ilmaantuvuus on kasvanut viime vuosikymmenten aikana, mutta diagnoosi viivästyy edelleen usein. Hyvänlaatuista insulinoomaa sairastavien potilaiden erinomaisesta elinajan- ja terveyteen liittyvän elämänlaadun odotteesta huolimatta insulinoomapotilaat sairastuvat taustaväestöä yleisemmin sydämen eteisvärinään, suolitukoksiin ja mahdollisesti myös rinta- ja munuaissyöpiin. Tulevaisuudessa laajemmat tutkimukset ovat tarpeen näiden tulosten varmistamiseksi ja insulinoomapotilaiden varhaisen diagnostiikan, hoidon ja pitkäaikaisseurannan kehittämiseksi.

CONTENTS

ABBREVIATIONS

ASVS	arterial stimulation venous sampling
BMI	body mass index (kg/m^2)
CD	Clavien-Dindo classification of surgical complications
CI	confidence interval
CT	computed tomography
15D	The 15D health-related quality of life instrument
EIHI	exercise-induced hyperinsulinaemic hypoglycaemia
ENETS	European Neuroendocrine Tumor Society
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
EUS	endoscopic ultrasound
FCR	Finnish Cancer Registry
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{18}F-DOPA	^{18}F-dihydroxyphenylalanine
G	(tumour) grade
^{68}Ga-DOTANOC	^{68}Ga-DOTA-1-Nal^3-octreotide
^{68}Ga-DOTATATE	^{68}Ga-DOTA-Tyr^3-octreotate
^{68}Ga-DOTATOC	^{68}Ga-DOTA-D-Phe^1-Tyr^3-octreotide
GEP	gastroenteropancreatic
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1c, glycated haemoglobin A1
HILMO	Hoitoilmoitusjärjestelmä/ the Care Register for Health Care (continuation of the National Hospital Discharge Register)
HR	hazard ratio
HRQoL	health-related quality of life
ICD	International Classification of Diseases
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
IOUS	intraoperative ultrasound
MEN1	multiple endocrine neoplasia type 1

MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
max	maximum
min	minimum
MiNEN	mixed neuroendocrine–non-neuroendocrine neoplasm
NA	not applicable
NEC	neuroendocrine carcinoma
NEN	neuroendocrine neoplasm
NET	neuroendocrine tumour
OR	odds ratio
OS	overall survival
PanNEC	pancreatic neuroendocrine carcinoma
PanNEN	pancreatic neuroendocrine neoplasm
PanNET	pancreatic neuroendocrine tumour
PET	positron emission tomography
PRRT	peptide receptor radionuclide therapy
QoL	quality of life
RR	rate ratio
SD	standard deviation
SPECT	single-photon emission computed tomography
THL	Terveyden ja hyvinvoinnin laitos / Finnish Institute for Health and Welfare
THPVS	transhepatic portal venous sampling
TNM	tumour node metastasis
US	ultrasound
Valvira	National Supervisory Authority for Welfare and Health
vHL	von Hippel-Lindau syndrome
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their roman numerals I-III.

I Peltola, E., Hannula, P., Huhtala, H., Metso, S., Kiviniemi, U., Vornanen, M., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Arola, J., Sirén, J., Piiroinen, A., Soinio, M., Nuutila, P., Söderström, M., Hämäläinen, H., Moilanen, L., Laaksonen, D., Pirinen, E., Sundelin, F., Ebeling, T., Salmela, P., Mäkinen, M. J., and Jaatinen, P. (2018). Characteristics and outcomes of 79 patients with an insulinoma: A nationwide retrospective study in Finland. International Journal of Endocrinology, Article ID 2059481, 10 pages. doi:10.1155/2018/2059481

II Peltola, E., Hannula, P., Huhtala, H., Sintonen, H., Metso, S., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Ebeling, T., and Jaatinen, P. (2021). Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010. Clinical Endocrinology, 94(2), 250-257. doi:10.1111/cen.14336

III Accepted manuscript: Peltola, E., Hannula, P., Huhtala, H., Metso, S., Sand, J., Laukkarinen J., Tiikkainen, M., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Laaksonen, D. E., Ebeling, T., Arola, J., Schalin-Jäntti, C., and Jaatinen, P. (2021). Long-term morbidity and mortality in patients diagnosed with an insulinoma. Accepted for publication in European Journal of Endocrinology. doi:10.1530/EJE-21-0230

AUTHOR'S CONTRIBUTION

Elina Peltola was the first and corresponding author of all the three original communications that are included in the dissertation. Regarding publication I, she participated in designing the study and applying for the required research permissions and collected the patient record data from Tampere and Helsinki University Hospitals. Peltola had full access to all the data in the study, and she conducted the statistical analyses in collaboration with a statistician. Peltola had an important role in interpreting the results and she drafted and revised the manuscript.

Regarding publication II, Peltola participated in designing the study and the health questionnaire. She wrote the notice to patients, posted the questionnaires to the patients and collected the data from the questionnaires. Peltola participated in conducting the statistical analyses, and she drafted and revised the manuscript.

Regarding publication III, Peltola participated in designing the study and applying for the required research permissions. She analysed the data together with a statistician, had an important role in interpreting the results, and drafted and revised the manuscript.

1 INTRODUCTION

Insulinomas are rare insulin-producing neuroendocrine neoplasms (NENs) of the pancreas, with an incidence of 1–4 cases per million persons per year (Jensen et al., 2012; Maggio et al., 2020; Mehrabi et al., 2014; Service F. J. et al., 1991). The incidence of all NENs has increased, at least partly because of improved clinical awareness and diagnostic sensitivity (Dasari et al., 2017; Leoncini et al., 2017).

The excessive insulin secretion by the insulinoma tumour tissue leads to a syndrome characterized by episodes of low blood glucose (hypoglycaemia). Hypoglycaemia causes severe symptoms resulting from the brain's deprivation of glucose (neuroglycopenic symptoms, such as confusion, drowsiness, visual disturbances, unconsciousness) and the activation of the autonomic nervous system (autonomic symptoms, such as diaphoresis, tremor and palpitations) (Jensen et al., 2012). The biochemical diagnosis of insulinoma is based on the documentation of the Whipple triad (symptoms or signs consistent with hypoglycaemia, a low plasma glucose level at the time of the symptoms, and relief of the symptoms when plasma glucose level is raised by glucose administration) and the measurement of a high serum insulin concentration concomitantly with a low blood glucose level (Cryer et al., 2009; Öberg et al., 2017; Whipple, 1938). The correct diagnosis of insulinoma is often delayed, as similar symptoms occur commonly in many other conditions, such as neurological and mental disorders (Service F. J. et al., 1991). Also, the localization of these typically small tumours may be challenging and often requires multiple imaging modalities, such as computed tomography, magnetic resonance imaging, endoscopic ultrasound and various functional nuclear imaging techniques (Sundin et al., 2017).

A majority of insulinomas are non-metastatic and considered cured by surgery. Yet, approximately 5 to 10% of insulinomas are metastatic and associated with a poor prognosis (de Herder et al., 2006; Mehrabi et al., 2014). The long-term prognosis of patients with a surgically cured, non-metastatic insulinoma is expected to be as good as that of the general population (Giannis et al., 2020; Mehrabi et al.,

2014). There are, however, hardly any studies with long-term follow-up of patients with insulinoma. During the period from the beginning of the symptoms until the correct diagnosis and treatment of insulinoma, the patients are exposed to long-lasting hyperinsulinemia and repeated episodes of hypoglycaemia. These factors may have unfavourable effects on the cardiovascular and nervous system, may also increase the incidence of cancer, and impair the health-related quality of life (HRQoL) of the patients. The long-term HRQoL in insulinoma patients has not been studied before.

The aim of this thesis was to study the incidence, clinical characteristics, diagnostics, treatment, and outcome of insulinomas diagnosed in Finland during 1980–2010. As former data on the long-term outcome of insulinoma patients are scarce, we wanted to investigate the long-term morbidity, HRQoL and mortality in patients previously diagnosed with an insulinoma, compared to age- and gender-adjusted controls from the Finnish general population.

2 REVIEW OF THE LITERATURE

2.1 Definition and epidemiology of insulinoma

Functioning, insulin-secreting neuroendocrine neoplasms are called insulinomas. The term functioning refers to the excessive insulin secretion by the neoplasm, causing a clinical syndrome, characterized by episodes of hypoglycaemia (Jensen et al., 2012). Virtually all insulinomas are located in the pancreas (Jensen et al., 2012; Modlin et al., 2008) but a few cases have been reported, for example in the duodenum, ileum, jejunum, spleen, liver, uterine cervix and kidney (Furrer et al., 2001; Liu et al., 2018; Mehrabi et al., 2014; Ramkumar et al., 2014; Seckl et al., 1999; WHO Classification of Tumours Editorial Board, 2019).

Insulinomas are rare with a reported incidence of 1–4 cases per million persons per year (Jensen et al., 2012; Maggio et al., 2020; Mehrabi et al., 2014; Service F. J. et al., 1991). Yet, they are the most common functioning pancreatic neuroendocrine neoplasms (PanNENs) (70 % of cases), followed by gastrinomas, VIPomas, glucagonomas, somatostatinomas, and other less common functioning PanNENs, each causing a distinct hormonal syndrome (Jensen et al., 2012; WHO Classification of Tumours Editorial Board, 2019). PanNENs account for only 2–5 % of all primary pancreatic neoplasms, with an estimated incidence of <1 case per 100 000 persons per year (Franko et al., 2010; Halfdanarson et al., 2008; Krampitz & Norton, 2013). According to their histopathological and molecular characteristics, PanNENs are divided into well differentiated, grade 1–3 pancreatic neuroendocrine tumours (PanNETs), and poorly differentiated pancreatic neuroendocrine carcinomas (PanNECs), which are by default considered high-grade.

Previous studies indicate that the general incidence of NENs has increased during the past few decades, which is at least partly due to improved clinical awareness and increased sensitivity of laboratory and imaging methods (Boyar Cetinkaya et al., 2017; Dasari et al., 2017; Hallet et al., 2015; Leoncini et al., 2017; Yao et al., 2008). The incidence of well-differentiated PanNENs has increased for both low- and high-grade tumours, and especially for non-functioning tumours, which account for 60–

90% of all PanNENs (Falconi et al., 2016; Kuo & Salem, 2013; Leoncini et al., 2017; Öberg et al.; Vagefi et al., 2007; WHO Classification of Tumours Editorial Board, 2019). It is currently unknown, whether the incidence of insulinomas has increased, as well.

2.2 Etiology and pathogenesis of insulinoma

2.2.1 Normal β-cell function and regulation of insulin secretion

The pancreas is a 12-15 cm long, lobulated organ located in the upper abdomen. It is anatomically divided into four main parts: head, neck, body, and tail. The pancreas has both exocrine and endocrine tissue. The exocrine pancreas consists mainly of acinar and ductal cells. Acinar cells are organized into clusters and secrete inactive digestive enzymes into the small, intercalated ducts, which they surround. The intercalated ducts, formed by column-shaped ductal cells, drain into larger intralobular, and finally interlobular ducts with an increasing diameter. (Kierszenbaum & Tres, 2016; Ross & Pawlina, 2011)

The endocrine pancreas accounts for only about 1 to 2% of the volume of the pancreas. It consists of clusters of neuroendocrine cells distributed within the exocrine tissue throughout the pancreas. These clusters are called pancreatic islets, or the islets of Langerhans, after their discoverer Paul Langerhans (Ovalle, et al., 2013). Pancreatic islets consist of glucagon-secreting α-cells, insulin-secreting β-cells, somatostatin-secreting δ-cells, pancreatic-polypeptide secreting PP-cells, and ghrelin-secreting ε-cells (Ovalle et al., 2013). The areas of pancreatic islets are richly innervated and contain several small arterioles and venules. (Kierszenbaum & Tres, 2016; Ross & Pawlina, 2011)

Apart from the endocrine pancreas, neuroendocrine cells can be found throughout the body. They are called neuroendocrine, because they have many characteristics of neurons, such as membrane excitability and dense core granules, but they also are capable of synthesizing and secreting hormones into the circulation, like the cells of the endocrine system. The neuroendocrine system includes endocrine glands (such as the pituitary, the parathyroid glands and the adrenal medulla), endocrine islets within glandular tissue (pancreatic islet cells, thyroid C cells), and

single or clustered endocrine cells scattered mainly in the gastrointestinal tract, gallbladder, and the respiratory tract, but also for example in the kidneys, liver, skin, thymus, uterine cervix, ovaries, testes, and the prostate. The neuroendocrine cells outside the pure endocrine organs are referred to as the diffuse endocrine system. (Oronsky et al., 2017; Rindi & Wiedenmann, 2011)

Pancreatic β-cells are neuroendocrine cells that are specialized in synthesizing, processing, storing and secreting insulin. Insulin is originally synthesized as a larger precursor molecule, preproinsulin, which is processed in the rough endoplasmic reticulum to form proinsulin (Guettier & Gorden, 2010; Ross & Pawlina, 2011). From the endoplasmic reticulum, proinsulin is further transported into β-cell granules, and at an optimum pH and calcium concentration, the proinsulin is cleaved into insulin and C-peptide and released into the circulation by exocytosis (Guettier & Gorden, 2010; Ovalle et al., 2013; Ross & Pawlina, 2011).

Under normal circumstances, the insulin secretion of pancreatic β-cells is strictly regulated by the blood glucose concentration, as the β-cells adjust the insulin secretion according to the glucose levels in the intercellular space (Ovalle et al., 2013; Ross & Pawlina, 2011). When glucose level rises after a meal, the adenosine triphosphate -sensitive potassium channels of the β-cells close, causing depolarization, calcium influx and release of insulin from the cell (Röder et al., 2016). The insulin secretion of the β-cells is further potentiated by the incretin effect of some peptides, such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide (Röder et al., 2016). By its effect on hepatocytes, insulin decreases gluconeogenesis and glycogenolysis, and enhances glycogen synthesis (Kierszenbaum & Tres, 2016). In peripheral tissue, insulin enhances the glucose entry to cells by translocating glucose transporters to the cell surface (Kierszenbaum & Tres, 2016).

When blood glucose level falls approximately below 4.5 mmol/l, the insulin secretion of pancreatic β-cells is decreased (Cryer, 2007). If the glucose level falls further, the secretion of insulin is discontinued, and the secretion of counterregulatory hormones, in particular glucagon and epinephrine, is increased (Cryer et al., 2009; Service F. J., 1995). In prolonged hypoglycaemia, also the secretion of cortisol and growth hormone is increased (Cryer et al., 2009).

2.2.2 Pathogenesis of insulinoma

Unlike normally functioning β-cells, insulinoma cells are characterized by incomplete processing and unregulated secretion of proinsulin and insulin (Guettier & Gorden, 2010). Insulinoma cells continue to secrete insulin and proinsulin at glucose concentrations below the physiological range. The molecular mechanisms leading to the development of insulinoma are poorly understood (Guettier & Gorden, 2010). Insulinomas may arise from mature, insulin-producing β-cells of the pancreas or from pancreatic stem cells (Guettier & Gorden, 2010; Jonkers et al., 2007; Sadanandam et al., 2015). Whole-genome/whole-exome sequencing of 84 insulinomas and 127 non-functioning PanNETs suggested different genetic backgrounds for insulinomas and non-functioning PanNETs (Hong et al., 2020). In insulinomas, chromosomal instability and distinct genetic alterations may predispose to the development and progression of oligo-/polyclonal precursor lesions and further to monoclonal tumours (Guettier & Gorden, 2010). In addition, a recent study on 9 insulinomas reported overexpression of an insulin messenger RNA splice variant, leading to increased insulin translation efficiency (Minn et al., 2004). In patients with the multiple endocrine neoplasia type 1 (MEN1) syndrome, a germline mutation in the MEN1 gene together with an insulinoma cell-specific MEN1 deletion ("second hit") predisposes to the development of insulinomas (Guettier & Gorden, 2010).

Recent evidence suggests that metastatic and non-metastatic insulinomas may differ in their origin and pathogenesis: metastatic insulinomas seem to share multiple features with non-functioning PanNENs, including ARX gene expression, biochemical profile (especially elevated chromogranin A levels), similar oncological treatment options, and natural history (Hackeng et al., 2020; Yu, 2020). Patients with a metastatic insulinoma may also have a past history of progressive non-functioning PanNEN, while a history of benign insulinoma is extremely rare (Veltroni et al., 2020; Yu, 2020).

2.2.3 Risk factors for insulinoma

In 90–95% of the patients, insulinomas occur sporadically, i.e., without any known genetic predisposition (de Herder et al., 2006). No common risk factors have been identified for the development of sporadic insulinomas. They are slightly more

common in women than in men (60% vs. 40%), and the incidence is highest during the 5th decade of life (Crippa et al., 2012; Jensen et al., 2012; Mehrabi et al., 2014; Sada et al., 2021; Service F. J. et al., 1991). Insulinomas are extremely rare in children and young adults under 30 years of age (Mehrabi et al., 2014).

A small minority of insulinomas are associated with rare hereditary tumour syndromes, most commonly with the MEN1 syndrome, which is diagnosed in 5–10% of insulinoma patients (de Herder et al., 2006; Falconi et al., 2016; Sada et al., 2021). Other genetic syndromes that may rarely be associated with insulinomas include tuberous sclerosis, neurofibromatosis type 1, von Hippel Lindau disease (vHL), and familial insulinomatosis caused by a MAFA germline mutation (Anlauf et al., 2007; Falconi et al., 2016; Iacovazzo et al., 2018; O'Shea & Druce, 2017).

The MEN1 syndrome is a rare genetic disorder caused by a mutation in the MEN1 gene that normally encodes a tumour suppressor protein, menin (Anlauf et al., 2007). The MEN1 syndrome mainly affects the endocrine glands: the most common manifestations of the MEN1 syndrome include hyperparathyroidism (in 95–100% of the patients with MEN1), and pancreatic and pituitary tumours (Jensen et al., 2008). Insulinomas occur in approximately 10% of patients with MEN1 (O'Shea & Druce, 2017). Compared to sporadic insulinomas, MEN1-related insulinomas typically occur at a younger age and may more often present as multiple or metastatic tumours (Anlauf et al., 2007; Crippa et al., 2012; Jensen et al., 2012; Jensen et al., 2008; O'Shea & Druce, 2017; Sakurai et al., 2012; Service F. J. et al., 1991; van Beek et al., 2020).

2.3 Clinical characteristics

Hypoglycaemia causes diverse symptoms resulting from the brain's deprivation of glucose (neuroglycopenic symptoms) and the activation of the autonomic nervous system secondary to hypoglycaemia (autonomic symptoms). Neuroglycopenic symptoms predominate the clinical picture and are reported in almost all insulinoma patients (Jensen et al., 2012). They are diverse and range from weakness, confusion, headache and visual disturbances to amnesia, transient loss of consciousness, seizures and even rarely hypoglycaemic coma or death (Jensen et al., 2012). Most patients also have symptoms due to the activation of the autonomic nervous system, including both adrenergic (palpitations, tremor, aggressiveness) and cholinergic

symptoms (sweating, hunger, paraesthesias) (Cryer et al., 2009; Jensen et al., 2012). In healthy persons, symptoms of hypoglycaemia develop at a plasma glucose level of 3.0 mmol/l or less, with autonomic symptoms appearing first and neuroglycopenic at slightly lower glucose levels (Cryer et al., 2009). In patients with recurrent hypoglycaemias, however, the symptoms of hypoglycaemia may appear at significantly lower glucose levels (Cryer et al., 2009).

In patients with an insulinoma, the hypoglycaemic symptoms typically develop during fasting or exercise, but up to 21% have also, and 6–9% exclusively, postprandial symptoms (Falconi et al., 2016; Placzkowski et al., 2009; Toaiari et al., 2013). Insulinoma patients typically learn to avoid the symptoms by frequent meals, and previous studies have reported weight gain in 14–44% of the patients prior to the treatment of insulinoma (Boukhman et al., 1998; Nikfarjam et al., 2008).

2.4 Tumour characteristics

Most insulinomas are small, solitary lesions, evenly distributed in the head/neck, body and tail of the pancreas (Jensen et al., 2012; Mehrabi et al., 2014). They are typically well-demarcated, encapsulated, trabecular or solid neoplasms with greyish-white to yellowish-tan colour and sometimes haemorrhagic cut surfaces (WHO Classification of Tumours Editorial Board, 2019). Two thirds of the tumours are 2 cm or less in diameter (de Herder et al., 2006; Mehrabi et al., 2014). Multiple neoplasms occur in approximately 10 % of insulinoma patients, often associated with the MEN1 syndrome (de Herder et al., 2006).

Approximately 10% of insulinomas are metastatic (de Herder et al., 2006; Nikfarjam et al., 2008; Service F. J. et al., 1991). Typical sites of metastasis include the liver in approximately 38% and lymph nodes in 18% of the patients with a metastatic disease (Jensen et al., 2012; Mehrabi et al., 2014). Less common sites of metastasis reported in the literature include peritoneum, lungs, brain and bones (Mehrabi et al., 2014).

2.5 Diagnostics of insulinoma

The possibility of spontaneous hyperinsulinism of pancreatic islet cells that leads to hypoglycaemia was first introduced by Seale Harris in 1924 (Harris, 1924). In 1927, Wilder et al reported the first case of malignant pancreatic islet-cell tumour, extracts of which caused marked hypoglycaemia in rabbits (Wilder et al., 1927). In the 1930s, when hormone concentration measurements and radiological imaging methods were not yet available, Allen O. Whipple introduced a triad of criteria to help identifying insulinoma patients among other patients with similar symptoms suggestive of hypoglycaemia (Whipple, 1938). The Whipple triad includes 1) symptoms, signs or both consistent with hypoglycaemia, 2) a low plasma glucose level measured at the time of the symptoms (≤2.2 or <3mmol/l) (Cryer et al., 2009; Öberg et al., 2017), and 3) relief of symptoms when the glucose level is raised. Whipple proposed that no pancreatic surgery for insulinoma should be performed unless all these criteria were met (Whipple, 1938).

With the improved diagnostic options today, the detection of the Whipple triad is no longer considered to justify surgical exploration of the pancreas, but rather an indication for biochemical and radiological investigations to confirm hyperinsulinaemic hypoglycaemia and to localize the tumour before surgery (Cryer et al., 2009; Giannis et al., 2020). After the surgical management of insulinoma, the diagnosis is confirmed by the histopathological and immunohistochemical analysis of the tumour specimen (WHO Classification of Tumours Editorial Board, 2019).

If the patient history, clinical characteristics, laboratory or imaging studies arise the suspicion of MEN1 or another hereditary tumour syndrome, the diagnostic investigations are supplemented by genetic germline DNA testing to confirm the diagnosis of a genetic syndrome. DNA testing should be considered when a patient has a personal or family history or clinical findings compatible with the MEN1 syndrome, tuberous sclerosis or vHL, has a young age at presentation (under 40 years), has multiple insulinomas or has disease recurrence after a complete surgical removal of the tumour (Anlauf et al., 2009; Falconi et al., 2016; Jensen et al., 2012; O'Shea & Druce, 2017).

2.5.1 Biochemical diagnostics

The biochemical diagnosis of insulinoma is based on the detection of inappropriately high serum insulin, C-peptide and proinsulin concentrations concomitantly with a low blood glucose level. The slightly different criteria for endogenous hyperinsulinism recommended by the Endocrine Society and the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines are shown in Table 1 (Cryer et al., 2009; Öberg et al., 2017). In addition to these hormone determinations, β-hydroxybutyrate concentration can be measured, with a level of 2.7 mmol/l or less confirming the inappropriate insulin or insulin-like hormone secretion in the presence of hypoglycaemia (Cryer et al., 2009; Öberg et al., 2017). Demonstration of glucose level rise of at least 1.4 mmol/l in response to 1 mg intravenous glucagon administration in a hypoglycaemic patient, corroborates the hyperinsulinaemic state (Cryer et al., 2009; Falconi et al., 2016). Drug screening for oral hypoglycaemic agents and determination of antibodies against insulin and insulin receptors is recommended in order to exclude the effect of exogenous insulin or insulin secretagogues, and insulin autoimmune hypoglycaemia (Cryer et al., 2009; Öberg et al., 2017).

The episode of hypoglycaemia can be spontaneous or induced by a fasting test. The golden standard for the clinical diagnosis of insulinoma is a prolonged fasting test, where fasting is continued with samples for hormone determinations taken every 6 hours (every 1 to 2 hours when the blood glucose level falls below 3.3 mmol/l), and at the time of symptoms, until the patient has signs or symptoms of hypoglycaemia, hypoglycaemia is documented (blood glucose level <2.2–2.5 mmol/l or <3.0 mmol/l, if the Whipple triad has been documented on a prior occasion) or until the standard duration of 72 hours (Cryer et al., 2009; Öberg et al., 2017). The sensitivity of the fasting test in identifying patients with an insulinoma is over 95%, and in approximately 70–80% of the patients, the hyperinsulinaemic hypoglycaemia occurs during the first 24 hours of fast (Donegan et al., 2017; Hirshberg et al., 2000; Öberg et al., 2017; Service F. J. & Natt, 2000). The required duration of fast cannot be predicted from e.g. the age, body mass index (BMI) or gender of the patient (Donegan et al., 2017).

In the rare cases, where the prolonged fasting test fails, the hyperinsulinaemic hypoglycaemia may be induced by a mixed-meal test (Cryer et al., 2009; Öberg et al., 2017). In the mixed-meal test, samples for glucose, insulin, C-peptide and proinsulin

are collected repeatedly every 30 minutes during the first 5 hours after a mixed meal, with hormone measures analysed, when plasma glucose level falls below 3.3 mmol/l (Cryer et al., 2009). An oral glucose tolerance test has been suggested as a tool for diagnosing insulinomas (Li et al., 2017; Liao et al., 2021), but it is currently not recommended because of low specificity and lacking diagnostic criteria (Cryer et al., 2009).

Table 1. Determination of endogenous hyperinsulinaemic hypoglycaemia by the Endocrine Society and the ENETS Consensus guidelines

the findings of symptoms, signs, or both of hypoglycaemia, together with plasma concentrations of	Endocrine Society (Modified from Cryer et al., 2009)	ENETS Consensus guidelines (Modified from Öberg et al., 2017)
glucose	< 3.0 mmol/l (55 mg/dl) or < 2.5 mmol/l if the Whipple triad has not been documented previously	≤ 2.2 mmol/l (40 mg/dl)
insulin	≥ 3.0 mU/l (18 pmol/l)	≥ 6.0 mU/l (36 pmol/l); ≥ 3.0 mU/l by immunochemiluminometric assay
C-peptide	≥ 0.2 nmol/l (0.6 ng/ml)	
proinsulin	≥ 5.0 pmol/l	
β-hydroxybutyrate	≤ 2.7 mmol/l	
Increase in plasma glucose in response to intravenous injection of 1.0 mg glucagon	≥ 1.4 mmol/l (25 mg/dl)	

2.5.2 Localization studies

The preoperative imaging of an insulinoma is important for determining the precise tumour location, multiplicity, proximity to the main pancreatic duct, and the disease stage, in order to select the most appropriate surgical approach and method, or an eventual non-surgical treatment strategy (de Herder et al., 2006; Partelli et al., 2017). The preoperative localization of insulinomas may be challenging and require the use of multiple imaging modalities (Mehrabi et al., 2014). The options for the preoperative localization of insulinomas can be divided into non-invasive and invasive methods. Non-invasive methods include computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasound (US), as well as

functional nuclear imaging, such as the previously used somatostatin receptor scintigraphy (SRS) and the newer methods single-photon emission computed tomography–computed tomography (SPECT/CT) or positron emission tomography–computed tomography (PET/CT) (Bural et al., 2012; de Herder et al., 2006). Invasive methods currently used for the localization of insulinomas include endoscopic ultrasound (EUS), as well as intraoperative ultrasound, inspection, and palpation of the tumour(s) (de Herder et al., 2006).

Previously, the invasive method of diagnostic angiography combined with selective intra-arterial calcium stimulation test and hepatic venous sampling (ASVS) was considered the golden standard of insulinoma localization (de Herder et al., 2006). ASVS (also referred to as SACST for selective arterial calcium stimulation test, IACS for intra-arterial calcium stimulation or IACIG for intra-arterial injection of calcium with hepatic venous insulin gradients) is based on traditional diagnostic angiography followed by sequential arterial calcium stimulation of different parts of the pancreas (via gastroduodenal, splenic, and superior mesenteric arteries), leading to release of insulin by insulinoma cells (Zhao, K. et al., 2020). The increased insulin secretion by the tumour cells is observed from blood samples collected from the hepatic veins, and the tumour can thus be localized to a certain region of the pancreas (Zhao, K. et al., 2020). ASVS was preceded by an even more invasive technique called transhepatic portal venous sampling (THPVS), where blood samples were taken by percutaneous and transhepatic catheterization from several of the main veins draining the different parts of the pancreas, for the measurement of insulin concentrations (Ingemansson et al., 1975; Shin et al., 2010). ASVS has a sensitivity of 84–90% or higher, but it is invasive, requires technical expertise (Guettier et al., 2009; Placzkowski et al., 2009; Zhao, K. et al., 2020), and has been largely replaced by the modern PET/CT imaging.

According to the current ENETS and European Society for Medical Oncology (ESMO) guidelines, contrast-enhanced CT or contrast-enhanced MRI are preferred as the first-line imaging methods, because they are non-invasive and easily available (Falconi et al., 2016; Pavel et al., 2020; Sundin et al., 2017). The typically small size of insulinomas, however, limits the sensitivity of these methods (de Herder et al., 2006). A recent systematic review reported a mean sensitivity of 44% for CT and 53% for MRI (Mehrabi et al., 2014). The technique and sensitivity of CT imaging have, however, improved over the past few decades, and sensitivities over 90% have been reported with a modern dual-phase thin-slice multidetector CT (Gouya et al.,

2003), angio-CT (Fu et al., 2020), dual-phase multidetector CT combined with pancreatic perfusion imaging (Zhu et al., 2017), as well as with one-stop pancreatic perfusion CT with calculated mean temporal imaging (Li et al., 2020). A typical finding of insulinoma on CT is a hypervascular, hyperattenuating pancreatic lesion in both the arterial and venous phases (de Herder et al., 2006). High detection rates can also be achieved with contrast-enhanced, diffusion-weighted MRI, avoiding the exposure to ionizing radiation (Mehrabi et al., 2014). In addition to traditional MRI, magnetic resonance cholangiopancreatography (MRCP) may be useful in selected cases, for evaluating the localization of the tumour in relation to the main pancreatic duct (Mehrabi et al., 2014).

If no visible lesions are detected with the CT or MRI, applying EUS is recommended (Falconi et al., 2016). In experienced hands, sensitivities up to 93–100% have been reported, especially for detection of lesions located in the pancreatic head (Gouya et al., 2003; Sotoudehmanesh et al., 2007; Sundin et al., 2017). As a limitation, EUS is invasive, operator-dependent and allows poor visualization of the pancreatic tail (Sotoudehmanesh et al., 2007).

If both conventional localizing studies and EUS are negative, as seen in <10% of insulinoma patients, imaging with radiolabelled glucagon-like peptide 1 (GLP-1) receptor analogues should be considered (Falconi et al., 2016). GLP-1-receptor PET/CT or SPECT/CT imaging using radiotracers, such as gallium-68, indium-111 or technetium-99m labelled exendin-4, have proved to be highly sensitive methods (sensitivity up to 98%) for localizing insulinomas, as especially benign insulinomas express a high density of GLP-1 receptors (Antwi et al., 2018; Christ et al., 2013; Christ et al., 2020; Falconi et al., 2016; Sowa-Staszczak et al., 2013). The sensitivity and specificity of GLP-1 PET/CT have been shown to be superior to those of GLP-1 SPECT/CT imaging (Shah et al., 2021). GLP-1 receptor imaging may also be useful in MEN1 patients, in localizing the insulin-secreting tumour among multiple non-functioning pancreatic tumours (Antwi et al., 2019; Christ et al., 2020), as well as in differentiating insulinomas from diffuse islet cell hyperplasia and proliferation (Kalff et al., 2020). In the future, the use of GLP-1 receptor imaging with a new radiotracer, fluorine-18 labelled exendin-4, may become more common due to its high sensitivity and concomitant low kidney radioactivity uptake (Mikkola et al., 2016).

Prior to the development of GLP-1 imaging, several methods of functional, nuclear imaging have been introduced, including somatostatin receptor imaging with

^{111}In-pentetreotide scintigraphy (OctreoScan) and PET/CT imaging using radiolabelled octreotide/octreotate (e.g. ^{68}Ga-DOTANOC, ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE), as well as PET/CT imaging using radiolabelled dihydroxyphenylalanin (^{18}F-DOPA PET/CT) or fluorodeoxyglucose (^{18}F-FDG PET/CT) (Christ et al., 2020; de Herder et al., 2006; Nockel et al., 2017; Kauhanen et al., 2007). The sensitivity of these methods is variable (20–87%), but inferior to that of GLP-1 receptor based imaging in the diagnostics of insulinomas (Christ et al., 2020; Garg et al., 2020; Zhao, K. et al., 2020). The lower sensitivity of somatostatin receptor imaging is explained by the low expression of somatostatin receptor subtype 2 in non-metastatic insulinomas (Andreassen et al., 2019; de Herder et al., 2006; Sundin et al., 2017). Metastatic insulinomas, in contrast, often seem to lack GLP-1 receptors but express the somatostatin receptor subtype 2, resulting in a higher sensitivity of somatostatin receptor-based imaging in metastatic insulinomas (Christ et al., 2020; Erhamamci et al., 2020; Veltroni et al., 2020; Vezzosi et al., 2005; Wild et al., 2011). ^{18}F-DOPA PET/CT imaging has been applied in only a few small studies of patients with an insulinoma or β-cell hyperplasia, with the sensitivity varying between 50 and 90% (Christ et al., 2020; Imperiale et al., 2015; Kauhanen et al., 2007). The sensitivity of ^{18}F-FDG PET/CT in localizing insulinomas is poor, presumably because of the low proliferative activity and glucose turnover in insulinomas (de Herder et al., 2006; Kauhanen et al., 2007).

Since the improvement of non-invasive imaging methods, the use of conventional, transabdominal US has declined, because of its low sensitivity, with especially poor visualization of small tumours and tumours located in the pancreatic tail (de Herder et al., 2006; Mehrabi et al., 2014; Zhao, K. et al., 2020). Intraoperative ultrasound (IOUS) together with intraoperative inspection and palpation are, however, helpful in assessing the anatomy, defining the proximity of the tumour to the main pancreatic duct and adjacent blood vessels and identifying eventual additional NENs, if multiple tumours are suspected (Andreassen et al., 2019; de Herder et al., 2006). These intraoperative localization techniques are highly sensitive, when performed by experienced surgeons and can sometimes detect lesions that remain undetected with all the preoperative localizing methods (Falconi et al., 2016; Mehrabi et al., 2014; Nikfarjam et al., 2008; Sundin et al., 2017; Zhao, K. et al., 2020). Regarding laparoscopic surgeries, the laparoscopic IOUS plays an important role because palpation of the tumour is impossible (Mehrabi et al., 2014). Without

successful preoperative localization, a small proportion of insulinomas may remain undetected intraoperatively (Mehrabi et al., 2014).

2.5.3 TNM Classification

Insulinomas, together with other well differentiated PanNENs, are staged according to the European Neuroendocrine Tumor Society (ENETS) and the 8th edition of the American Joint Committee on Cancer / Union for International Cancer Control (AJCC-UICC) TNM staging classifications (Table 2). (Rindi et al., 2006; Brierley et al., 2017). The extremely rare cases of poorly differentiated or high-grade well differentiated insulinomas should be staged according to the general criteria for classifying PanNECs and carcinomas of the exocrine pancreas (Brierley et al., 2017).

The TNM system has been developed for assessing the anatomical extent of the disease, and thereby the prognosis of the patient, based on three components: the extent of the primary tumour (T), the presence/absence and extent of regional lymph node metastases (N), and the presence/absence of distant metastases (M) (Brierley et al., 2017). Staging is made on the basis of physical examination, radiological imaging, and/or surgical exploration. The clinical TNM stage guides the selection of primary therapy, and the classification is later supplemented and specified by histopathological classification (pTNM), for more accurate prognosis estimation and selection of adjuvant therapy (Brierley et al., 2017). In a recent study of 85 surgically treated sporadic insulinomas, 60% of insulinomas were classified as stage I, 27% stage II, 8% stage III and 5% as stage IV tumours (Wang et al., 2015). Similarly, in a previous study on 977 PanNENs, including 328 insulinomas, over 80% of insulinomas were at stage I or II (Zhu et al., 2016).

Table 2. Tumour, node, metastasis classification for well differentiated pancreatic neuroendocrine tumours. Modified from Rindi et al., 2006; and Brierley et al., 2017.

Primary tumour (T)			
TX	Tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour limited to the pancreas* and ≤ 2 cm in greatest dimension		
T2	Tumour limited to the pancreas* and 2–4 cm in greatest dimension		
T3	Tumour limited to the pancreas* and > 4 cm in greatest dimension or invading duodenum or bile duct		
T4	Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (coeliac axis or superior mesenteric artery)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
MX	Distant metastases cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
	M1a	Hepatic metastasis (es) only	
	M1b	Extrahepatic metastasis (es) only	
	M1c	Hepatic and extrahepatic metastases	
Stage			
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

*Invasion of adjacent peripancreatic adipose tissue is accepted but invasion of adjacent organs is excluded

2.5.4 Histopathological diagnostics and grading

The definite diagnosis of insulinoma requires the biochemical demonstration of hyperinsulinaemic hypoglycaemia, together with the confirmation of neuroendocrine histology on histological examination of the tumour. The neuroendocrine origin is confirmed by immunohistochemical staining for the neuroendocrine markers chromogranin A and synaptophysin (Perren et al., 2017). Staining for insulin is not obligatory for the diagnosis of a solitary insulinoma (Zhao, Y.-P. et al., 2011), but is recommended for identification of insulinoma when multiple tumours are present (Anlauf et al., 2009; WHO Classification of Tumours Editorial Board, 2019). In addition to insulin, insulinomas often show scattered staining for other hormones, such as glucagon, pancreatic polypeptide and somatostatin (WHO Classification of Tumours Editorial Board, 2019).

Insulinomas are histologically classified according to the WHO 2019 classification and grading criteria for NENs of the gastrointestinal tract and hepatopancreatobiliary organs (Nagtegaal et al., 2020; WHO Classification of Tumours Editorial Board, 2019). This classification has been developed to predict more reliably the clinical course and the outcome of patients with gastroenteropancreatic (GEP) NENs, which have previously turned out to be poorly predictable. According to their histopathological and molecular characteristics, the neoplasms are divided into well differentiated, grade 1–3 (low to high-grade) neuroendocrine tumours (NETs) with increasingly aggressive behaviour, and into poorly differentiated neuroendocrine carcinomas (NECs) that are by default considered high-grade neoplasms with highly aggressive behaviour (WHO Classification of Tumours Editorial Board, 2019). A third class called mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs), includes rare neoplasms with discrete neuroendocrine and non-neuroendocrine components (Table 3).

Virtually all insulinomas are well differentiated PanNENs, previously referred to as islet cell tumours or pancreatic endocrine neoplasms. The well-differentiated histology means that the tumour cells have strong resemblance to normal pancreatic neuroendocrine cells (including expression of neuroendocrine markers and pancreas-specific peptide hormones) with an organoid architecture, minimal to moderate atypia, and no necrosis (WHO Classification of Tumours Editorial Board, 2019). In genetic analyses, well differentiated PanNENs are typically characterized

by mutations in MEN1, DAXX and ATRX genes (WHO Classification of Tumours Editorial Board, 2019). PanNETs are graded according to their proliferative activity assessed by Ki-67 immunohistochemical staining or mitotic index, whichever places the neoplasm in a higher-grade category (Table 3). Up to 90–99% of insulinomas are classified as grade 1–2 with well differentiated morphology and low to moderate grade proliferative activity (Andreassen et al., 2019; Wang et al., 2015; WHO Classification of Tumours Editorial Board, 2019; Zhu et al., 2016).

Poorly differentiated insulinomas are extremely rare, but a few cases have been described in the literature (Basturk et al., 2014; Sada et al., 2020). In general, poorly differentiated PanNECs are highly aggressive neoplasms, which frequently metastasize and are associated with a poor survival of typically less than a year (Basturk et al., 2014; Taskin et al., 2020; WHO Classification of Tumours Editorial Board, 2019). Histologically they are poorly developed with sheet-like growing, extensive necrosis and less organoid architecture compared to well differentiated PanNENs, but have still recognizable morphological and immunohistochemical features of neuroendocrine differentiation, including diffuse or faint staining for synaptophysin and faint or focal staining for chromogranin A (WHO Classification of Tumours Editorial Board, 2019). PanNECs are usually hormonally non-functioning, but may rarely express hormones, leading to the occurrence of a distinct hormonal syndrome, as in the case of poorly differentiated pancreatic insulinomas. In genetic analyses, PanNECs often have mutations in TP53 or RB1 genes. Based on morphological features, NECs are divided into small cell NECs (SCNECs) and large cell NECs (LCNECs) (WHO Classification of Tumours Editorial Board, 2019).

Table 3. The 2019 WHO classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatopancreatobiliary organs. Modified from Nagtegaal et al., 2020; and WHO Classification of Tumours Editorial Board, 2019.

Terminology	Differentiation	Grade	Ki-67 index[a]	Mitotic rate[b] (mitoses/2 mm^2)
NET, G1	Well differentiated	Low	<3%	<2
NET, G2		Intermediate	3–20%	2–20
NET, G3		High	>20%	>20
NEC, small-cell type (SCNEC)	Poorly differentiated	High	>20%	>20
NEC, large-cell type (LCNEC)			>20%	>20
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

[a]MIB1 antibody, % of at least 500 tumour cells in areas of highest nuclear labelling, [b]at least 40 fields evaluated in areas of highest mitotic activity.

2.5.5 Differential diagnostics

Due to the diverse and often nonspecific symptoms related to insulinomas, the correct diagnosis of insulinoma is often delayed up to several years after the initial symptoms (Hirshberg et al., 2000; Nikfarjam et al., 2008). Similar symptoms occur commonly in many other pathological conditions, such as epilepsy, psychiatric diseases, transient ischaemic attack, and cardiac arrhythmias, and the patients are often misdiagnosed with a neurological or mental disorder, before the correct diagnosis of insulinoma (Agarwal et al., 2020; Ding et al., 2010; Dizon et al., 1999; Harrington et al., 1983; Qi et al., 2019; Service F. J. et al., 1991). Thus, broad differential diagnostics is required, when investigating patients with unsolved symptomatic attacks.

The critical step in the diagnostic procedure of insulinomas is the detection of hypoglycaemia at the time of the typical symptoms. The evaluation and management of hypoglycaemia is recommended only after a reliable documentation of the Whipple triad (Cryer et al., 2009). The most common cause of hypoglycaemia in adults, is the insulin or insulin secretagogue treatment of patients with diabetes (Cryer et al., 2009). Several other drugs, alcohol, critical illnesses, hereditary syndromes and non-islet cell tumours may cause hypoglycaemia also in patients

without diabetes (Table 4) (Cryer et al., 2009). In patients without an obvious cause for hypoglycaemia, a careful review of personal and family history and physical findings is needed, followed by biochemical investigations (see: Biochemical diagnostics) (Cryer et al., 2009).

Apart from insulinoma, other rare causes of endogenous hyperinsulinaemic hypoglycaemia include proinsulinomas, post gastric bypass hypoglycaemia, non-insulinoma pancreatogenous hypoglycaemia syndrome and insulin autoimmune hypoglycaemia. Proinsulin-producing PanNENs, proinsulinomas, are extremely rare, with only a few cases reported in the literature. Instead of insulin, they produce the prohormone proinsulin, causing clinical hypoglycaemia with positive Whipple triad, but normal or decreased plasma insulin levels (Kriger et al., 2019; Murtha et al., 2017). Post gastric bypass hypoglycaemia develops several months after bariatric surgery and is characterized by episodes of postprandial hypoglycaemia. The underlying mechanisms of post gastric bypass hyperinsulinaemic hypoglycaemia are not completely understood, but islet cell hyperplasia, hyperfunction and enhanced incretin hormone, particularly GLP-1 effect have been proposed (Rariy et al., 2016; Service G. J. et al., 2005; Shantavasinkul et al., 2016). Non-insulinoma pancreatogenous hypoglycaemia syndrome without the history of bariatric surgery is an extremely rare cause of endogenous hyperinsulinaemic hypoglycaemia, in which episodes of hyperinsulinaemic hypoglycaemia occur postprandially without any indication of an insulinoma. In contrast to insulinomas, the non-insulinoma pancreatogenous hypoglycaemia syndrome, or adult-onset nesidioblastosis, is associated with diffuse islet cell hypertrophy, proliferation or neodifferentiation of the pancreatic islets from pancreatic duct epithelium (Anderson et al., 2016; Jabri & Bayard, 2004; Rumilla et al., 2009; Thompson et al., 2000). Hypoglycaemia due to development of antibodies against endogenous insulin or insulin receptors is also extremely rare, reported mainly in Japanese, Korean or African-American persons, often associated with another autoimmune disease (Cryer et al., 2009).

Table 4. Differential diagnosis of hypoglycaemia without diabetes. Modified from Cryer et al., 2009.

Cause		Clinical characteristics
Medication	For example, insulin, oral antidiabetic drugs, non-steroidal anti-inflammatory drugs (such as indomethacin), some antimicrobial agents (such as gatifloxacin, pentamidine, quinine).	Hypoglycaemia after intentional or accidental use of medication predisposing to hypoglycaemia. Occurs typically in patients with other simultaneous risk factors, such as hepatic or renal failure or other acute or chronic illnesses.
Alcohol		Hypoglycaemia provoked by several days of heavy alcohol consumption, often together with malnutrition, acute infections or other diseases
Critical illness	Including sepsis, hepatic or renal failure, severe malnutrition, anorexia nervosa	
Hypocortisolism		Postprandial hypoglycaemia
Other than islet cell tumours	Via accelerated use of glucose by rapidly dividing tumour cells, decreased gluconeogenesis and glycogen storage in hepatic failure due to metastases, adrenal metastases causing hypocortisolism, or overproduction of insulin-like growth factors (typically mesenchymal tumours)	Hypoglycaemia associated with advanced cancers
Endogenous hyperinsulinism		
	Insulinoma or proinsulinoma	Fasting (rarely postprandial) hypoglycaemia
	Post gastric bypass hypoglycaemia	Postprandial hypoglycaemia
	Non-insulinoma pancreatogenous hypoglycaemia	Postprandial hypoglycaemia
	Insulin autoimmune hypoglycaemia	Late postprandial hypoglycaemia
Rare gene defects or inborn errors of metabolism	For example, exercise-induced hyperinsulinaemic hypoglycaemia (EIHI), hereditary fructose intolerance and other hereditary metabolic syndromes causing hypoglycaemia	Hypoglycaemia provoked by intensive exercise (EIHI) or hypoglycaemia associated with other signs or symptoms of a hereditary metabolic syndrome

2.6 Treatment and outcome of insulinoma

The principal treatment strategy of insulinoma is the surgical removal of the insulin-secreting tumour(s). For a non-metastatic insulinoma surgery is usually curative. Medical treatment may be needed preoperatively for symptom control, and in

patients with a metastatic, inoperable or recurrent insulinoma (Falconi et al., 2016). Mild hypoglycaemic symptoms may be relieved by having frequent, small, carbohydrate-rich meals, but during the course of the disease, even continuous intravenous glucose infusion may be required in some patients to maintain the plasma glucose concentration within normal limits (de Herder et al., 2011; Mehrabi et al., 2014). The treatment of metastatic insulinomas is planned case-by-case, based on the individual characteristics of the disease and the patient. It often requires multidisciplinary approach with surgery of the primary tumour and/or metastases, as well as oncological and medical treatment options. In Finland, the treatment and follow-up of insulinomas have been organized according to the most recent European (Falconi et al., 2016; Pavel & de Herder, 2017; Pavel et al., 2020) and Nordic guidelines (Tiensuu Janson et al., 2021).

2.6.1 Surgical treatment

The first cure of insulinoma by surgical removal of the pancreatic tumour was reported in 1929 (Howland et al., 1929). Surgery is still the only curative treatment for insulinomas, and surgical exploration with a curative aim is recommended for all insulinoma patients in the absence of an inoperable or metastatic disease (Falconi et al., 2016). Palliative resection of the tumour and (liver) metastases may also relieve symptoms and improve survival in patients with a metastatic insulinoma, and is generally recommended for this indication (Mehrabi et al., 2014; Pavel et al., 2020; Zhao, Y.-P. et al., 2011).

Pancreas-sparing surgery, i.e., enucleation or limited resection, is recommended whenever possible, in order to preserve exocrine and endocrine pancreatic function and avoid comorbidities, such as exocrine dysfunction and insulin-dependent diabetes (Falconi et al., 2016; Mehrabi et al., 2014). Pancreas-sparing surgical methods are also primary in patients with the MEN1 syndrome (Bartsch et al., 2013; Falconi et al., 2016; van Beek et al., 2020). Most insulinomas can be enucleated (Mehrabi et al., 2014), and the less invasive enucleation is generally preferred instead of resection with small (<2cm in diameter), solitary, non-metastatic tumours located superficially and at a safe distance from the pancreatic duct and major vessels (Falconi et al., 2016; Mehrabi et al., 2014; Partelli et al., 2017; Pavel et al., 2020; Zhao, Y.-P. et al., 2011). A distance of at least 2 to 3 mm to the main pancreatic duct is recommended, in order to prevent the formation of pancreatic fistulas (Mehrabi et

al., 2014). On the other hand, enucleations may be associated with a slightly higher risk for reoperations compared to pancreatic resections (Crippa et al., 2012). After enucleation, the second most common surgical method is distal pancreatic resection (applied in one-third of surgically treated patients), followed by pancreatico-duodenectomy (sometimes referred to as Whipple procedure) in less than 3% of the surgically treated patients. Rare surgical methods, such as partial, central, subtotal, or total pancreatectomy are also applied in selected patients (Mehrabi et al., 2014). Concomitant lymphadenectomy is not routinely needed in patients with a non-metastatic insulinoma (Jensen et al., 2012).

Since first reported in 1996 (Gagner, et al., 1996), the laparoscopic approach has become increasingly common in insulinoma surgery. The laparoscopic technique is generally recommended for enucleation or distal resection of small, non-metastatic sporadic insulinomas of the body or tail of pancreas, as it has high cure and low complication rates similar to the open approach, but is associated with faster recovery and shorter postoperative hospitalization (Aggeli et al., 2016; Antonakis et al., 2015; Ayav et al., 2005; Drymousis et al., 2014; Hu et al., 2011; Isla et al., 2009; Jensen et al., 2012; Mehrabi et al., 2014; Richards et al., 2011; Roland et al., 2008; Su AP et al., 2014). Indications for open approach include multiple, MEN1-related or metastatic insulinomas, tumours located deep in the pancreatic head, as well as surgical exploration of tumours that could not be localized preoperatively (Mehrabi et al., 2014; van Beek et al., 2020; Zhao, Y.-P. et al., 2011). If the laparoscopic approach fails for example due to technical difficulties or difficulties in identifying the tumour, it can be converted to an open approach, as reported in less than 20% of the cases (Mehrabi et al., 2014). Blind pancreatic resection is not recommended for tumours that remain undetected in the pre- and intraoperative localizing studies, because of its low success rate and increased risk for surgical complications, including the development of diabetes due to endocrine pancreatic insufficiency (Hirshberg et al., 2002; Jensen et al., 2012; Mehrabi et al., 2014; Nikfarjam et al., 2008). In addition to the open and laparoscopic approach, a few cases of successful robot-assisted surgeries have been recently reported for insulinomas, and their use may become more common in the future treatment of insulinoma patients (Alfieri et al., 2019; Belfiori et al., 2018; Kang et al., 2020; Lopez et al., 2016).

Surgical complications occur commonly after pancreatic surgery. A recent systematic review reported no significant difference in the morbidity rate of laparoscopic or open surgery (33 vs. 35%, respectively) (Mehrabi et al., 2014). The

most common surgical complication is pancreatic fistula, which occurs in 3–60% of patients (Crippa et al., 2012; Giannis et al., 2020; Mehrabi et al., 2014; Nikfarjam et al., 2008; Zhao, Y.-P. et al., 2012). A mean rate of 6.2% has been reported for pancreatic fistulas after laparoscopic and 14.6% after open approach surgery (Mehrabi et al., 2014). Risk factors for pancreatic fistula include for example tumour enucleation, proximity of the tumour to the main pancreatic duct and the need for extensive manipulation of pancreatic tissue to identify the tumour (Mehrabi et al., 2014). Male gender and operative time >3 hours were associated with an increased risk of pancreatic fistula in a retrospective study of 292 surgically treated insulinoma patients (Zhao, Y.-P. et al., 2012). Depending on their severity, pancreatic fistulas may heal spontaneously or require medical or surgical treatment. Other less common surgical complications include abscess, wound infection, pancreatitis, pseudocyst, and bleeding, each with a rate of 0 to 5% of surgeries (Mehrabi et al., 2014). Postoperative pancreatic endocrine or exocrine insufficiency may develop in 2–8% of patients, practically only after a larger pancreatic resection (Crippa et al., 2012; Mehrabi et al., 2014). Postoperative pulmonary embolism occurs in less than 2% of insulinoma patients (Mehrabi et al., 2014). A mean postoperative mortality rate of 3.7% has been reported for open approach and 0% for laparoscopic surgery (Mehrabi et al., 2014).

In addition to surgical resection of the primary tumour and the metastases, other invasive treatment options have been applied to selected patients with a metastatic or inoperable insulinoma, including ablative and embolization therapies, and even liver transplantation (Ahlman et al., 2004; Mehrabi et al., 2014; Zhao, Y.-P. et al., 2011). Endoscopic, percutaneous or laparoscopic ablative therapies with ethanol injections or radiofrequency waves have been successfully carried out in patients with insulinomas (Brown, N. G. et al., 2020; Falconi et al., 2016; Furnica et al., 2020; Kluz et al., 2020; Mele et al., 2018; Yao et al., 2020). Hyperthermic radiofrequency ablation causes irreversible cellular injury and necrosis of the precisely targeted lesion (Brown, N.G. et al., 2020). Radiofrequency ablation may be an ideal and safe treatment for patients with a benign, otherwise inoperable insulinoma, but larger studies are still needed to confirm the long-term effectiveness of this technique (Mele et al., 2018; Furnica et al., 2020; Yao et al., 2020). Hepatic artery embolization with bland embolization, chemoembolization or radioembolization may be helpful in insulinomas with liver metastases (Brown, E. et al., 2018).

2.6.2 Medical treatment

In patients with an operable, non-metastatic insulinoma, the surgical removal of the tumour should be conducted without delay, and the use of preoperative medication is not generally recommended (Kaltsas et al., 2017). Prior to, during and after the operation, careful glucose monitoring is indicated, and some patients may require preoperative intravenous glucose infusion to avoid hypoglycaemia (Kaltsas et al., 2017). Administration of dextrose, intramuscular glucagon and potassium replacement may also be used in the treatment of acute, severe hypoglycaemias (Kaltsas et al., 2017). During the first few days after the surgery, small doses of insulin and/or glucose may be required to maintain normal blood glucose concentration (Kaltsas et al., 2017).

Medical treatment of insulinoma is needed in patients with a metastatic disease, in patients who are inoperable or unwilling to undergo surgery, and sometimes preoperatively for symptom control (Jensen et al., 2012). The most effective medication for controlling hypoglycaemia is diazoxide. It inhibits the secretion of insulin by tumour cells and enhances glycogenolysis, and is effective in preventing hypoglycaemias in 50–60% of the patients (de Herder et al., 2011; Mehrabi et al., 2014). It is usually well-tolerated, but may have several adverse effects, most commonly oedema due to retention of sodium and fluid, and hirsutism (Gill et al., 1997). Thiazide diuretics are often used in combination with diazoxide to counteract the edema, and to potentiate the glycaemic effect of diazoxide (de Herder et al., 2011; Gill et al., 1997).

Somatostatin analogues (octreotide, lanreotide and the next-generation somatostatin analogue pasireotide) affect by binding to distinct somatostatin receptor subtypes, leading to antiproliferative and antisecretory effects (de Herder et al., 2011; Gomes-Porras et al., 2020; Siddiqui et al., 2021). They are effective in controlling hypoglycaemia in at least 35–50% of insulinoma patients, but should be used with caution, because of the risk for worsening hypoglycaemia in some patients, due to inhibition of the counterregulatory effects of glucagon and growth hormone (Mehrabi et al., 2014; Tirosh et al., 2016; Vezzosi et al., 2008; Vezzosi et al., 2005). The effectiveness of somatostatin analogues depend on the varying expression of somatostatin receptor subtypes on the insulinoma cells, and malignant, metastatic insulinomas that often express somatostatin receptor subtype 2, may respond better to the somatostatin analogue treatment (de Herder et al., 2011; Gomes-Porras et al.,

2020; Pavel et al., 2017; Vezzosi et al., 2005). Compared to octreotide and lanreotide, pasireotide has higher affinity to somatostatin receptors 1, 2, 3 and 5 (Gomes-Porras et al., 2020; Tirosh et al., 2016). Due to this wider receptor affinity profile, pasireotide might be successful in controlling hypoglycaemia in metastatic and recurrent insulinomas resistant to other treatment options (Tirosh et al., 2016, Gomes-Porras 2020, Brown E. et al., 2018).

Other less commonly used medications for controlling the hypoglycaemia in insulinoma patients include glucocorticoids, β-blockers, calcium channel blockers, diphenylhydantoin, interferon-α and recently, a multi-kinase inhibitor sunitinib and a mammalian target of rapamycin inhibitor everolimus (Mehrabi et al., 2014; Pavel et al., 2017). Sunitinib may control tumour progression and improve survival in patients with advanced PanNENs, but does not prevent hypoglycaemias (Brown E. et al., 2018). Everolimus has proved to be effective in both controlling the tumour growth and preventing hypoglycaemia in patients with a low-grade metastatic, inoperable insulinoma (Bernard et al., 2013; Brown E. et al., 2018; Davì et al., 2017; Falconi et al., 2016; Yao et al., 2009). Peptide-receptor-targeted radionuclide therapy (PRRT) with radiolabelled somatostatin analogues may be effective in patients with a somatostatin receptor positive insulinoma (Brown E. et al., 2018; Falconi et al., 2016). Favourable response has recently been reported for example with ^{177}Lu-DOTATATE therapy of a patient with a metastatic insulinoma, with partial regression of the primary tumour and significant regression in hepatic and peripancreatic lymph node metastases (Erhamamci et al., 2020). High-grade, metastatic insulinomas may also respond to systemic chemotherapy with cytotoxic agents, such as capecitabine, temozolomide, streptozotocin, doxorubicin and 5-fluorouracil (Brown E. et al., 2018; Garcia-Carbonero et al., 2017). In patients with highly proliferating (high Ki-67 index), poorly differentiated insulinomas, systemic chemotherapy is preferred, as it may result in a better treatment response, compared to somatostatin analogues or PRRT (Brown E. et al., 2018).

2.7 Prognosis of patients diagnosed with an insulinoma

2.7.1 Short- and long-term morbidity

Patients treated for an insulinoma may be at increased risk for long-term morbidity due to several reasons. Firstly, insulinoma patients are exposed to the effects of long-lasting hyperinsulinemia and repeated episodes of hypoglycaemia, which may affect the long-term morbidity of patients with an insulinoma. Secondly, most patients undergo surgical treatment and/or invasive diagnostic procedures, bearing a risk for both short-term complications and long-term gastrointestinal morbidity, as well as a risk for endocrine or exocrine pancreatic insufficiency. Thirdly, a small proportion of insulinoma patients is diagnosed with a MEN1 or another genetic syndrome, which may increase the risk for additional morbidity for example due to other endocrine disorders or malignancies.

Regarding the first aspect on the eventual long-term effects of hyperinsulinemia and hypoglycaemia, no increased prevalence of cardiovascular morbidity (hypertension, dyslipidaemia) has been found in previous studies on insulinoma patients (Leonetti et al., 1993; O'Brien et al., 1993). In these studies, however, the prevalence of hypertension and dyslipidaemia were studied at the time of insulinoma diagnosis or shortly after the surgical treatment of insulinoma, without long-term follow-up. Prior to the treatment, insulinoma patients typically gain weight and a significant weight loss occurs in most patients after the surgical removal of insulinoma. For example, in a recent study on 51 overweight patients (BMI $\geq$ 25kg/m^2) who underwent a complete resection of insulinoma, a significant weight reduction (median -13%) was detected already at 3 months after surgery, and hypertension resolved in 64% of the 11 hypertensive patients within the first postoperative year (Dai et al., 2017).

Cognitive impairment has been detected in a recent small series of insulinoma patients (Dai et al., 2019). The cognitive impairment seemed to be at least partly reversible, and improved in most patients, when the cognitive function was reassessed one year after the surgery (Dai et al., 2019). There is, however, a lack of long-term follow-up data on the incidence of cognitive impairment or dementia in patients previously diagnosed with and treated for an insulinoma. Studies on patients with diabetes have indicated that repeated hypoglycaemias may cause permanent

neuronal damage, and increase the risk for impaired cognitive function and dementia (Cryer, 2007; Sheen & Sheu, 2016).

The long-term cancer morbidity has not been previously studied specifically in insulinoma patients. Previous studies have indicated that long-acting hyperinsulinemia could be associated with increased cancer morbidity in patients with type 2 diabetes (Gallagher & LeRoith, 2011; Gallagher & LeRoith, 2020; Lega & Lipscombe, 2020), but whether this association exists in patients with an insulinoma, is currently not known. A study on 115 patients with a sporadic PanNET reported a secondary malignancy in two (4%) of the 47 insulinoma patients, which was similar to the risk of multiple primary malignancies in the general population (Fendrich et al., 2008). The two malignancies reported were an endometrial cancer and an adenocarcinoma of unknown origin. The number of insulinoma patients in this study was too small to draw firm conclusions regarding cancer morbidity among insulinoma patients.

Regarding the second aspect, the short-term complications and morbidity, as well as endocrine and exocrine pancreatic insufficiency associated with pancreatic surgery have been extensively studied, as discussed above. Data on the long-term gastrointestinal morbidity of insulinoma patients, however, are scarce. In general, pancreatic surgery is associated with an increased risk, for example, for intestinal obstruction and abdominal hernias (Brown, J. A. et al., 2020; Chen-Xu et al., 2019). A recent study on insulinoma patients reported an incisional hernia in 9% of the 56 patients with a benign, sporadic insulinoma treated with open enucleation (Belfiori et al., 2018).

Regarding the third aspect, the role of genetic syndromes in the long-term morbidity of insulinoma patients, significant endocrine and cancer morbidity is known to be associated with the MEN1 syndrome (Callender et al., 2008). Insulinomas may also rarely be associated with other hereditary tumour syndromes, such as vHL or neurofibromatosis, with their specific clinical features. Interestingly, recent studies propose that several currently unidentified genetic mutations may exist among patients with a sporadic insulinoma (Jyotsna et al., 2015; Larouche et al., 2019).

2.7.2 Survival

The overall survival of insulinoma patients is generally good, and, after a surgical removal of a non-metastatic tumour, the patients are usually considered to be cured and to have a normal life expectancy (Mehrabi et al., 2014; Service F. J. et al., 1991). Compared to patients with a non-insulinoma functioning PanNET or a non-functioning PanNET, patients with an insulinoma have a significantly longer overall survival (Gao et al., 2019). Disease recurrence after curative-intent insulinoma surgery is uncommon (3–8%) (Crippa et al., 2012; Mehrabi et al., 2014; Nikfarjam et al., 2008), but may occur slightly more commonly in patients with the MEN1 syndrome (Nikfarjam et al., 2008; Service F. J. et al., 1991). On the other hand, the overall survival in patients with a distant metastatic insulinoma is significantly impaired, with a median of less than 2 years (Jensen et al., 2012), and does not significantly differ from that of patients with a non-functioning PanNET (Gao et al., 2019) or a NEC (Bilimoria et al., 2008; Roland et al., 2012).

The presence of distant metastases is the most significant predictor of poor prognosis in patients with an insulinoma. Some patients with a metastatic insulinoma, however, show prolonged survival of up to several decades, indicating that metastatic insulinomas may have a variable natural history and the presence of distant metastases is not a sufficient prognostic factor per se (Hirshberg et al., 2005). In the absence of distant metastases, regional lymph node involvement does not inevitably lead to an impaired overall survival, and the significance of lymph node involvement and lymph node dissection remains controversial (Câmara-de-Souza et al., 2018; Hirshberg et al., 2005; Mehrabi et al., 2014; Sada et al., 2020; Veltroni et al., 2020). Apart from metastases, previous studies have aimed at identifying other tumour-, patient- and treatment-related factors that could predict the clinical course of the disease and the prognosis of patients with an insulinoma.

Regarding tumour-related factors, a larger tumour size (generally $\geq$ 2cm) has been associated with a metastatic disease and impaired overall survival in several studies (Câmara-de-Souza et al., 2018; Jensen et al., 2012; Keutgen et al., 2016; Sada et al., 2021; Wang et al., 2015). Considering the TNM Classification, a recent study on 85 insulinoma patients demonstrated statistically significant survival disadvantage for patients with stage II, III or IV tumours, compared to stage I insulinomas (Wang et al., 2015).

In addition to the extent of the disease, the biochemical measurements of fasting levels of glucose, insulin, proinsulin and C-peptide may, to some extent, reflect the characteristics of the tumour. For example, in previous studies, a higher C-peptide level has been associated with a larger tumour diameter, tumour multiplicity (Donegan et al., 2017; Wolf et al., 2015), a malignant or metastatic disease (Câmara-de-Souza et al., 2018; Queiroz Almeida et al., 2006; Sada et al., 2021) and a higher Ki-67 index (Wolf et al., 2015). Higher proinsulin levels have been associated with a larger tumour diameter and a metastatic disease (Donegan et al., 2017; Sada et al., 2021). Likewise, lower initial blood glucose levels and higher levels of insulin have been associated with a higher Ki-67 index, a larger tumour diameter and a malignant disease (Câmara-de-Souza et al., 2018; Wolf et al., 2015).

Regarding histopathological factors, there are currently no definitive markers that could distinguish between insulinomas with benign or malignant behaviour, and thus predict the overall survival of the patients (Mehrabi et al., 2014). Patients with a grade 1 or 2 insulinoma have generally longer overall survival than patients with a high-grade insulinoma (Wang et al., 2015). Similarly, a recent study on 31 patients with a lymph node or distant metastatic insulinoma, showed a trend, although not statistically significant, towards increased survival for lower-grade tumours, with a 5-year overall survival of 100% for grade 1, 77% for grade 2 and 33% for grade 3 tumours (Veltroni et al., 2020). Recent studies have identified several pathological and molecular features that may be associated with a malignant disease and/or worse overall survival. For example, chromosomal instability and alternative lengthening of telomeres have been associated with metastatic disease in insulinoma patients (Hackeng et al., 2020; Jonkers et al., 2005). Also, differences have been reported in the expression of endocrine transcription factors, epithelial adhesion molecule EpCAM, and GLP-1 and somatostatin receptors between metastatic and non-metastatic insulinomas, but their diagnostic value has not yet been established (Hackeng et al., 2020; Portela-Gomes et al., 2007; Raffel et al., 2010; Waser et al., 2015; Wild et al., 2011).

Considering patient-related factors, older age is associated with impaired overall survival (Keutgen et al., 2016). Whether the gender of the patient affects the survival is unclear. In a recent study of 121 insulinomas retrospectively gathered from the SEER database, female gender was associated with significantly worse overall and cancer-specific survival (Sada et al., 2020).

Regarding treatment-related factors, the resection of the primary tumour may improve survival also in patients with a metastatic insulinoma (Danforth et al., 1984; Sada et al., 2020; Veltroni et al., 2020), as may the invasive treatment of distant metastases with chemoembolization, radiofrequency thermoablation or liver transplantation (Ahlman et al., 2004; Begu-Le Corroller et al., 2008; Starke et al., 2005). Somatostatin analogue treatment, PRRT and everolimus may also prolong survival in patients with a somatostatin receptor positive and/or metastatic insulinoma (Bernard et al., 2013; Falconi et al., 2016; Magalhães et al., 2019; van Schaik et al., 2011; Veltroni et al., 2020; Vezzosi et al., 2005). Because of the rarity of metastatic insulinoma, however, large prospective randomized studies of patients treated with different treatment options have not been conducted.

2.7.3 Health-related quality of life (HRQoL)

The wide variety, severity and high frequency of hypoglycaemic symptoms is likely to affect the QoL in patients with a current insulinoma (Topping et al., 2017). The most commonly reported symptoms that are likely to impair the QoL in insulinoma patients include confusion, sweating, weight gain and temporary loss of consciousness (Topping et al., 2017). Fear of disease recurrence or eventual comorbidities might impair the long-term quality of life even after a curative treatment of the tumour. The HRQoL in patients with a current or a previously treated insulinoma, however, has not been studied before.

2.8 Current recommendations for the follow-up of insulinoma

According to the current ENETS Guidelines, patients with a solitary, surgically treated, non-metastatic G1–G2 insulinoma are invited to a clinical follow-up 3 to 6 months after the surgery, with the measurement of fasting glucose, insulin, C-peptide and proinsulin levels. A fasting test and EUS is recommended, if a recurrence is suspected. For locally advanced or metastatic, inoperable insulinomas, a regular follow-up with hormone analyses and imaging every 3 to 6 months is recommended, depending on the severity of symptoms and aggressiveness of the tumour. Somatostatin receptor imaging can be utilized at yearly controls, if positive at diagnosis, and EUS may be useful, if progression is suspected. (Knigge et al., 2017)

3 AIMS OF THE STUDY

The aim of the study was to clarify the incidence, diagnostics and treatment of patients diagnosed with an insulinoma, and to study their long-term prognosis compared to the general population.

The detailed study questions were:

1. Has the incidence of insulinomas changed in Finland during 1980–2010?
2. Have the clinical characteristics of insulinomas changed during that period?
3. How have the diagnostic and localization methods of insulinomas evolved in Finland during 1980–2010? Has the diagnostic delay changed during that period?
4. Is there any difference in the long-term HRQoL between the patients diagnosed with an insulinoma and the general population?
5. Is there any difference in the long-term endocrine, cardiovascular, gastrointestinal, psychiatric or cancer morbidity between the patients diagnosed with an insulinoma and the general population?
6. Does the survival of patients diagnosed with an insulinoma differ from the general population?

4 SUBJECTS AND METHODS

4.1 Subjects (I–III)

4.1.1 The Finnish insulinoma cohort (I, III)

All adult patients (≥ 18 years of age) diagnosed with an insulinoma in Finland during 1980–2010 were included in the study. This study was preceded by a pilot study including the patients diagnosed with an insulinoma in Tampere University Hospital Special Responsibility Area during the same study period (Uitto et al., 2015). In this nationwide study, the patients were identified from the patient record registries of all the Finnish University Hospitals (Tampere, Helsinki, Kuopio, Turku and Oulu University Hospitals), and at the Finnish Cancer Registry (FCR). The search in the patient record registers was based on the diagnosis codes compatible with benign neoplasms of the pancreas, malignant neoplasms of the endocrine pancreas, and disorders of pancreatic internal secretion other than diabetes (International Classification of Diseases (ICD), 8th revision (codes 211,6 and 251), 9th revision (codes 1574, 2117, 2511) and 10th revision (codes C25.4, D13.6, D13.7, E 16.1). The search in the FCR was performed by the morphological codes *8150 Pancreatic endocrine tumour* and *8151 Insulinoma*, according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).

The case histories of all the patients identified from these registers were reviewed to verify that the inclusion criteria were fulfilled. The inclusion criteria were 1) documentation of the Whipple triad and/or hyperinsulinaemic hypoglycaemia, and 2) histopathological verification of an insulinoma. Inclusion of the four inoperable patients and the two patients, who died due to complications of pancreatic surgery or diagnostic angiography before the histopathological confirmation could be obtained, required 1) documentation of the Whipple triad and/or hyperinsulinaemic hypoglycaemia, and 2) imaging findings of a pancreatic tumour compatible with an insulinoma.

4.1.2 Participants of the HRQoL survey (II)

All living patients of the Finnish insulinoma cohort were recruited by mail to participate in a survey studying their HRQoL in September and October 2017. The Finnish Population Register Centre provided address information of the study population.

4.1.3 Reference subjects for the morbidity and mortality analyses (III)

The reference population for morbidity and mortality analyses was obtained from the Finnish Population Register Center, where four controls were chosen for each patient, individually matched for age (+/- 6 months), gender and the place of residence at the index date, set as the date of insulinoma diagnosis. The controls had to be alive at the index date.

4.1.4 Reference subjects for the HRQoL analyses (II)

The reference population for the analysis of HRQoL, measured with the 15D instrument, included an age- and gender-matched sample (n=4692) of the Finnish population, obtained from the National Health 2011 survey (Koskinen et al., 2012).

4.2 Methods (I–III)

4.2.1 Incidence (I)

The yearly incidence of insulinomas was calculated by dividing the number of new cases by the number of Finnish adult population on the 31st of December each year. The official population data was obtained from the public web database of Statistics Finland (Statistics Finland's PxWeb database).

4.2.2 Diagnostics and treatment (I–III)

The clinical data of insulinoma patients were collected from the patient records in Tampere, Kuopio, Helsinki, Turku and Oulu University Hospitals, as presented in Table 5.

The hormone determinations during the fasting test were analysed by the criteria for endogenous hyperinsulinaemic hypoglycaemia, defined by the Endocrine Society (Table 1) (Cryer et al., 2009). The blood glucose values were multiplied by 1.15, to align them with the plasma glucose measurements. Complications of the surgical treatment of insulinomas were classified according to the Clavien-Dindo (CD) classification (Table 6) (Clavien et al., 2009; Dindo et al., 2004).

Table 5. Data collected from the patient records

Data	Details
Date and age at the onset of symptoms	
Date and age at the clinical diagnosis of insulinoma	
Previous diseases and medication	
Gender	
Clinical picture	Neuroglycopenic and autonomic symptoms, provoking factors, evolving of the symptoms over time, frequency of the symptoms
Weight and height	Weight and height at diagnosis, changes in weight over time
Examinations by other specialities	Information on examinations of the patients for insulinoma-related symptoms by specialities other than endocrinology before the correct diagnosis of insulinoma
Laboratory findings	Lowest incidental blood glucose concentration and highest incidental serum insulin and C-peptide concentrations pre- and postoperatively; measurements of glycated haemoglobin (HbA1c) and other endocrinological tests, results of fasting tests and prolonged (5-hour) oral glucose tolerance tests
Associated genetic syndromes	Including MEN1 and vHL
Preoperative imaging	Imaging methods, findings, and success rates
Preoperative medical treatment	Medications, duration of treatment, applied doses and drug response
Surgery	Date, surgical method (enucleation/ distal resection/ pancreatico-duodenectomy, open vs. laparoscopic approach), surgical complications
Pathological and histological characteristics	Tumour size and multiplicity, location in the pancreas, histopathological diagnosis, including WHO class, tumour grade, stage, and immunohistochemistry
Postoperative medical treatment	Medications, duration of treatment, doses, and drug response
Metastatic insulinomas	Sites of metastases, treatment of metastatic disease
Recurrences	Date, type (progression/ recurrence), and treatment of recurrent/progressive disease
Follow-up	Duration and site of follow-up (university hospital/other hospital/primary healthcare) Date and cause of death

Table 6. Clavien-Dindo classification of surgical complications. Adapted from Clavien et al., 2009; and Dindo et al., 2004.

Grade		Definition
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention without general anaesthesia
	IIIb	Intervention under general anaesthesia
IV		Life-threatening complication requiring intensive care management
	IVa	Single organ dysfunction
	IVb	Multiorgan dysfunction
V		Death of patient

4.2.3 Morbidity (III)

Morbidity of the patients vs. controls was evaluated based on the diagnoses registered at the Care Register for Health Care (HILMO) between January 1, 1980 and December 31, 2015. The Care Register for Health Care, maintained by the Finnish Institute of Health and Welfare (THL), is a continuation of the Hospital Discharge Registry, which has data on all Finnish residents discharged from any Finnish hospital between 1969 and 1993. In addition to inpatient hospital admissions, the specialized outpatient care visits have been included in the HILMO database since 1998. Recording diagnoses to the database is obligatory in Finland. The diagnoses have been coded according to the Finnish version of the 8th revision of the International Classification of Diseases (ICD) from 1969 to 1986, the 9th revision of the ICD from 1987 to 1995, and the 10th revision of the ICD since 1996. Both the primary and the secondary diagnoses were included in the analyses.

The morbidity analyses were focused on endocrine, cardiovascular, gastrointestinal and psychiatric disorders, and cancers. The classification of the disorders analysed according to the Finnish version of the 8th, 9th, and 10th revision of the ICD, is shown in Table 7. The diagnosis codes for hyperinsulinism and

hypoglycaemia were excluded from the analyses of endocrine disorders, and rheumatic heart diseases and infectious endo-, peri- and myocardial diseases were excluded from the analyses of cardiovascular diseases.

Cancer morbidity was evaluated separately, based on the diagnoses registered at the FCR, where Finnish health care organizations statutorily provide information on all new cancer cases. The FCR data included information on the date of diagnosis, age at diagnosis, number of total cancer diagnoses for each person, topography, morphology and behaviour of each tumour according to the ICD-O-3, cancer types by ICD-10, cancer stage, laterality, method of diagnosis, as well as municipality and hospital district, where the notification came from. In the analyses, the cancer notifications related to insulinomas were excluded case-by-case, by comparing the notifications with the data collected from the patient records.

Table 7. Classification of endocrine, cardiovascular, gastrointestinal, and mental and behavioural disorders, according to the Finnish version of the 8th, 9th and 10th revision of the International Classification of Diseases (ICD). Adapted from Peltola et al., 2021b.

Disease category	Classification of diseases		
	ICD-8	ICD-9	ICD-10
Endocrine disorders	240–250, 252–258	240–250, 252–259	E00–E14, E20–E35
Diabetes	250	250	E10–E14
Thyroid disorders	240–246	240–246	E00–E07
Parathyroid disorders	252	252	E20–E21
Other endocrine disorders	253–258	253–258	E22–E29, E31–E35
Cardiovascular diseases	400–414, 423–458	401–417, 423–459	I10–I28, I31, I34–I37, I42–I99
Cerebrovascular diseases	430–438	430–438	I60–I69
Hypertension	400–404	401–405	I10–I15
Arrhythmias and conduction disorders	427,2–427,98	426–427	I44–I49
Atrial fibrillation and flutter	427,92	4273A	I48
Coronary artery disease	410–414	410–414	I20–I25
Diseases of the arteries and veins	440–448, 451–458	440–448, 451–459	I70–I89
Valvular diseases and cardiomyopathies	423–425	423–425	I31, I34–I37, I42–I43
Heart failure	427.0, 427.1, 428	428	I50
Diseases of the pulmonary circulation	426, 450	415–417	I26–I28
Gastrointestinal diseases	530–577	530–579	K20–K93
Diseases of the oesophagus, stomach, and duodenum	530–537	530–537	K20-K31
Abdominal hernias	550–553	550–553	K40–K46
Chronic inflammatory bowel diseases	563	555–556	K50–K51
Diseases of the appendix	540–543	540–543	K35–K38
Other bowel diseases	560–562, 564–569	557–569	K52–K67, K90–K93
Diseases of the liver, biliary tract, and gallbladder	570–576	570–576	K70–K83
Diseases of the pancreas	577	577	K85–K87
Mental and behavioural disorders	290–315	290–315	F00–F99
Dementia	290	290	F00–F03

4.2.4 Mortality (III)

For mortality analyses, the dates and causes of death of the patients and the controls were obtained from Statistics Finland between January 1, 1980 and December 31, 2015. This database includes the dates and causes of death of all Finnish citizens deceased since 1971, classified according to the ICD (Statistics Finland, 2017). From the causes of death recorded in this database (underlying, contributing, intermediate and immediate cause of death), the underlying cause of death was used in the analyses, defined as the disease which has initiated the series of illnesses leading directly to death. In addition to the ICD, the causes of death are classified into 54 categories according to a national time series classification, convertible with the ICD (Statistics Finland, 2017). The national time series classification has been created to enable comparisons of the causes of death over time, regardless of the different versions of the ICD.

4.2.5 Health-related quality of life (II)

The long-term HRQoL of insulinoma patients was evaluated with a validated HRQoL instrument, 15D (Appendix 1). The 15D questionnaire was accompanied by a questionnaire on current health (Appendix 2), in order to identify factors associated with the HRQoL. Both questionnaires were mailed to all living patients of the insulinoma cohort in September and October 2017.

4.2.5.1 The 15D instrument (II)

The 15D instrument is a generic, validated tool for the measurement of the HRQoL among adults, with a high discriminatory power and responsiveness to change (Hawthorne et al., 2001; Moock & Kohlmann, 2008; Sintonen, 2001). It consists of 15 dimensions rated on a 5-level scale: mobility/moving, vision/seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. For each dimension, the participant chooses the level that best describes his or her current health status. To create the 15D profile, the level values on each dimension are

calculated on a scale of 0–1, with a higher score reflecting better HRQoL on that dimension.

In addition to the profile instrument, the 15D can be used as a single index instrument representing the overall HRQoL (Sintonen, 2001). The total (single index) 15D score is generated from the dimensional level values by using a set of population-based preference or utility weights. Like the level values on each dimension, the single index 15D score is calculated on a scale of 0–1, with 1 indicating no problems on any dimension, and 0 equalling to being dead. In a cross-sectional setting, the minimum important difference in the single index 15D score has been estimated to be ± 0.015 (Alanne et al., 2015).

4.2.5.2 Health questionnaire (II)

The health questionnaire consisted of 14 multiple choice questions, as well as questions on current height, weight, and regular medication (Appendix 2). The multiple-choice questions included questions on demographic factors, glucose metabolism, other chronic diseases and medical interventions, participants' own opinion on their current health, as well as the current follow-up status of insulinoma.

4.2.6 Statistical analysis (I–III)

The statistical analyses were conducted with the IBM SPSS Statistics for Windows, versions 22.0, 25.0 and 27.0 (IBM Corp., Armonk, NY, USA), the STATA Statistical Software, Release 13 (StataCorp LP, College Station, TX, USA) and the OpenEPI Collection of Epidemiologic Calculators, Version 3.01.

4.2.6.1 Data presentation and comparison of subgroups (I–III)

The data are presented as mean (standard deviation, SD) for normally distributed variables, median [minimum (min)–maximum (max)] for other numerical variables and number (%) for categorical variables. The differences in clinical and treatment-related factors (age, gender, diagnostic delay, sensitivity of imaging methods, tumour diameter, type and period of surgery and occurrence of surgical complications) were

compared between different subgroups of patients with an insulinoma (patients with a non-metastatic or a metastatic insulinoma; patients with or without MEN1 syndrome; patients treated in the 1980s, 1990s or 2000s; patients treated with different surgical methods; and participants or non-participants of the HRQoL survey) using the Mann-Whitney *U* test, Student t-test, Kruskal-Wallis test, or Fisher's exact test, as appropriate. A two-sided *p*-value below 0.05 was considered statistically significant. Poisson regression analysis was conducted to analyse the changes in the incidence of insulinomas during the study period.

4.2.6.2 Statistical analysis of morbidity (III)

First, the incidence of endocrine, cardiovascular, gastrointestinal, psychiatric and cancer diseases diagnosed before the diagnosis of insulinoma was compared between the patients and controls using Fisher's exact test and conditional logistic regression. Secondly, the incidence rates of these diseases after the diagnosis of insulinoma were analysed for the patients and the controls and compared by calculating the incidence rate ratios (RR) with the 95% Confidence Intervals (95% CI), using the Mantel-Haenszel method. The follow-up time of each patient for each disease or disease group lasted until the diagnosis of that disease or the common closing date (December 31, 2015), unless death or emigration occurred first. Because only the first notification of each disease or disease group was included in the analyses, persons with a disease diagnosed before the index date were excluded from the incidence calculations of that disease category and were included only in the analyses regarding morbidity before the diagnosis of insulinoma. If a patient was diagnosed with a disease before the index date, also the corresponding controls were excluded from the analyses, to ensure a more reliable comparison between the patient group and the control group. In order to eliminate detection bias in the morbidity analyses of the patients vs. controls, a sensitivity analysis was performed for all disease categories, excluding persons diagnosed with a disease within the category being analysed, during the first year after the index date.

4.2.6.3 Statistical analysis of mortality (III)

For the mortality analyses, individual follow-up times were calculated from the diagnosis of insulinoma until death, emigration or the common closing date (December 31, 2015), whichever occurred first. The overall survival was compared between the patients and the controls, using Kaplan-Meier analysis with the log-rank test. Cox regression analysis was used to assess the hazard ratios (HR) and 95% CIs for mortality rates in patients with a non-metastatic or a metastatic insulinoma, and their controls. The insulinomas were retrospectively classified according to their largest diameter (≥ vs. <2 cm) and the current TNM Classification (Brierley et al., 2017). Uni- and multivariate Cox regression analyses were used to identify eventual clinical, biochemical, and tumour- and treatment-related factors associated with the overall survival. The distribution of the causes of death, according to the national time series classification, was compared between the patients and the controls with the Fisher's exact test.

4.2.6.4 Statistical analysis of HRQoL (II)

The mean total 15D score, as well as the mean scores on the fifteen distinct dimensions of the HRQoL, were compared between the patients and the controls using the independent samples *t* test, according to the validated 15D protocol (Sintonen, 2001). The mean difference in the total 15D score was compared to the minimum clinically important difference, previously defined as ± 0.015 (Alanne et al., 2015). Because the 15D variables were non-normally distributed in the insulinoma cohort, the analyses were also performed by using the Mann-Whitney *U* test.

Spearman correlation coefficients were calculated to examine the association of numerical factors with the HRQoL among patients with an insulinoma. For categorical variables, the differences in the 15D scores were analysed with the Mann-Whitney *U* test or the Kruskal-Wallis test, as appropriate. The body mass indexes of the participants were calculated from the self-reported weight and height measures and compared with those registered at the time of clinical insulinoma diagnosis, using the Wilcoxon signed rank test.

4.2.7 Ethical considerations

This study was undertaken in accordance with the Declaration of Helsinki. The Regional Ethics Committee of the Tampere University Hospital catchment area reviewed and approved the study protocol. The University Hospitals of Tampere, Helsinki, Kuopio, Turku, and Oulu gave permissions to use data from their patient record registries. The Finnish Institute for Health and Welfare yielded permission for the use of data from the FCR and HILMO. Statistics Finland gave permission for the dates and causes of death derived from their database. The Population Register Centre gave permission for choosing the control population from the data of their register, and for using the patients' contact information for the HRQoL survey. Each participant of the HRQoL survey gave a written informed consent and a permission to combine the information received from the questionnaires with the data from the registers mentioned above. Participation in the HRQoL study was voluntary, free of charge, and uncompensated.

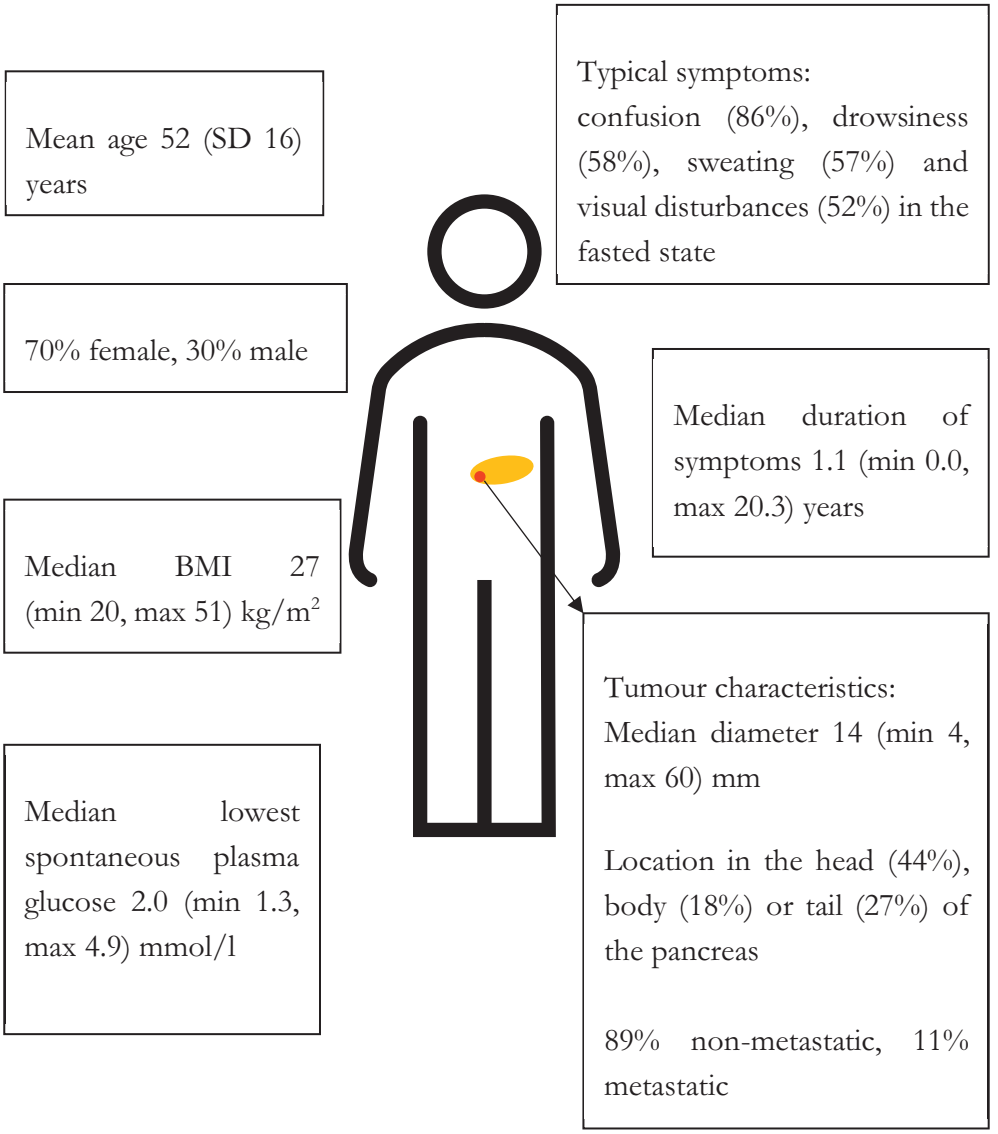
5 SUMMARY OF THE RESULTS

5.1 Clinical characteristics of the patients

5.1.1 All patients diagnosed with an insulinoma in Finland 1980–2010 (I, III)

A total of 79 adult patients (≥ 18 years of age) were diagnosed with an insulinoma in Finland during the study period. Characteristics of the patients are presented in Figure 1. Two (3%) patients had a MEN1 syndrome associated with a benign, solitary insulinoma. No other hereditary syndromes were detected. During the follow-up time (until December 31, 2015), twenty-five (32 %) patients and 63 (20%) controls deceased, and one subject emigrated from Finland. The median duration of follow-up beginning from the diagnosis of insulinoma was 10.7 (0.2–32.6) years for patients and 12.2 (1.2–35.5) years for controls.

Figure 1. Characteristics of the insulinoma patients.



5.1.2 Patients participating in the HRQoL survey (II)

Of the 79 patients diagnosed with an insulinoma, fifty-one (65%) were alive in September 2017, and were invited to participate in the HRQoL survey. Of the 51 patients, 38 gave their informed consent, and filled in and returned the 15D and health questionnaires (response rate 75%). All the HRQoL study participants had undergone curative-intent pancreatic surgery for their insulinoma, a median of 13 (7–34) years earlier. The characteristics of the HRQoL study participants are shown in Table 8. When the participants and non-participants were compared, no significant difference was found in the patient characteristics (age at survey, gender, age at diagnosis and time since diagnosis) or insulinoma-specific factors (surgical method, period of surgery and prevalence of metastatic disease). By contrast, a metastatic disease was significantly more common among the patients deceased before the survey (n=28) compared to the participants alive and the non-participants (25% vs. 5% and 0%, respectively, p=0.026, Fisher's exact test).

Table 8. Characteristics of the HRQoL survey participants, previously diagnosed with an insulinoma (n=38). Modified from Peltola et al., 2021a.

		n / median	% / min–max
Age, years		64	31–85
Gender, female		28	74
Current BMI[a], kg/m^2		25	19–51
Marital status			
	Married or cohabiting	26	68
	Single, divorced or widowed	12	32
Education			
	Lower education	7	18
	High school or above	31	82
Age at diagnosis of insulinoma, years		46	21–76
Time since diagnosis of insulinoma, years		14	7–34
Surgical methods			
	Tumour enucleation	16	42
	Distal pancreatic resection	16	42
	Pancreatico-duodenectomy	6	16
Major, grade III-V surgical complications[b]		7	18
Distant metastases		2	5
Follow-up status for insulinoma at the time of survey			
	No follow-up	29	76
	Primary healthcare	3	8
	Regional or university hospital	5	13
	Data missing	1	3
Self-reported chronic diseases			
	Any chronic disease	27	71
	Hypertension	18	47
	Other cardiovascular diseases	4	11
	Hypercholesterolemia	5	13
	Peripheral joint disease	6	16
	Spondyloarthrosis	5	13
	Diabetes	4	11
	Asthma	4	11
	Depression and other psychiatric disorders	4	11
	Other[c]	7	18

[a]Calculated on the basis of self-reported height and weight measures of the survey participants. [b]Classified according to the Clavien-Dindo classification (Table 6, Clavien et al., 2009; Dindo et al., 2004). [c]Other chronic diseases included gastroesophageal reflux disease (n=2), osteoporosis (n=2), stroke, anaemia, sleep apnoea, diverticulosis, goitre and chronic pain syndrome (n=1 each).

5.2 Incidence of insulinoma (I)

The incidence of insulinomas over the whole study period, 31 years, was 0.6 per million adults per year. The incidence increased significantly, from 0.5 and 0.4 in the 1980s and 1990s, to the 0.9 per million per year in the 2000s (yearly incidence rate ratio 1.043, p=0.002, Poisson regression analysis). From the 9 patients with a metastatic insulinoma, 3 (33%) were diagnosed in the 1980s, 2 (22%) in the 1990s and 4 (44%) in the 2000s.

5.3 Clinical picture and diagnostic delay of insulinoma (I)

Criteria for the Whipple triad (symptomatic hypoglycaemia relieved by rising the glucose level) were met in all but two patients prior to the diagnosis of insulinoma. The mean age at the onset of symptoms was 49 (SD 15) years. The clinical presentation of insulinoma in the patients is shown in Table 9. The symptoms were usually provoked by fasting, but 8% had additionally postprandial symptoms, and 44% had symptoms provoked by exercise. No patient had exclusively postprandial symptoms. Neuroglycopenic symptoms predominated the clinical picture, and severe hypoglycaemia leading to unconsciousness was documented in 36 (46%) patients prior to the diagnosis of insulinoma. Excessive sweating was the most common autonomic symptom, followed by tremor and anxiety or aggressiveness. Over half of the patients gained weight, and one-third of them more than 10 kilograms. The median body mass index (BMI) was 27 (20–51) kg/m^2 at the time of the diagnosis.

There was no significant difference in the clinical presentation (presence of autonomic and neuroglycopenic symptoms, presence of fasting and postprandial symptoms, history of severe hypoglycaemia leading to unconsciousness, age at the onset of symptoms, BMI at the diagnosis, or gender distribution) between patients diagnosed in the 1980s, 1990s and 2000s, nor between patients with a metastatic or a non-metastatic insulinoma. The two patients with the MEN1 syndrome were younger than the patients with a sporadic insulinoma (mean age 42 vs. 52 years, respectively) at the time of the diagnosis, but the difference was not statistically significant (p=0.368).

The median duration of hypoglycaemic symptoms at diagnosis (diagnostic delay) was 13 months and it did not significantly differ between the patients diagnosed in the 1980s, 1990s and 2000s (17, 11 and 17, respectively, p=0.784, Kruskal-Wallis test). Thirty-one (39%) of the patients were first examined for their symptoms by specialties other than endocrinology or internal medicine, most often by neurology or neurosurgery (27 patients), cardiology (7 patients), psychiatry (2 patients) and ophthalmology (2 patients).

Two patients did not have a history of hypoglycaemias at diagnosis: one patient was diagnosed with a MEN1-related insulinoma in the connection of MEN1-investigations of the patient's sibling, and hypoglycaemic symptoms appeared 3 years after the diagnosis of the tumour. The other patient was diagnosed with a pancreatic tumour during investigations due to jaundice and diarrhoea. The tumour was operated on, with a histopathological diagnosis of islet cell carcinoma, and episodes of symptomatic hypoglycaemia occurred 8 months after the surgery, concurrently with the detection of liver metastases.

Table 9. Clinical presentation of insulinoma in 79 patients diagnosed in Finland in 1980–2010. Modified from Peltola et al., 2018.

		n (%)
Neuroglycopenic symptoms		76 (96)
	Confusion	68 (86)
	Drowsiness	46 (58)
	Visual disturbances	41 (52)
	Unconsciousness	36 (46)
	Amnesia	35 (44)
	Lightheadedness	26 (33)
	Hunger	24 (30)
	Paraesthesias	20 (25)
	Headache	16 (20)
	Seizures	15 (19)
Autonomic symptoms		61 (77)
	Sweating	45 (57)
	Tremor	21 (27)
	Anxiety, aggressiveness	16 (20)
	Palpitations	14 (18)
Evolvement of the symptoms		
	Progressive	41 (52)
	Stable	4 (5)
	Data missing	34 (43)
Symptom frequency at worst		
	Daily	32 (41)
	Weekly	10 (13)
	Monthly	6 (8)
	Data missing	31 (39)
Weight gain		
	Yes	44 (56)
	No	14 (18)
	Data missing	21 (27)

5.4 Preoperative diagnostics of insulinoma (I)

5.4.1 Biochemical diagnostics

Before the surgical treatment of insulinoma, the median lowest plasma glucose in the patients, apart from the fasting and glucose tolerance tests, was 2.0 (1.3–4.9) mmol/l (n=62), and the median glycated haemoglobin (HbA1c) value was 4.9 (3.7–5.7) %, i.e., 30 (17–39) mmol/mol (n=31). Sixty-five (82%) patients underwent a prolonged fasting test, aiming at the fast duration of 24, 36 or 72 hours (accurate data for analysis missing in one of these patients). The fasting test resulted in hyperinsulinaemic hypoglycaemia, defined according to the criteria of the Endocrine Society (Cryer et al., 2009), in 59 (92%) patients, after a median fasting duration of 14 (0–36) hours. Four of the five patients with a negative fasting test had the fast terminated prematurely against the current recommendation of 72 hours.

When the determinations of glucose, insulin and C-peptide obtained preoperatively and in the fasting test (Table 10) were compared between patients with metastatic vs. non-metastatic insulinoma, patients with a metastatic insulinoma had a significantly higher spontaneous preoperative serum C-peptide level [3.0 (2.2–3.6) vs. 1.0 (0.4–4.4) nmol/l, p=0.004. No significant difference was found between the glucose or insulin concentrations, or the duration of fast in the fasting test, between patients with a metastatic or a non-metastatic insulinoma. An oral glucose tolerance test was performed in eleven (14%) patients, with hyperinsulinaemic hypoglycaemia confirmed in three of these tests.

Table 10. Glucose and hormone concentrations in spontaneous samples and during prolonged fasting test in 64 patients diagnosed with an insulinoma in Finland in 1980–2010 (Peltola et al., 2018)

	median (min–max)
Lowest spontaneous plasma glucose, mmol/l (n=62)	2.0 (1.3–4.9)
Highest spontaneous serum insulin, mU/l (n=49)	26.0 (3.10–271.0)
Highest spontaneous serum C-peptide, nmol/l (n=39)	1.2 (0.4–4.4)
Plasma glucose nadir in the fasting test, mmol/l (n=64)	2.2 (0.8–4.5)
Corresponding serum insulin in the fasting test, mU/l (n=55)	16.0 (1.5–154.0)
Corresponding serum C-peptide in the fasting test, nmol/l (n=44)	0.9 (0.3–4.4)

5.4.2 Localization studies

A total of 234 preoperative imaging procedures were performed on the 79 patients diagnosed with an insulinoma, with a median of 3 (1–7) imaging modalities used per patient. The ratio of tumours successfully localized preoperatively increased from 39% and 56% in the 1980s and 1990s, respectively, to 98% in the 2000s. Preoperative localizing methods and sensitivities are presented in Table 11, arranged according to their frequency.

A CT scan was performed on 90% of the patients, with an overall sensitivity of 32%. Despite the limited sensitivity of CT over the whole study period, the sensitivity of CT scanning improved remarkably from 6% and 18% in the 1980s and 1990s, respectively, to 51% in the 2000s (p=0.001). The sensitivities of other imaging modalities in the 2000s were 82% for EUS (n=17), 63% for angiography (n=11), 58% for ^{18}F-DOPA-PET/CT (n=19), 55% for MRI (n=22), and 36% for abdominal US (n=11). The sensitivity of octreotide scintigraphy (n=9) was only 11%. In one patient, the insulinoma was successfully localized with MRCP. In a subgroup analysis including only tumours with a diameter of 1 cm or less, the highest sensitivity was achieved with EUS (78%), while the sensitivities of other methods were 43% for ^{18}F-DOPA-PET/CT, 40% for MRI, 33% for octreotide scintigraphy, 23% for CT, and 0% for transabdominal US.

In addition to preoperative imaging, also intraoperative US was used on 19 patients (26% of the surgically treated ones). It could localize the tumour in 15 of these patients (sensitivity 79%), including 3 patients whose tumour remained undetected by the preoperative imaging methods. One patient died of complications in a diagnostic angiography. Other lethal complications did not occur in relation to the invasive localization of insulinomas.

Table 11. Preoperative localizing methods and their sensitivities in 79 patients diagnosed with an insulinoma in Finland 1980–2010 (Peltola et al., 2018).

Localizing method (n)	Proportion of patients, %	Rate of correct localization, %
CT scan (71)	90	32
Abdominal US (35)	44	17
Angiography (34)	43	38
MRI (28)	35	50
EUS (23)	29	78
^{18}F-DOPA PET/CT (20)	14	55
Octreotide scintigraphy (15)	19	20
THPVS (4)	5	75
ERCP (2)	3	0
MRCP (1)	1	100
^{18}F-FDG-PET/CT (1)	1	0

CT computed tomography, US ultrasound, MRI magnetic resonance imaging, EUS endoscopic ultrasound, PET/CT positron emission tomography-computed tomography, THPVS transhepatic portovenous sampling, ERCP endoscopic retrograde cholangiopancreatography, MRCP magnetic resonance cholangiopancreatography.

5.4.3 Tumour characteristics and histopathology

Insulinoma was solitary in 73 (92%) patients and multiple in 5 (6%) patients (data missing in one patient). Median tumour diameter was 14 mm and 70% of the tumours were less than 2 cm in diameter. Metastatic insulinomas were significantly larger than non-metastatic insulinomas [a median diameter of 35 (10–60) vs. 14 (4–40) mm, p=0.004]. Fifty-one per cent of insulinomas were located in the head or neck and 49% in the body or tail parts of the pancreas. When the tumours were retrospectively classified according to the current TNM classification (Brierley et al., 2017), 58 (73%) insulinomas fell into stage I, 10 (13%) into stage II, 0 into stage III, and 9 (11%) into stage IV (data not available for analysis in 2 patients).

In 73 of the 79 patients, the diagnosis was confirmed histopathologically, whereas in 6 patients, including 4 inoperable patients, the diagnosis was based on the documentation of the Whipple triad or biochemical detection of hyperinsulinaemic hypoglycaemia, together with imaging findings compatible with an insulinoma. Insulin staining was positive in all the 59 tested specimens. Most tumours also stained positively for chromogranin A [39/42 (93%)] and synaptophysin [32/35

(91%)]. The Ki-67 index was determined in 29 specimens and was <3% in 20 (69%), 3–20% in 6 (21%) and >20% in 2 (7%) of the tested specimens.

According to the patient record and pathology registry data, the insulinomas were originally classified as benign in 58 (73%), malignant in 11 (14%), and undetermined in 6 (8%) patients. Of the 11 insulinomas originally classified as malignant, 9 (11% of all insulinomas) presented with distant metastases. In the specimens of the two patients without distant metastases, the histopathological diagnosis of malignancy was based on a high proliferation index (Ki-67 labelling index 9%) in one tumour, and on microscopic perineural invasion in the other tumour. Of the 9 patients with distant metastases, 8 had metastases in the liver, 3 in the lungs, 3 in distant lymph nodes (mesothelial, mediastinal and subcarinal), 1 in the mesothelium of the jejunum and 1 in the neck. No patient presented with solely lymph nodal metastases. The original pathology report -based classification into malignant vs. benign or undetermined insulinomas was applied in reporting the management and outcome of insulinomas in Publication I. In line with the current WHO Classification, by which all NETs are considered to be malignant (WHO Classification of Tumours Editorial Board, 2019), the terms benign and malignant were avoided in Publications II and III, and the tumours were classified simply based on the presence of distant metastases, into metastatic and non-metastatic insulinomas.

5.5 Treatment and outcome of patients with insulinoma (I, III)

5.5.1 Surgical treatment

Seventy-one (89.9%) patients diagnosed with an insulinoma underwent curative-intent surgery. The curative-intent surgical methods included 31 (44%) tumour enucleations, 31 (44%) distal resections and 9 (13%) pancreatico-duodenectomies. Two distal resections were successfully performed laparoscopically. Conversion from laparoscopic to open approach was made in additional 5 patients. Data on the surgical approach (open vs. laparoscopic) was missing in 6 patients. In addition to the patients with curative-intent surgery, 2 patients with a metastatic insulinoma underwent distal pancreatic resections as palliative-intent surgery. There was no

significant difference in the distribution of the surgical methods applied between the 1980s, 1990s and 2000s.

The surgical operations were performed in the University Hospitals of Helsinki (n=24, 33%), Tampere (n=19, 26%), Kuopio (n=12, 16%), Turku (n=9, 12%), and Oulu (n=7, 10%), and in Päijät-Häme Central Hospital in Lahti (n=2, 3%). In a subgroup analysis of the patients who underwent surgery in the Helsinki University Hospital, the enucleation rate increased from 0 in the 1980s to 44% in the 2000s, while the rate of pancreatic resections decreased from 100 to 56%, respectively (p=0.021).

Two patients died due to surgical complications, the postoperative mortality being 2.7%. One patient died due to bleeding during a pancreatic tail resection, and the other patient died during a reoperation performed for a pancreatic fistula, complicated by severe pancreatitis and sepsis, after the primary enucleation of a benign insulinoma in the pancreatic head. Postoperative complications occurred in 51% of the surgically treated patients, the most common complications being pancreatic fistula (19%), intra-abdominal abscess (14%), pancreatitis (10%) and wound infection (10%). Surgical complications required one or more relaparotomies in 3 (4%) of the surgically treated patients. The incidence of pancreatic fistulae showed no significant difference between the surgical methods (23% after enucleations, 12% after distal resections and 33% after pancreatico-duodenectomies, p=0.293). There was also no significant difference in the CD complication grade (Clavien et al., 2009; Dindo et al., 2004) between the surgical methods (Table 12, p=0.062), between the periods of surgery (1980s, 1990s or 2000s) or between the surgical centres. Based on the information on the diagnosis codes for exocrine pancreatic insufficiency in HILMO and the self-reported use of pancreatic enzyme preparation (Creon®) in the health questionnaire of the HRQoL study, exocrine pancreatic insufficiency developed in 4 (5%) of the surgically treated patients.

Table 12. Postoperative complications, graded according to the Clavien-Dindo classification (Clavien et al., 2009; Dindo et al., 2004), in the 73 insulinoma patients who underwent surgical treatment in Finland during 1980–2010 (Peltola et al., 2018).

Complication grade	Enucleation (n=31)	Distal resection (n=33)	Pancreaticoduodenectomy (n=9)	Total (n=73)
0	15 (48%)	19 (58%)	2 (22%)	36 (49%)
I	2 (6%)	0	0	2 (3%)
II	9 (29%)	6 (18%)	2 (22%)	17 (23%)
III	4 (13%)	6 (18%)	4 (44%)	14 (19%)
IV	0	1 (3%)	1 (11%)	2 (3%)
V	1 (3%)	1 (3%)	0	2 (3%)

Among the 71 patients treated with curative-intent surgery, three disease progressions and three recurrences occurred, with the 5-, 10- and 15-years disease-free survival being 94, 93 and 90%, respectively. Two progressions and 2 recurrences were due to a metastatic insulinoma. One patient with a non-metastatic insulinoma developed a tumour recurrence 10 years after the primary enucleation of a single, non-metastatic insulinoma, located in the head of the pancreas. In one patient, the tumour could not be localized in the primary surgery, and the symptoms progressed despite the blind pancreatico-duodenectomy. A diagnostic angiography was performed postoperatively to localize the tumour, but during this angiography, a lethal intra-abdominal bleeding developed.

In addition to the traditional pancreatic surgery, other invasive treatments of insulinomas and metastases included a superselective embolization of a branch of the gastroduodenal artery, dearterialization and embolization of liver metastases, chemoembolization of liver metastases, and resection and thermoablation of liver metastases (n=1, each).

5.5.2 Medical treatment

Sixty-one (77%) of the insulinoma patients used medical treatment for insulinoma either pre- or postoperatively or instead of surgical treatment. The most common medications were diazoxide and somatostatin analogues (Table 13). A favourable response to diazoxide was documented in 63% of the 30 patients with data available.

Of the 70 patients with a non-metastatic insulinoma, 48 (69%) used medication prior to surgery and one patient (1%) instead of surgery, most commonly diazoxide (n=40), or a somatostatin analogue (n=5) or both (n=2). One patient with a non-metastatic insulinoma was treated with frequent meals only, during the 13 years of follow-up.

In addition to the surgical and medical treatment of insulinomas, two patients (3%) received radiation therapy for insulinoma metastases.

Table 13. Medical treatment of 79 insulinoma patients diagnosed in Finland 1980–2010 (Peltola et al., 2018).

Medication	n (%)
Diazoxide	50 (63)
Somatostatin analogue	25 (32)
Prednisolone or other glucocorticoids	14 (18)
Intravenous glucose infusion	11 (14)
Interferon-α	6 (8)
Streptozotocin-5-fluorouracil	5 (6)
Streptozotocin	1 (1)
Diphenylhydantoin	1 (1)
Doxorubicin-dacarbazine	1 (1)
Doxorubicin	1 (1)
Epirubicin	1 (1)
Sunitinib	1 (1)

5.5.3 Follow-up of insulinoma patients in the University Hospitals

After the diagnosis of insulinoma, the patients were followed up at the University Hospital for a median of 0.9 (0.1–31) years. In the subgroup of patients with a curatively treated non-metastatic insulinoma, the median follow-up time at the University Hospital was 3.5 months after the surgery.

5.6 Long-term morbidity in insulinoma patients (III)

The median duration of the whole register-based follow-up of the patients and controls between January 1, 1980, and December 31, 2015, was 36 (3–36) years. Before the diagnosis of insulinoma, the patients and the controls were followed up for a median of 22.7 (0.5–30.8) years. During the pre-diagnosis period, there was no statistically significant difference in the endocrine, cardiovascular, gastrointestinal, psychiatric or cancer morbidity between the insulinoma patients and their controls, matched for age, gender and the place of residence.

After the diagnosis of insulinoma, the patients were followed up for a median of 10.7 (0.2–32.6) years and the controls for a median of 12.2 (1.2–35.5) years. Regarding endocrine disorders, only the incidence of thyroid disorders [RR 2.76 (1.00–7.60, p=0.040] was increased among the insulinoma patients vs. controls. The cumulative incidence of thyroid disorders increased gradually, starting from the diagnosis of insulinoma. After excluding the first post-diagnostic year, however, no significant difference was found in the thyroid morbidity of the patients vs. controls. Neither the prevalence of diabetes before the diagnosis of insulinoma [4 cases in the patients vs. 6 in the controls, OR 2.67 (95% CI 0.75–9.45), p=0.163] nor the incidence of diabetes after the diagnosis of insulinoma [8 cases in the patients vs. 22 in the controls, RR 1.67 (95% CI 0.74–3.75), p=0.210], did significantly differ between the patients and the controls. A parathyroid disorder was diagnosed in only two patients, one of whom had a confirmed MEN1 syndrome.

Regarding cardiovascular diseases, only the incidence of atrial fibrillation [RR 2.07 (1.02–4.22), p=0.039] was significantly increased in the patients vs. controls. The cumulative incidence of atrial fibrillation increased gradually after the diagnosis of insulinoma in the patients, and after excluding the first post-diagnostic year from the analyses, a trend, although not statistically significant, was detected towards an increased cumulative incidence of atrial fibrillation also in the long-term follow-up of insulinoma patients vs. controls [2.08 (0.98–4.45), p=0.053].

As for gastrointestinal diseases, including postoperative morbidity, the incidence of intestinal obstruction [18.65 (2.09–166.86), p<0.001] and pancreatic diseases [12.86 (3.41–48.49), p<0.001] was increased in the patients vs. controls. Intestinal obstruction was diagnosed in 5% of the patients who underwent surgical treatment, a median of 5.9 years after surgery. The increased incidence of pancreatic diseases

was explained by acute postoperative pancreatitis in 5% of the surgically treated patients, diagnosed usually within 2 months after surgery.

Regarding specific cancer types, breast [4.46 (1.29–15.39, p=0.010] and kidney cancers (RR not applicable, NA, p<0.001) were diagnosed significantly more often in the patients vs. controls. When the MEN1-patients and their controls were excluded from the analysis of breast cancer, the difference in the breast cancer incidence between the patients vs. controls was no longer statistically significant [2.64 (0.63–11.04), p=0.167]. All the kidney cancers occurred in patients with a sporadic, non-metastatic insulinoma.

The overall incidence of mental and behavioural disorders did not significantly differ between the patients and the controls [RR 1.52 (95% CI 0.79–2.92), p=0.208)]. Similarly, the long-term incidence of dementia did not significantly differ in the patients vs. controls [1.28 (0.42–3.90), p=0.658].

5.7 Long-term mortality of insulinoma patients (III)

5.7.1 Overall survival

Twenty-five (32%) of the insulinoma patients and 63 (20%) of the matched controls deceased, during the median follow-up of 10.7 (0.2–32.6) years for the patients vs. 12.2 (1.2–35.5) years for the controls after the diagnosis of insulinoma, respectively. The Kaplan-Meier survival curves of the patients and the controls are shown in Figure 2. The overall survival of the patients with a non-metastatic insulinoma did not differ from that of matched controls [median 27.5 (95% CI 24.1–30.8) vs. 33.2 (29.8–36.7) years, respectively, HR 1.5 (0.9–2.6), p=0.128, Cox regression analysis]. In the patients with a metastatic insulinoma, the survival was significantly impaired [median 3.4 (2.9–4.0) years vs. not reached in the controls, HR 5.1 (1.9–13.3), p=0.001, Cox regression analysis]. Still, three of the patients with a metastatic insulinoma survived significantly longer: one patient lived 11 years with the disease, and two patients were alive at the end of the follow-up, 6 and 30 years after the initial diagnosis.

In addition to the presence of distant metastases, older age [HR 1.05 (95% CI 1.02–1.08, p=0.001], higher preoperative serum insulin level [1.10 (1.01–1.20),

p=0.037, calculated for a 10 mU/l rise in plasma insulin concentration], lack of curative-intent surgery [9.86 (3.60–27.00), p<0.001 for no surgery, and 17.01 (3.45–83.92), p=0.001 for palliative surgery)], tumour size ≥2cm [2.79 (1.19–6.55), p=0.018)], need for postoperative medication [3.09 (1.23–7.75), p=0.016)], and the occurrence of major surgical complications (grades III–V of the CD classification (Clavien et al., 2009; Dindo et al., 2004) [3.06 (1.15–8.12), p=0.025)] were associated with impaired overall survival in the univariate Cox regression analyses. After the exclusion of surgical deaths (grade V complication, n=2) from the analysis, there was no significant association between major (grade III–IV) vs. no or minor (grade 0–II) surgical complications and impaired overall survival.

In multivariate analyses, older age and distant metastases were independent predictors of impaired survival in both the whole cohort (Table 14, four patients excluded due to missing data regarding tumour size or localization) and in the subgroup of surgically treated insulinoma patients (Table 15).

Figure 2. Overall survival of patients with a non-metastatic insulinoma vs. their controls (p=0.125, log-rank test), and of patients with a metastatic insulinoma vs. their controls (p<0.001). (Preliminary results were presented at the European Congress of Endocrinology, May 2021)

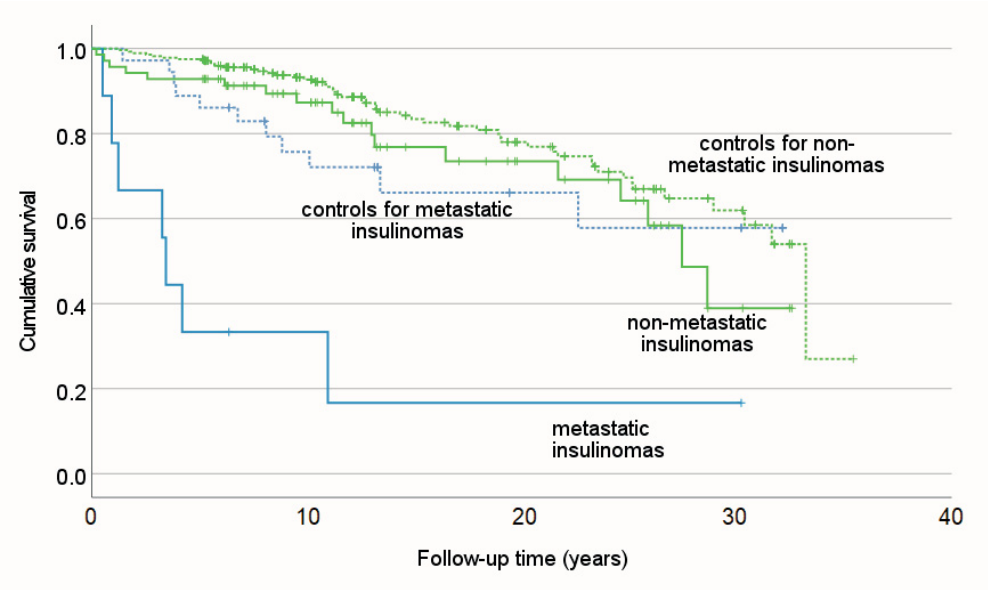


Table 14. Multivariate Cox regression analysis of factors associated with survival in 75 patients diagnosed with an insulinoma in Finland 1980–2010. Modified from Peltola et al., 2021b.

Variable	Hazard Ratio	95% CI	Significance
Age at diagnosis	1.05	1.02–1.08	**0.003**
Tumour localization (head/neck vs. body/tail)	1.90	0.72–5.03	0.197
Tumour size (≥ 2 cm vs. < 2 cm)	2.49	0.93–6.65	0.070
Distant metastases	3.71	1.18–11.67	**0.025**

Table 15. Multivariate Cox regression analysis of factors associated with survival in 73 surgically treated insulinoma patients. Modified from Peltola et al., 2021b.

Variable		Hazard Ratio	95% CI	Significance
Age at surgery		1.08	1.03–1.13	**0.001**
Surgical method (reference: enucleation)				
	Distal resection	0.81	0.27–2.44	0.704
	Pancreatico-duodenectomy	4.07	0.80–20.87	0.092
Time period of surgery (reference: 1980–1989)				
	1990–1999	1.20	0.35–4.12	0.775
	2000–2010	0.39	0.09–1.73	0.213
Distant metastases		4.58	1.29–16.25	**0.018**

5.7.2 Causes of death

Six insulinoma patients died of metastatic insulinoma and three patients with a non-metastatic insulinoma died due to complications of invasive diagnostics (n=1) or surgical treatment of insulinoma (n=2). With these two postoperative deaths that occurred in the 73 surgically treated patients, the perioperative mortality rate, defined as any death occurring within 30 days after surgery, was 2.7%.

During the follow-up, 16 patients died due to other than insulinoma-related causes, compared to 54 deaths in their controls. When these 16 patients with a non-insulinoma related cause of death were compared to their controls, no significant difference was found in the distribution of the most common causes of death [diseases of the circulatory system (50 vs. 44%), cancer (25 vs 22%) and other causes (25 vs 33%), respectively, p=0.765]. Similarly, there was no significant difference in

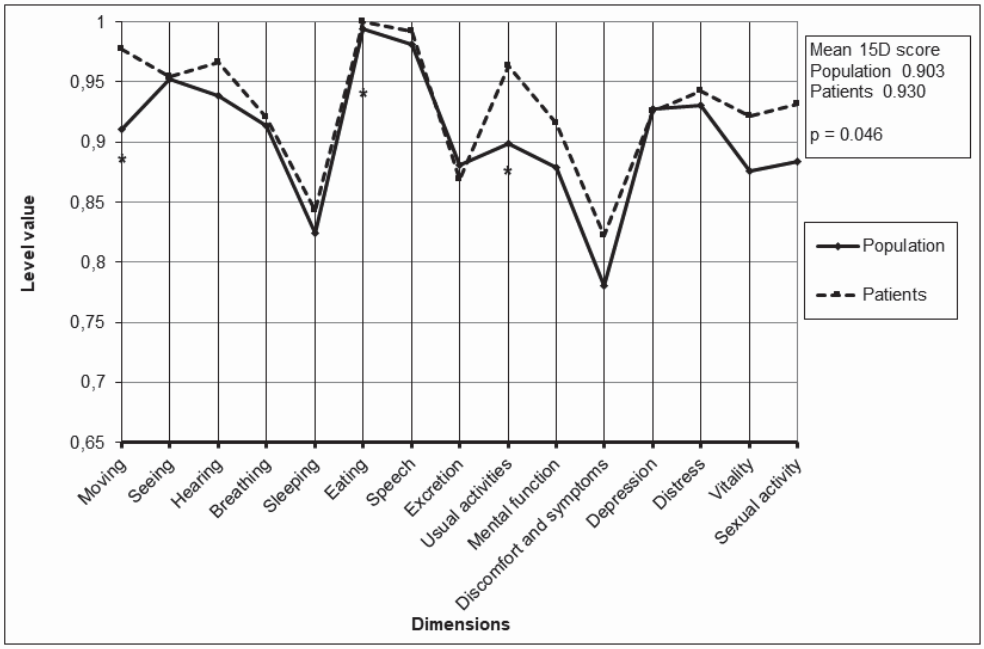
the distribution of the causes of death analysed according to the time series classification of Statistics Finland (p=0.363).

5.8 Long-term HRQoL in patients treated for an insulinoma (II)

In the health questionnaire, 74% of the HRQoL study participants assessed their general health as quite good or very good, on a Likert-scale from very bad to very good. In insulinoma patients, the mean total 15D score, reflecting the overall HRQoL, was significantly higher than in the controls (Figure 3), and the magnitude of the mean difference (0.027) was also clinically important (≥0.015) (Alanne et al., 2015). The slightly better overall HRQoL of insulinoma patients vs. controls was explained by the significantly better scores on the dimensions of usual activities, moving and eating. The results remained the same, when the analyses were repeated with the non-parametric Mann-Whitney *U* test (data not shown).

Among the insulinoma patients, older age at survey (r=-0.414, p=0.010), higher number of chronic diseases and medications (r=-0.550, p<0.001; r=-0.573, p<0.001, respectively), diagnosis of hypertension (mean 15D score 0.898±0.88 vs. 0.959±0.036 in patients without hypertension, p=0.017) and lower level of education (mean 15D score 0.844±0.081 vs. 0950±0.054 in patients with education level high school or above, p<0.001) were associated with a significantly lower total 15D score. Current BMI was not significantly associated with the total 15D score, but showed a negative correlation with scores on the dimensions of moving (r=-0.343, p=0.038) and breathing (r=-0.366, p=0.026). On the other hand, gender, cohabiting status or the follow-up status of insulinoma (in healthcare follow-up vs. no follow-up due to insulinoma) were not significantly associated with the mean total 15D score, nor were the age at the diagnosis of insulinoma, duration of symptoms before the diagnosis, time since surgical treatment, surgical method (enucleation, distal resection or pancreatico-duodenectomy) or occurrence of major, grade III–V surgical complications (Clavien et al., 2009; Dindo et al., 2004) (data not shown).

Figure 3. The HRQoL profile in 38 patients previously treated for an insulinoma, compared to 4692 age- and gender-matched controls of the Finnish general population. Adapted from Peltola et al., 2021a. *indicates a statistically significant difference (p<0.05) between the groups.



6 DISCUSSION

6.1 Major findings of this study

6.1.1 Incidence and clinical picture of insulinomas

The vast majority of insulinomas were sporadic and non-metastatic, and were diagnosed at a mean age of 52 years, with 70% vs. 30% female predominance, which is in line with previous studies (Jensen et al., 2012; Maggio et al., 2020; Mehrabi et al., 2014). Neuroglycopenic symptoms predominated the clinical picture, and there was no significant difference in the clinical presentation between patients diagnosed in the 1980s, 1990s and 2000s, nor between patients with a metastatic or a non-metastatic insulinoma. The incidence of insulinomas increased almost two-fold during the study period, from 0.5 in the 1980s to 0.9 cases per million persons per year in the 2000s. In line with our findings, previous studies have reported a rising incidence for all NENs during the past few decades. The rising incidence of NENs may at least partly be due to an improved clinical awareness and diagnostic sensitivity (Dasari et al., 2017; Leoncini et al., 2017).

6.1.2 Biochemical diagnostics of insulinomas

Regarding biochemical diagnostics, hypoglycaemia had been detected in 97% of the patients prior to the diagnosis of insulinoma, either spontaneously or in a fasting test. The present study showed a high sensitivity of the prolonged fasting test, provoking hyperinsulinaemic hypoglycaemia in over 90% of the insulinoma patients within the first 36 hours of fast. Previous literature supports the use of a prolonged fasting test in the diagnostics of insulinoma (Cryer et al., 2009; Öberg et al., 2017). Recently, Placzkowski et al. reported that the fast can be successfully conducted also in an outpatient setting in an increasing number of patients, assuming that the patient

is accompanied by a family member and returns to hospital when hypoglycaemic symptoms occur or at 22 hours of fast, when the test is continued as an inpatient (Placzkowski et al., 2009).

The diagnostic value of other potential tests that could help avoiding the need for long hospital admissions, such as the oral glucose tolerance test (Liao et al., 2021), determinations of HbA1c and glycated albumin levels (Torimoto et al., 2019), as well as the proinsulin level after an overnight fast (Vezzosi et al., 2017) require further investigations. In the present study, a prolonged oral glucose tolerance test was performed only in a small minority of patients and was rarely able to confirm the diagnosis of hyperinsulinaemic hypoglycaemia. Preoperative HbA1c determinations were available for only one-third of the patients and proinsulin levels after an overnight fast were not routinely measured during the fasting tests. Continuous glucose monitoring was not applied in any of the patients of our cohort. It is, however, widely used in patients with diabetes and might be useful in detecting hypoglycaemic episodes in patients with an insulinoma suffering from hypoglycaemia unawareness, and in evaluating therapeutic responses (Suminaga et al., 2020; Munir et al., 2008).

6.1.3 Preoperative localization of insulinomas

Considering preoperative tumour localization, the main finding of this study is that both the availability and the sensitivity of imaging methods for localizing insulinomas in Finland have improved remarkably during the study period. Up to 98% of the tumours could be localized preoperatively in the 2000s. The sensitivity of CT and MRI, which are considered the first-line imaging methods for localizing insulinomas (Falconi et al., 2016), improved remarkably during the study period, reaching a sensitivity of 51% and 55%, respectively, in the 2000s. EUS, which is considered a second-line imaging method (Falconi et al., 2016), proved to be the most sensitive imaging method among insulinomas diagnosed in the 2000s, with a sensitivity of 82%. The high sensitivity of EUS is in line with previous studies (Mehrabi et al., 2014; Sotoudehmanesh et al., 2007). In accordance with earlier reports, the sensitivity of abdominal US and octreotide scintigraphy remained low, less than 50% (Mehrabi et al., 2014; Andreassen et al., 2019).

The preoperative localization techniques of insulinomas have developed rapidly over the past few decades. Recently, especially the imaging with GLP-1-receptor

PET/CT has proved to be a promising, highly sensitive method for localizing insulinomas, with a sensitivity exceeding 90% (Christ et al., 2020; Falconi et al., 2016; Zhao, K. et al., 2020). In this study, we were not able to study the sensitivity of GLP-1-receptor PET/CT imaging, as this method was not available in Finland during the study period.

6.1.4 Diagnostic delay

During the study period from 1980s to 2000s, the diagnostic delay from the initial symptoms to the diagnosis of insulinoma remained unchanged, with a median delay of 13 months. This includes the delay of the insulinoma patients to seek medical assistance, and the delay in the health care system to initiate biochemical and radiological investigations confirming the diagnosis of insulinoma. As symptoms of insulinoma are often nonspecific, diverse and may be controlled by frequent meals in the beginning, the patients typically do not immediately seek medical help for their symptoms. Due to the rarity of insulinoma, the possibility of this diagnosis often remains unnoticed in the healthcare system, which delays the beginning of the diagnostic investigations.

The significance of the delay caused by the healthcare system is underlined by the fact that 40% of the insulinoma patients in our cohort were first examined for their symptoms in specialities other than endocrinology. Long diagnostic delays of up to several years or even decades, as well as cases with misdiagnosis and mistreatment of insulinoma patients have also been reported in the literature (Ding et al., 2010; Ghannam et al., 2020; Hirshberg et al., 2000; Mehrabi et al., 2014; Service F. J. et al., 1991). The early suspicion of hypoglycaemia and recognition of the Whipple triad are critical steps in the diagnostic path of insulinomas, enabling the shortening of the diagnostic delay and avoiding unnecessary investigations in other specialities. The determination of blood glucose during the symptoms belongs to the first line investigations in patients with unsolved symptomatic attacks (Kallela, 2018).

6.1.5 Treatment and outcome

A vast majority of insulinoma patients (90%) underwent curative-intent surgery, and 89% of them were considered cured and showed no signs of disease progression or

recurrence during the follow-up. The recurrence rate of 8% was comparable to the 7.2% reported previously (Mehrabi et al., 2014). The use of preoperative treatment with diazoxide or a somatostatin analogue was common, but the medication could be discontinued after curative surgery in the patients with a non-metastatic insulinoma. Metastatic insulinomas were treated on a case-by-case judgement, with a wide spectrum of medications, together with invasive surgical, ablative and embolization therapies of the primary tumour and the metastases.

Postoperative complications occurred in 51% and pancreatic fistulas in 19% of the surgically treated patients, which is in line with previous literature (Mehrabi et al., 2014; Zhao, K. et al., 2012). Complications in pancreatic surgery are common (Partelli et al., 2017), and insulinoma patients commonly have risk factors for pancreatic fistula, such as soft pancreatic tissue and enucleation of the tumour (Mehrabi et al., 2014; Partelli et al., 2017). In our study, the postoperative mortality rate of 2.7% was similar to the previously reported 3.7% for open and 0% for laparoscopic approach (Mehrabi et al., 2014). To minimize perioperative mortality and risk for other complications, the surgical treatment of insulinomas, like all pancreatic tumours, should be performed in experienced centres (Ahola et al., 2017; Ahola et al., 2019; Ahola et al., 2020; Antila et al., 2019; de Wilde et al., 2012; Partelli et al., 2017).

After the study period, the use of laparoscopic or robot-assisted approach has become more common in the surgical treatment of insulinomas. This change is due to the comparable long-term results and faster recovery time compared to open approach surgery (Partelli et al., 2017; Su et al., 2014). As only two patients of our cohort underwent laparoscopic surgery, we were not able to evaluate the short- and long-term outcome of insulinoma patients treated with laparoscopic surgery.

6.1.6 Long-term morbidity in patients diagnosed with an insulinoma

The most important finding regarding cardiovascular morbidity is the steadily increasing incidence of atrial fibrillation in the long-term follow-up of insulinoma patients compared to controls. The incidence of atrial fibrillation in insulinoma patients has not been studied before and the underlying causes remain unclear. Possible explanations include the effect of long-lasting hyperinsulinemia or repeated hypoglycaemias, which are both associated with increased risk of cardiac arrhythmias and other cardiovascular diseases in patients with diabetes (Ko et al., 2018). Except

for atrial fibrillation, the incidence of other cardiovascular diseases did not significantly differ between the patients and the controls. For example, the incidence of hypertension was similar in patients and controls, which is in line with previous studies on insulinoma patients (Leonetti et al., 1993; O'Brien et al., 1993).

The analysis of endocrine morbidity demonstrated that the incidence of thyroid disorders, was significantly increased in insulinoma patients vs. controls during the first year after insulinoma diagnosis, but not later on. This may, at least partly, be explained by a detection bias caused by the careful examination of these patients by endocrinologists, but an actual difference in thyroid morbidity between the patients and the controls cannot be ruled out. Diabetes was diagnosed in 15% of the insulinoma patients, either pre- or postoperatively, and the incidence of diabetes did not significantly differ from that of the controls. In contrast, a recent study on 28 insulinoma patients, reported diabetes significantly more often, in 28% of the surgically treated patients (Neves et al., 2021).

Considering gastrointestinal morbidity, the incidence of acute pancreatitis and late intestinal obstruction was increased in the insulinoma patients compared to the controls. The increased risk for acute pancreatitis is a known complication associated with insulinoma surgery, and pancreatic surgery in general (Crippa et al., 2012; Mehrabi et al., 2014). The increased incidence of intestinal obstruction has also been reported previously after pancreatic and other abdominal surgery (Brown, J. A. et al., 2020; Norrbom et al., 2019; ten Broek et al., 2013).

Regarding morbidity due to mental and behavioural disorders, no difference was found in the incidence of all psychiatric disorders, nor in the incidence of dementia, between the patients and the controls. This was against our hypothesis, as repeated episodes of hypoglycaemia, which occur commonly prior to the treatment of insulinoma, are known to be associated with cognitive impairment and dementia in patients with type 2 diabetes (Sheen & Sheu, 2016). As the incidence of dementia increases with age, detecting a possible difference between insulinoma patients and controls might, however, require a longer follow-up time.

This is to our knowledge the first study suggesting an increased incidence of breast and kidney cancer in patients previously treated for an insulinoma. Previous studies have not thoroughly studied the long-term cancer morbidity in insulinoma patients. A previous study on PanNENs reported multiple malignancies in two (4.2%) of the 47 insulinoma patients, corresponding to the risk for multiple primary malignancies in the general population (Fendrich et al., 2008). In our study, another

malignancy was detected significantly more commonly, in 15 (19%) of the insulinoma patients, either before or after the diagnosis of insulinoma, during the median follow-up of 36 years. Fendrich et al. did not report the median duration of follow-up for the subgroup of patients with an insulinoma, but the median follow-up time of all the 115 patients with sporadic pancreatic endocrine tumours was 105 months.

The patients with a MEN1 syndrome are known to have an increased risk for breast cancer (Marx, 2018; van Leeuwaarde et al., 2017), and after the exclusion of MEN1 patients and their controls from the analyses, no significant difference was found in the incidence of breast cancer between the patients and the controls. All the kidney cancers, however, occurred in patients with a sporadic insulinoma. Possible explanations for the increased risk of cancer in patients with an insulinoma include the effects of hyperinsulinemia as well as eventual, unidentified genetic mutations, besides the known mutations in the MEN1 gene, which could increase the risk of both insulinoma and additional malignancies (Larouche et al., 2019; Matsubayashi et al., 2017; Varshney et al., 2017). The association of hyperinsulinemia and an increased risk of many cancers, such as breast cancer, have been reported in patients with diabetes or metabolic syndrome (Gallagher & LeRoith, 2020; Kang et al., 2018; Solarek et al., 2015), but not in patients with insulinoma. The risk of cancer in insulinoma patients may also increase due to the radiation exposure caused by, e.g., conventional CT or functional PET/CT imaging, used for preoperative tumour localization (Brenner & Hall, 2007; Christ et al., 2020). In addition, renal cell cancers are often detected incidentally in connection with radiological imaging for other reasons (Barrett et al., 2009; Znaor et al., 2014). Therefore, the effect of a detection bias caused by frequent CT scanning due to insulinoma cannot be excluded, though it is unlikely in our cohort, as the kidney cancers of the patients were diagnosed as late as 2.7–20 years after the diagnosis of insulinoma, when two of the three patients were no longer followed up due to their previous insulinoma. As the results regarding breast and kidney cancers in insulinoma patients were based on a small number of patients, larger studies are needed to verify the increased cancer morbidity of insulinoma patients and to clarify the underlying causes.

6.1.7 Long-term survival of patients diagnosed with an insulinoma

In this study, the OS of patients with a non-metastatic insulinoma did not differ from that of the general population, but in patients with a metastatic insulinoma, the median OS was only 3.4 years. As expected, older age and the presence of distant metastases were associated with a significantly decreased survival in multivariate analysis, in line with previous studies (Keutgen et al., 2016; Nikfarjam et al., 2008; Service F. J. et al., 1991). In univariate analyses, also tumour size over 2 cm, the need for preoperative medication and higher preoperative serum insulin concentration were associated with significantly impaired survival, but these could not be included in the multivariate analyses, because of missing data in several patients.

Although the median OS of patients with a metastatic insulinoma in our cohort was only 3.4 years, it was better than the median OS of less than 2 years reported previously for patients with a metastatic insulinoma (Jensen et al 2012). Our result is in accordance with a recent study by Veltroni et al., reporting a median OS of 40 months (3.3 years) among the 31 patients with a metastatic insulinoma (Veltroni et al., 2020). In addition, one third of the patients with a metastatic insulinoma in our cohort showed a remarkably long survival time of 6–30 years. Previous studies on metastatic insulinomas have reported prolonged survival in patients treated with debulking surgery of the primary tumour and/or metastases, and with the newer methods, such as novel targeted biological therapies (everolimus, sunitinib, pasireotide) and PRRT, which were not available for the treatment of most of the patients with a metastatic insulinoma in our cohort, diagnosed in 1980–2010 (Bernard et al., 2013; Brown E. et al., 2018; Tiensuu Janson et al., 2014; Partelli et al., 2017; Sada et al., 2020; Veltroni et al., 2020).

6.1.8 Long-term HRQoL in patients diagnosed with an insulinoma

Regarding the HRQoL, the main result of this study was that in the long-term follow-up, the HRQoL in patients previously treated for an insulinoma was similar or even better than that of the age- and gender-adjusted general population. The HRQoL was measured with the validated 15D instrument (Appendix 1) after a median of 14 years after the diagnosis of insulinoma, and the patients had significantly better scores regarding the overall HRQoL, as well as the dimensions of usual activities, moving, and eating, compared to the control population. Among the HRQoL study

participants, older age at the survey and the number of chronic diseases and medications were the most important factors associated with impaired HRQoL. These findings are important, since the long-term HRQoL in insulinoma patients has, to our knowledge, not been studied before.

In line with our results of a good long-term HRQoL in insulinoma patients, previous studies have reported similar or better QoL outcomes in patients with a curatively treated neuroendocrine or pancreatic neoplasm, compared to the general population (Beaumont et al., 2012; Cloyd et al., 2017). Patients with a current, uncured GEP-NET, however, often suffer from a decreased HRQoL, due to various physical and psychological symptoms (Chau et al., 2013; Jimenez-Fonseca et al., 2015; Karppinen et al., 2018; Martini et al., 2016; Sorbye et al., 2020; Topping et al., 2017). As only two of the HRQoL survey participants in the present study had a current, metastatic insulinoma, we could not comprehensively assess the HRQoL in this subgroup, nor could we assess the HRQoL in patients with a current, non-metastatic insulinoma.

6.2 Strengths and limitations of the study

6.2.1 Patient records of the Finnish University Hospitals

In this study, a nationwide cohort of all patients diagnosed with an insulinoma in Finland over a 3-decade period was collected for the first time. The patients were identified from the patient records of all the five Finnish University Hospitals. The diagnosis-based search in the patient records was supplemented by a search in the FCR. All potential cases were reviewed separately in the patient records to identify the patients with an insulinoma. This nationwide register enabled us to comprehensively assess the incidence of insulinomas, as well as the evolving trends in the diagnostics and treatment of insulinomas in Finland. Previously, a cohort of 10 Finnish insulinoma patients has been described in 1974 (Pelkonen et al., 1974), and a cohort of 26 patients in 1993 (Ellä et al., 1993).

Despite this comprehensive search strategy, it is possible that some patients may have remained unidentified: For example, according to Finnish legislation, the patient record data of patients deceased over 20 years ago may have been destroyed

at the University Hospitals, and thus some patients diagnosed with an insulinoma in the 1980s may not have been identified. It is also possible that some rare patients may have been diagnosed and treated completely in a central hospital and may thus have been undetected by the searches in the University Hospitals' patient records. This comprehensive search strategy, however, enabled us to identify a vast majority of the patients diagnosed with an insulinoma in Finland during the study period.

6.2.2 Enrolment of the patients in the HRQoL study

All the patients diagnosed with an insulinoma in Finland during 1980–2010, and alive in September 2017, were invited to participate in the HRQoL study. The response rate was high, 75%, and the respondents and non-respondents of the HRQoL survey were similar regarding demographic and insulinoma-specific features (age, time since diagnosis, gender, type and period of surgery, and occurrence of surgical complications), contributing to the highly representative data.

As a limitation to this study, a metastatic disease was under-represented among the participants of the HRQoL survey, reflecting the poor overall survival of patients with a metastatic insulinoma. Both patients with a metastatic disease that were alive, however, participated in the survey and returned the questionnaires.

6.2.3 Controls

The long-term morbidity and mortality of insulinoma patients was compared to that of a four-fold number of reference subjects, obtained from the Finnish Population Register Centre. The controls were individually matched for age, gender and the place of residence of each patient, and they had to be alive at the diagnosis of insulinoma of the corresponding patient. The controls for the HRQoL survey came from an age- and gender-matched sample of the general population, from the National Health 2011 survey (n=4692) (Koskinen et al., 2012). These matched reference subjects constituted representative and reliable control populations for the analysis of long-term morbidity, mortality and HRQoL in patients previously diagnosed with an insulinoma. Due to the limited background information of the controls, however, we could not exclude the effect of all potential confounding factors, such as a difference in weight between the patients and the controls.

6.2.4 Diagnostics and treatment of insulinomas

The comprehensive data including all the patients diagnosed with an insulinoma over a three-decade period, enabled a detailed evaluation of the diagnostics and treatment of insulinomas in Finland. The criteria for classifying insulinomas into benign and malignant have varied during the study period, and as we were not able to reanalyse the original histopathological specimens, and as the current WHO Classification considers all NETs malignant by definition (WHO Classification of Tumours Editorial Board, 2019), the survival analyses in this study were performed in the subgroups of metastatic and non-metastatic insulinomas, based on the presence or absence of distant metastases.

Due to the small number of MEN1-related and metastatic insulinomas, the distinctive features in the diagnostics and treatment of these rare patient groups could not be comprehensively analysed. As modern genetic, histopathological, and molecular diagnostics were not available during the study period, some of the MEN1 patients may have remained undiagnosed, and we were not able to assess the effects of the genetic background or specific molecular features on the prognosis of insulinomas and on the eventual comorbidities. Because of the rapid development of imaging modalities and surgical treatment methods, we were not able to evaluate the sensitivity of the most recent imaging modalities, such as the GLP-1-receptor or ^{68}Ga-DOTA peptide PET/CT imaging, which were adopted in clinical use only after the study period. Neither could we analyse the effect of laparoscopic vs. open surgery on the outcome of patients, as only two patients in our cohort underwent a laparoscopic operation.

6.2.5 Morbidity and mortality

The incidence of cardiovascular, endocrine, gastrointestinal, psychiatric and cancer diseases in insulinoma patients compared to controls, was evaluated based on the comprehensive data on the diagnoses registered at the HILMO and the FCR. Registering diagnoses at hospital discharge is obligatory, contributing to a comprehensive, high-quality register well suitable for research purposes (Sund, 2012). Similarly, all confirmed cancer cases are registered at the FCR, enabling reliable analysis of the cancer incidence between the patients and the controls. The OS and the causes of death of the patients and the controls could be reliably

compared, based on the comprehensive data on the dates and causes of death provided by Statistics Finland.

As a limitation, the National Hospital Discharge Register includes only information on the hospital admissions and outpatient visits in the specialized health care, and no information was obtained on the eventual diseases diagnosed in the primary health care. The specialized health care investigations due to insulinoma may have led to some detection bias, especially regarding endocrine disorders during the first year after the diagnosis of insulinoma. The detection bias was controlled by sensitivity analyses, from which the first year after the diagnosis of insulinoma was excluded.

Due to the retrospective register-based study design we were not able to study the potential mechanisms underlying the increased long-term morbidity of insulinoma patients. The total burden of hyperinsulinemia and episodes of hypoglycaemia in each patient could not be reliably quantified retrospectively. Neither were we able to perform any genetic testing, which could have shed light on the significance of currently identified or unidentified genetic mutations in the long-term morbidity of insulinoma patients. These factors need to be studied in future prospective studies.

6.2.6 Assessment of the HRQoL

The HRQoL of insulinoma patients was assessed with the 15D instrument, which is a generic HRQoL instrument with a good sensitivity, validity and reliability (Alanne et al., 2015; Sintonen, 2001), and with reference values available from a large, representative sample of the general Finnish population (Koskinen et al., 2012). In addition to the 15D questionnaire, the HRQoL participants filled in a questionnaire on their current health and medication, enabling us to study factors associated with the HRQoL in insulinoma patients. The 15D has previously proved to be a sensitive instrument for assessing the HRQoL in patients with other endocrine tumours, such as small intestine NENs (Karppinen et al., 2018), thyroid carcinomas (Pelttari et al., 2009), pituitary adenomas (Karppinen et al., 2016; Ritvonen et al., 2015) and primary hyperparathyroidism (Ryhänen et al., 2015).

The use of validated, disease-specific HRQoL instruments has been recommended in assessing the quality of life in patients with GEP-NENs (Jimenez-Fonseca et al., 2015; Martini et al., 2016). An insulinoma-specific HRQoL

instrument, including questions assessing the effects of the diverse insulinoma-specific symptoms on the quality of life, has thus far not been developed (Topping et al., 2017). Although there is a clear need for a disease-specific instrument for assessing the HRQoL in patients with a current insulinoma (Topping et al., 2017), the benefit of such an instrument might have been limited in our study, as all except for two of the HRQoL survey participants were considered cured of the insulinoma at the time of the survey.

7 SUMMARY AND CONCLUSIONS

Insulinomas are rare insulin-secreting PanNENs, causing repeated episodes of hypoglycaemia with diverse neuroglycopenic and autonomic symptoms. The incidence of all NENs has increased during the past few decades, at least partly due to an improved clinical awareness and developed imaging methods. Insulinomas are usually non-metastatic and considered cured after a surgical removal of the tumour. The long-lasting hyperinsulinemia and repeated episodes of hypoglycaemia prior to the accurate diagnosis and treatment may still have long-term effects on the morbidity, HRQoL and mortality of insulinoma patients. Previous data on the long-term prognosis of insulinoma patients, however, are almost non-existent.

This study demonstrated that the incidence of insulinomas in Finland has increased almost two-fold, from 0.5 in the 1980s to 0.9 cases per million adults per year in the 2000s. Neuroglycopenic symptoms predominated the clinical picture, and no significant changes were detected in the clinical presentation of insulinomas during the study period. The success rates of preoperative imaging improved, and in the 2000s, all tumours could be localized preoperatively. The delay from symptoms to diagnosis, however, remained stable, with a median of slightly over a year. Of the total of 79 patients diagnosed with an insulinoma, only 9 (11%) patients had a metastatic disease. 73 (92%) patients underwent curative-intent surgery, with a 5-year disease-free survival of 94%.

During the median follow-up of 11 years after the diagnosis of insulinoma, it was detected that patients previously diagnosed with and treated for an insulinoma had a significantly higher risk for long-term morbidity due to atrial fibrillation, intestinal obstruction and possibly breast and kidney cancers. Endocrine disorders and pancreatic diseases were diagnosed more commonly in the patients vs. controls during the first year after the diagnosis of insulinoma, but not later on. Despite the increased long-term morbidity, the overall survival of patients with a non-metastatic insulinoma did not significantly differ from that of the general population, whereas patients with a metastatic disease had a significantly decreased overall survival, with a median of 3.4 years.

Regarding the HRQoL, this study demonstrated that a median of 14 years after the diagnosis of insulinoma, the HRQoL of patients with a non-metastatic insulinoma was similar to or even slightly better than that of age- and gender-matched controls. In addition to the slightly better overall HRQoL, insulinoma patients had better scores on the dimensions of moving, eating and usual activities, compared to the controls. Despite the generally good HRQoL in patients with a previous insulinoma, however, a higher number of chronic diseases and medications were associated with a significantly lower HRQoL.

In conclusion, the incidence of insulinomas seems to be increasing, and despite the probable surgical cure of most insulinomas, the patients are at an increased risk of atrial fibrillation, intestinal obstruction and possibly breast and kidney cancers in the long term. This is the first study to report increased cardiovascular and cancer morbidity among patients previously treated for an insulinoma, and further studies are needed to examine the factors resulting in the increased long-term morbidity of insulinoma patients. The results of this study indicate that an early diagnosis and treatment of insulinoma and eventual comorbidities could be essential in ensuring the best possible prognosis and HRQoL in insulinoma patients. In the future, further knowledge is needed regarding the determinants of long-term prognosis in insulinoma patients, to improve the personalized treatment and follow-up strategies of this rare patient group.

8 REFERENCES

Agarwal, S., Saxena, K., & Dhami, A. (2020). Rare tumor - insulinoma mimicking dissociative disorder. *Indian Journal of Psychiatry, 62*(3), 331-332. doi:10.4103/psychiatry.IndianJPsychiatry_129_19

Aggeli, C., Nixon, A. M., Karoumpalis, I., Kaltsas, G., & Zografos, G. N. (2016). Laparoscopic surgery for pancreatic insulinomas: An update. *Hormones (Athens, Greece), 15*(2), 157-69. doi:10.14310/horm.2002.1670

Ahlman, H., Friman, S., Cahlin, C., Nilsson, O., Jansson, S., Wangberg, B., & Olausson, M. (2004). Liver transplantation for treatment of metastatic neuroendocrine tumors. *Annals of the New York Academy of Sciences, 1014*, 265-269. doi:10.1196/annals.1294.029

Ahola, R., Sand, J., & Laukkarinen, J. (2019). Pancreatic resections are not only safest but also most cost-effective when performed in a high-volume centre: A Finnish register study. *Pancreatology: Official Journal of the International Association of Pancreatology, 19*(5), 769-774. doi:10.1016/j.pan.2019.06.007

Ahola, R., Sand, J., & Laukkarinen, J. (2020). Centralization of pancreatic surgery improves results: Review. *Scandinavian Journal of Surgery, 109*(1), 4-10. doi:10.1177/1457496919900411

Ahola, R., Siiki, A., Vasama, K., Vornanen, M., Sand, J., & Laukkarinen, J. (2017). Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. *British Journal of Surgery, 104*(11), 1532-1538. doi:10.1002/bjs.10560

Alanne, S., Roine, R. P., Räsänen, P., Vainiola, T., & Sintonen, H. (2015). Estimating the minimum important change in the 15D scores. *Quality of Life Research, 24*(3), 599-606. doi:10.1007/s11136-014-0787-4

Alfieri, S., Butturini, G., Boggi, U., Pietrabissa, A., Morelli, L., Vistoli, F., . . . Italian Robotic pNET Group. (2019). Short-term and long-term outcomes after robot-assisted versus laparoscopic distal pancreatectomy for pancreatic neuroendocrine tumors (pNETs): A multicenter comparative study. *Langenbecks Archives of Surgery, 404*(4), 459-468. doi:10.1007/s00423-019-01786-x

Andreassen, M., Ilett, E., Wiese, D., Slater, E. P., Klose, M., Hansen, C. P., . . . Knigge, U. (2019). Surgical management, preoperative tumor localization, and histopathology of 80 patients operated on for insulinoma. *Journal of Clinical Endocrinology & Metabolism, 104*(12), 6129-6138. doi:10.1210/jc.2019-01204

Anlauf, M., Bauersfeld, J., Raffel, A., Koch, C. A., Henopp, T., Alkatout, I., . . . Klöppel, G. (2009). Insulinomatosis: A multicentric insulinoma disease that frequently causes early recurrent hyperinsulinemic hypoglycemia. *American Journal of Surgical Pathology, 33*(3), 339-346. doi:10.1097/PAS.0b013e3181874eca

Anlauf, M., Garbrecht, N., Bauersfeld, J., Schmitt, A., Henopp, T., Komminoth, P., . . . Klöppel, G. (2007). Hereditary neuroendocrine tumors of the gastroenteropancreatic

system. *Virchows Archiv: An International Journal of Pathology, 451*, 29-38. doi:10.1007/s00428-007-0450-3

Antila, A., Ahola, R., Sand, J., & Laukkarinen, J. (2019). Management of postoperative complications may favour the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012–2014. *Pancreatology: Official Journal of the International Association of Pancreatology, 19*(1), 26-30. doi:10.1016/j.pan.2018.11.012

Antonakis, P. T., Ashrafian, H., & Martinez-Isla, A. (2015). Pancreatic insulinomas: Laparoscopic management. *World Journal of Gastrointestinal Endoscopy, 7*(16), 1197-1207. doi:10.4253/wjge.v7.i16.1197

Antwi, K., Fani, M., Heye, T., Nicolas, G., Rottenburger, C., Kaul, F., . . . Wild, D. (2018). Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: Evaluation of diagnostic accuracy in a prospective crossover imaging study. *European Journal of Nuclear Medicine and Molecular Imaging, 45*(13), 2318-2327. doi:10.1007/s00259-018-4101-5

Antwi, K., Nicolas, G., Fani, M., Heye, T., Pattou, F., Grossman, A., . . . Christ, E. (2019). 68Ga-exendin-4 PET/CT detects insulinomas in patients with endogenous hyperinsulinemic hypoglycemia in MEN-1. *The Journal of Clinical Endocrinology and Metabolism, 104*(12), 5843-5852. doi:10.1210/jc.2018-02754

Ayav, A., Bresler, L., Brunaud, L., Boissel, P., SFCL (Societe Francaise de Chirurgie Laparoscopique), & AFCE (Association Francophone de Chirurgie Endocrinienne). (2005). Laparoscopic approach for solitary insulinoma: A multicentre study. *Langenbecks Archives of Surgery, 390*(2), 134-140. doi:10.1007/s00423-004-0526-3

Barrett, T. W., Schierling, M., Zhou, C., Colfax, J. D., Russ, S., Conatser, P., . . . Wrenn, K. (2009). Prevalence of incidental findings in trauma patients detected by computed tomography imaging. *The American Journal of Emergency Medicine 27*(4), 428-435. doi:10.1016/j.ajem.2008.03.025

Bartsch D. K., Albers M., Knoop R., Kann P. H., Fendrich V., & Waldmann J. (2013). Enucleation and limited pancreatic resection provide long-term cure for insulinoma in multiple endocrine neoplasia type 1. *Neuroendocrinology, 98*(4), 290-298. doi:10.1159/000357779

Basturk, O., Tang, L., Hruban, R. H., Adsay, V., Yang, Z., Krasinskas, A. M., . . . Klimstra, D. S. (2014). Poorly differentiated neuroendocrine carcinomas of the pancreas: A clinicopathologic analysis of 44 cases. *American Journal of Surgical Pathology, 38*(4), 437-447. doi:10.1097/PAS.0000000000000169

Beaumont, J. L., Cella, D., Phan, A. T., Choi, S., Liu, Z., & Yao, J. C. (2012). Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas, 41*(3), 461-466. doi:10.1097/MPA.0b013e3182328045

Begu-Le Corroller, A., Valero, R., Moutardier, V., Henry, J.-F., Le Treut, Y.-P., Gueydan, M., . . . Vialettes, B. (2008). Aggressive multimodal therapy of sporadic malignant insulinoma can improve survival: A retrospective 35-year study of 12 patients. *Diabetes & Metabolism, 34*(4 Pt 1), 343-348. doi:10.1016/j.diabet.2008.01.013

Belfiori, G., Wiese, D., Partelli, S., Wachter, S., Maurer, E., Crippa, S., . . . Bartsch, D. K. (2018). Minimally invasive versus open treatment for benign sporadic insulinoma

comparison of short-term and long-term outcomes. *World Journal of Surgery, 42*(10), 3223-3230. doi:10.1007/s00268-018-4628-4

Bernard, V., Lombard-Bohas, C., Taquet, M. C., Caroli-Bosc, F. X., Ruszniewski, P., Niccoli, P., . . . French Group of Endocrine Tumors. (2013). Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *European Journal of Endocrinology, 168*(5), 665-674. doi:10.1530/EJE-12-1101

Bilimoria, K. Y., Talamonti, M. S., Tomlinson, J. S., Stewart, A. K., Winchester, D. P., Ko, C. Y., & Bentrem, D. J. (2008). Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors analysis of 3851 patients. *Annals of Surgery, 247*(3), 490-500. doi:10.1097/SLA.0b013e31815b9cae

Borodulin, K., Saarikoski, L., Lund, L., Juolevi, A., Grönholm, M., Helldán, A., . . . Vartiainen, E. (2013a). *The National FINRISK 2012 Study – part 1: Study protocol and methods. Raport 22/2013, part I.* The National Institute for Health and Welfare (THL). http://urn.fi/URN:ISBN:978-952-302-053-5. Accessed Jul 2020.

Borodulin, K., Levälahti, E., Saarikoski, L., Lund, L., Juolevi, A., Grönholm, M., . . . Vartiainen, E. (2013b). *The National FINRISK 2012 Study – part 2: Tables. Raport 22/2013, part II.* The National Institute for Health and Welfare (THL). http://urn.fi/URN:ISBN:978-952-302-054-2. Accessed Jul 2020.

Boukhman, M. P., Karam, J. H., Shaver, J., Siperstein, A. E., Duh, Q.-Y., & Clark, O. H. (1998). Insulinoma--experience from 1950 to 1995. *Western Journal of Medicine, 169*(2), 98-104.

Boyar Cetinkaya, R., Aagnes, B., Thiis-Evensen, E., Tretli, S., Bergestuen, D. S., & Hansen, S. (2017). Trends in incidence of neuroendocrine neoplasms in Norway: A report of 16,075 cases from 1993 through 2010. *Neuroendocrinology*, 104(1), 1-10. doi:10.1159/000442207

Brenner, D. J., & Hall, E. J. (2007). Computed tomography--an increasing source of radiation exposure. *New England Journal of Medicine*, 357(22), 2277-2284. doi:10.1056/NEJMra072149

Brierley, J. D., Gospodarowicz, M.K., Wittekind, C., O'Sullivan, B. (Eds.) (2017). Well-differentiated neuroendocrine tumours – pancreas (G1 and G2). In *TNM Classification of Malignant Tumours*, edn 8 (pp. 102–103). Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc., 2017.

Brown, E., Watkin, D., Evans, J., Yip, V., & Cuthbertson, D. J. (2018). Multidisciplinary management of refractory insulinomas. *Clinical Endocrinology, 88*(5), 615-624. doi:10.1111/cen.13528

Brown, J. A., Zenati, M. S., Simmons, R. L., Al Abbas, A. I., Chopra, A., Smith, K., . . . Zureikat, A. H. (2020). Long-term surgical complications after pancreatoduodenectomy: Incidence, outcomes, and risk factors. *Journal of Gastrointestinal Surgery*, 24(7), 1581-1589. doi:10.1007/s11605-020-04641-3

Brown, N. G., Patel, A. A., & Gonda, T. A. (2020). Immediate and durable therapeutic response after EUS-guided radiofrequency ablation of a pancreatic insulinoma. *VideoGIE: An Official Video Journal of the American Society for Gastrointestinal Endoscopy, 5*(12), 676-678. doi:10.1016/j.vgie.2020.07.021

Bural, G. G., Muthukrishnan, A., Oborski, M. J., & Mountz, J. M. (2012). Improved benefit of SPECT/CT compared to SPECT alone for the accurate localization of endocrine

and neuroendocrine tumors. *Molecular Imaging and Radionuclide Therapy*, 21(3), 91-96. doi:10.4274/Mirt.80299

Callender, G. G., Rich, T. A., & Perrier, N. D. (2008). Multiple endocrine neoplasia syndromes. *The Surgical Clinics of North America, 88*(4), 863-895. doi:10.1016/j.suc.2008.05.001

Câmara-de-Souza, A. B., Toyoshima, M. T. K., Giannella, M. L., Freire, D. S., Camacho, C. P., Lourenco, D. M. J., . . . Pereira, M. A. A. (2018). Insulinoma: A retrospective study analyzing the differences between benign and malignant tumors. *Pancreatology, 18*(3), 298-303. doi:10.1016/j.pan.2018.01.009

Chau, I., Casciano, R., Willet, J., Wang, X., & Yao, J. C. (2013). Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: A systematic review. *European Journal of Cancer Care, 22*(6), 714-725. doi:10.1111/ecc.12085

Chen-Xu, J., Bessa-Melo, R., Graca, L., & Costa-Maia, J. (2019). Incisional hernia in hepatobiliary and pancreatic surgery: Incidence and risk factors. *Hernia, 23*(1), 67-79. doi:10.1007/s10029-018-1847-4

Christ, E., Wild, D., Ederer, S., Behe, M., Nicolas, G., Caplin, M. E., . . . Forrer F. (2013). Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: A prospective multicentre imaging study. *The Lancet Diabetes & Endocrinology, 1*(2), 115-122. doi:10.1016/S2213-8587(13)70049-4

Christ, E., Antwi, K., Fani, M., & Wild, D. (2020). Innovative imaging of insulinoma: The end of sampling? A review. *Endocrine-Related Cancer, 27*(4), R79-R92. doi:10.1530/ERC-19-0476

Clavien, P.-A., Barkun, J., de Oliveira, M. L., Vauthey, J. N., Dindo, D., Schulick, R. D., . . . Makuuchi, M. (2009). The Clavien-Dindo classification of surgical complications: Five-year experience. *Annals of Surgery, 250*(2), 187-196. doi:10.1097/SLA.0b013e3181b13ca2

Cloyd, J. M., Tran Cao, H. S., Petzel, M. Q. B., Denbo, J. W., Parker, N. H., Nogueras-Gonzalez, G. M., . . . Katz, M. H. G. (2017). Impact of pancreatectomy on long-term patient-reported symptoms and quality of life in recurrence-free survivors of pancreatic and periampullary neoplasms. *Journal of Surgical Oncology, 115*(2), 144-150. doi:10.1002/jso.24499

Crippa, S., Zerbi, A., Boninsegna, L., Capitanio, V., Partelli, S., Balzano, G., . . . Falconi, M. (2012). Surgical management of insulinomas: Short- and long-term outcomes after enucleations and pancreatic resections. *Archives of Surgery, 147*(3), 261-266. doi:10.1001/archsurg.2011.1843

Cryer, P. E. (2007). Hypoglycemia, functional brain failure, and brain death. *The Journal of Clinical Investigation; J Clin Invest, 117*(4), 868-870. doi:10.1172/JCI31669

Cryer, P. E., Axelrod, L., Grossman, A. B., Heller, S. R., Montori, V. M., Seaquist, E. R., & Service, F. J. (2009). Evaluation and management of adult hypoglycemic disorders: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism, 94*(3), 709-728. doi:10.1210/jc.2008-1410

Dai, H., Xu, Q., Hong, X., Wang, X., Pang, H., Wu, W., & Zhao, Y. (2017). Surgery in overweight patients with insulinoma: Effects on weight loss. *Scandinavian Journal of Gastroenterology, 52*(9), 1037-1041. doi:10.1080/00365521.2017.1335768

Dai, H., Chen, H., Hong, X., Han, X., Xu, Q., Pang, H., . . . Wu, W. (2019). Early detection of cognitive impairment in patients with insulinoma. *Endocrine, 65*(3), 524-530. doi:10.1007/s12020-019-01994-x

Danforth, D. N. J., Gorden, P., & Brennan, M. F. (1984). Metastatic insulin-secreting carcinoma of the pancreas: Clinical course and the role of surgery. *Surgery, 96*(6), 1027-1037.

Dasari, A., Shen, C., Halperin, D., Zhao, B., Zhou, S., Xu, Y., . . . Yao, J. C. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncology, 3*(10), 1335-1342. doi:10.1001/jamaoncol.2017.0589

Davì, M. V., Pia, A., Guarnotta, V., Pizza, G., Colao, A., & Faggiano, A. (2017). The treatment of hyperinsulinemic hypoglycaemia in adults: An update. *Journal of Endocrinological Investigation, 40*(1), 9-20. doi:10.1007/s40618-016-0536-3

de Herder, W. W., Niederle, B., Scoazec, J. Y., Pauwels, S., Klöppel, G., Falconi, M., . . . Ferone, D & all other Frascati Consensus Conference participants (2006). ENETS Guidelines: Well-differentiated pancreatic tumor/carcinoma: Insulinoma. *Neuroendocrinology, 84*(3), 183-188. doi:10.1159/000098010

de Herder, W. W., van Schaik, E., Kwekkeboom, D., & Feelders, R. A. (2011). New therapeutic options for metastatic malignant insulinomas. *Clinical Endocrinology, 75*(3), 277-284. doi:10.1111/j.1365-2265.2011.04145.x

de Wilde, R. F., Besselink, M. G. H., van der Tweel, I., de Hingh, I. H. J. T., van Eijck, C. H. J., Dejong, C. H. C., . . . Molenaar, I. Q., for the Dutch Pancreatic Cancer Group. (2012). Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *British Journal of Surgery, 99*(3), 404-410. doi:10.1002/bjs.8664

Dindo, D., Demartines, N., & Clavien P.-A. (2004). Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery, 240*(2), 205-213. doi:10.1097/01.sla.0000133083.54934.ae

Ding, Y., Wang, S., Liu, J., Yang, Y., Liu, Z., Li, J., . . . Ding, M. (2010). Neuropsychiatric profiles of patients with insulinomas. *European Neurology, 63*(1), 48-51. doi:10.1159/000268166

Dizon, A. M., Kowalyk, S., & Hoogwerf, B. J. (1999). Neuroglycopenic and other symptoms in patients with insulinomas. *The American Journal of Medicine, 106*(3), 307-310. doi:10.1016/S0002-9343(99)00021-2

Donegan, D., Jakubikova, I., & Vella, A. (2017). Anthropometric features are not predictive of 72-hour fast duration in insulinomas. *Endocrine Practice, 23*(8), 923-928. doi:10.4158/EP171872.OR

Drymousis, P., Raptis, D. A., Spalding, D., Fernandez-Cruz, L., Menon, D., Breitenstein, S., . . . Frilling, A. (2014). Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: A systematic review and meta-analysis. *HPB - the Official Journal of the International Hepato-Pancreato-Biliary Association, 16*(5), 397-406. doi:10.1111/hpb.12162

Ellä, K., Sane, T., Huikuri, K., & Pelkonen, R. (1993). Insulinooma - edelleen vaikeasti tunnistettava sairaus. *Suomen Lääkärilehti - Finlands Läkartidning, 48*(16), 1541-1544.

Erhamamci, S., Sager, S., Asa, S., Uslu, L., Akgun, E., & Sonmezoglu, K. (2020). Malignant insulinoma: 18F-DOPA and 68Ga-DOTATATE PET/CT and treatment with

177Lu-DOTATATE. *Revista Espanola De Medicina Nuclear e Imagen Molecular (English ed.), 39*(6), 383-386. doi:10.1016/j.remn.2019.12.002

Falconi, M., Eriksson, B., Kaltsas, G., Bartsch, D. K., Capdevila, J., Caplin, M., . . . Jensen, R. T. & all other Vienna Consensus Conference participants (2016). ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology, 103*(2), 153-171. doi:10.1159/000443171

Fendrich, V., Waldmann, J., Bartsch, D. K., Schlosser, K., Rothmund, M., & Gerdes, B. (2008). Multiple primary malignancies in patients with sporadic pancreatic endocrine tumors. *Journal of Surgical Oncology, 97*(7), 592-595. doi:10.1002/jso.21044

FINRISKI 2012 National Health Study. Questionnaire 1. Retrieved from https://thl.fi/en/web/thlfi-en/research-and-expertwork/population-studies/the-national-finrisk-study/questionnaires. Updated 8 Oct 2019. Accessed Jul 2020.

Franko, J., Feng, W., Yip, L., Genovese, E., & Moser, A. J. (2010). Non-functional neuroendocrine carcinoma of the pancreas: Incidence, tumor biology, and outcomes in 2,158 patients. *Journal of Gastrointestinal Surgery, 14*(3), 541-548. doi:10.1007/s11605-009-1115-0

Fu, J., Zhang, J., Wang, Y., Yan, J., Yuan, K., & Wang, M. (2020). Comparison of angio-CT versus multidetector CT in the detection and location for insulinomas. *Clinical Radiology, 75*(10), 796.e11-796.e16. doi:10.1016/j.crad.2020.05.012

Furnica, R. M., Deprez, P., Maiter, D., Vandeleene, B., & Borbath, I. (2020). Endoscopic ultrasound-guided radiofrequency ablation: An effective and safe alternative for the treatment of benign insulinoma. *Annales d Endocrinologie, 81*(6), 567-571. doi:10.1016/j.ando.2020.11.009

Furrer, J., Hättenschwiler, A., Komminoth, P., Pfammatter, T., & Wiesli, P. (2001). Carcinoid syndrome, acromegaly, and hypoglycemia due to an insulin-secreting neuroendocrine tumor of the liver. *The Journal of Clinical Endocrinology and Metabolism, 86*(5), 2227-2230. doi:10.1210/jcem.86.5.7461

Gagner, M., Pomp, A., & Herrera, M. F. (1996). Early experience with laparoscopic resections of islet cell tumors. *Surgery, 120*(6), 1051-1054. doi:10.1016/s0039-6060(96)80054-7

Gallagher, E. J., & LeRoith, D. (2011). Minireview: IGF, insulin, and cancer. *Endocrinology, 152*(7), 2546-2551. doi:10.1210/en.2011-0231

Gallagher, E. J., & LeRoith, D. (2020). Hyperinsulinaemia in cancer. *Nature Reviews Cancer 20* 629-644. doi:10.1038/s41568-020-0295-5

Gao, H., Wang, W., Xu, H., Wu, C., Jin, W., Zhang, S., . . . Liu, L. (2019). Distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis. *Pancreatology, 19*(3), 472-477. doi:10.1016/j.pan.2019.02.011

Garcia-Carbonero, R., Rinke, A., Valle, J. W., Fazio, N., Caplin, M., Gorbounova, V., . . . Pavel, M. & all other Antibes Consensus Conference participants (2017). ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: Systemic therapy - chemotherapy. *Neuroendocrinology, 105*(3), 281-294. doi:10.1159/000473892

Garg, R., Shah, R., Tiwari, A., Purandare, N., Lele, V. R., Malhotra, G., . . . Bandgar, T. (2020). Exendin-4-based imaging in endogenous hyperinsulinemic hypoglycaemia

cohort: A tertiary Endocrine centre experience. *Clinical Endocrinology, 93*(6), 678-686. doi:10.1111/cen.14299

Ghannam, M., Beran, A., Ghazaleh, D., Lyerla, R., Al-Assadi, R., Ferderer, T., . . . Berry, B. (2020). Insulinoma as a potential insidious presenter in medical refractory epilepsy. *Neuroendocrinology Letters, 41*(1), 46-52.

Giannis, D., Moris, D., Karachaliou, G. S., Tsilimigras, D., Karaolanis, G., Papalampros, A., & Felekouras, E. (2020). Insulinomas: From diagnosis to treatment. A review of the literature. *Journal of B.U.on, 25*(3), 1302-1314.

Gill, G. V., Rauf, O., & MacFarlane, I. A. (1997). Diazoxide treatment for insulinoma: A national UK survey. *Postgraduate Medical Journal, 73*(864), 640-641. doi:10.1136/pgmj.73.864.640

Gomes-Porras, M., Cárdenas-Salas, J., & Álvarez-Escolá, C. (2020). Somatostatin analogs in clinical practice: A review. *International Journal of Molecular Sciences, 21*(5), 1682. doi:10.3390/ijms21051682

Gouya, H., Vignaux, O., Augui, J., Dousset, B., Palazzo, L., Louvel, A., . . . Legmann, P. (2003). CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *AJR American Journal of Roentgenology, 181*(4), 987-992. doi:10.2214/ajr.181.4.1810987

Guettier, J.-M., Kam, A., Chang, R., Skarulis, M. C., Cochran, C., Alexander, H. R., . . . Gorden, P. (2009). Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: The NIH experience. *Journal of Clinical Endocrinology & Metabolism, 94*(4), 1074-1080. doi:10.1210/jc.2008-1986

Guettier, J.-M., & Gorden, P. (2010). Insulin secretion and insulin-producing tumors. *Expert Review of Endocrinology & Metabolism, 5*(2), 217-227. doi:10.1586/eem.09.83

Hackeng, W. M., Schelhaas, W., Morsink, F. H. M., Heidsma, C. M., van Eeden, S., Valk, G. D., . . . Brosens, L. A. A. (2020). Alternative lengthening of telomeres and differential expression of endocrine transcription factors distinguish metastatic and non-metastatic insulinomas. *Endocrine Pathology, 31*(2), 108-118. doi:10.1007/s12022-020-09611-8.

Halfdanarson, T. R., Rabe, K. G., Rubin, J., & Petersen, G. M. (2008). Pancreatic neuroendocrine tumors (PNETs): Incidence, prognosis and recent trend toward improved survival. *Annals of Oncology, 19*(10), 1727-1733. doi:10.1093/annonc/mdn351

Hallet, J., Law, C. H. L., Cukier, M., Saskin, R., Liu, N., & Singh, S. (2015). Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer, 121*(4), 589-597. doi:10.1002/cncr.29099

Harrington, M. G., McGeorge, A. P., Ballantyne, J. P., & Beastall, G. (1983). A prospective survey for insulinomas in a neurology department. *The Lancet (British Edition), 321*(8333), 1094-1095. doi:10.1016/S0140-6736(83)91923-2

Harris, S. (1924). Hyperinsulinism and dysinsulinism. *Journal of the American Medical Association, 83*(10), 729-733. doi:10.1001/jama.1924.02660100003002

Hawthorne, G., Richardson, J., & Day, N. A. (2001). A comparison of the assessment of quality of life (AQoL) with four other generic utility instruments. *Annals of Medicine, 33*(5), 358-370. doi:10.3109/07853890109002090

Hirshberg, B., Libutti, S. K., Alexander, H. R., Bartlett, D. L., Cochran, C., Livi, A., . . . Gorden, P. (2002). Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure. *Journal of the American College of Surgeons, 194*(6), 761-764. doi:10.1016/s1072-7515(02)01177-8

Hirshberg, B., Cochran, C., Skarulis, M. C., Libutti, S. K., Alexander, H. R., Wood, B. J., . . . Gorden, P. (2005). Malignant insulinoma: Spectrum of unusual clinical features. *Cancer, 104*(2), 264-272. doi:10.1002/cncr.21179

Hirshberg, B., Livi, A., Bartlett, D. L., Libutti, S. K., Alexander, H. R., Doppman, J. L., . . . Gorden, P. (2000). Forty-eight-hour fast: The diagnostic test for insulinoma. *Journal of Clinical Endocrinology & Metabolism, 85*(9), 3222-3226. doi:10.1210/jcem.85.9.6807

Hong, X., Qiao, S., Li, F., Wang, W., Jiang, R., Wu, H., . . . Wu, W. (2020). Whole-genome sequencing reveals distinct genetic bases for insulinomas and non-functional pancreatic neuroendocrine tumours: Leading to a new classification system. *Gut, 69*(5), 877-887. doi:10.1136/gutjnl-2018-317233

Howland, G., Campbell, W. R., Maltby, E. J., & Robinson, W. L. (1929). Dysinsulinism: convulsions and coma due to islet cell tumor of the pancreas, with operation and cure. *JAMA, 93*(9), 674-679. doi:10.1001/jama.1929.02710090014006

Hu M., Zhao G., Luo Y., & Liu R. (2011). Laparoscopic versus open treatment for benign pancreatic insulinomas: An analysis of 89 cases. *Surgical Endoscopy, 25*(12), 3831-3837. doi:10.1007/s00464-011-1800-4

Iacovazzo, D., Flanagan, S. E., Walker, E., Quezado, R., de Sousa Barros, F. A., Caswell, R., . . . Ellard, S. (2018). MAFA missense mutation causes familial insulinomatosis and diabetes mellitus. *Proceedings of the National Academy of Sciences of the United States of America, 115*(5), 1027-1032. doi:10.1073/pnas.1712262115

Imperiale, A.., Sebag, F., Vix, M., Castinetti, F., Kessler, L., Moreau, F., . . . Taïeb, D. (2015). 18F-FDOPA PET/CT imaging of insulinoma revisited. *European Journal of Nuclear Medicine and Molecular Imaging, 42*(3), 409-418. doi:10.1007/s00259-014-2943-z

Ingemansson, S., Lunderquist, A., Lundquist, I., Lovdahl, R., & Tibblin, S. (1975). Portal and pancreatic vein catheterization with radioimmunologic determination of insulin. *Surgery, Gynecology & Obstetrics, 141*(5), 705-711.

Isla A., Arbuckle J. D., Kekis P. B., Lim A., Jackson J. E., Todd J. F., & Lynn J. (2009). Laparoscopic management of insulinomas. *British Journal of Surgery, 96*(2), 185-190. doi:10.1002/bjs.6465

Jabri, A. L., & Bayard, C. (2004). Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: Review of the literature. *European Journal of Internal Medicine*, 15(7), 407-410. doi:10.1016/j.ejim.2004.06.012

Jensen R. T., Cadiot G., Brandi M. L., de Herder W. W., Kaltsas G., Komminoth P, . . . Kianmanesh, R., & all other Barcelona Consensus Conference participants (2012). ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes. *Neuroendocrinology, 95*(2), 98-119. doi:10.1159/000335591

Jensen, R. T., Berna, M. J., Bingham, D. B., & Norton, J. A. (2008). Inherited pancreatic endocrine tumor syndromes: Advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer, 113*, 1807-1843. doi:10.1002/cncr.23648

Jiménez-Fonseca, P., Carmona-Bayonas, A., Martín-Pérez, E., Crespo, G., Serrano, R., Llanos, M., . . . Grande, E., on behalf of the Spanish Neuroendocrine Tumor Group (GETNE) (2015). Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. *Cancer & Metastasis Reviews, 34*(3), 381-400. doi:10.1007/s10555-015-9573-1

Jonkers, Y. M. H., Claessen, S. M. H., Perren, A., Schmid, S., Komminoth, P., Verhofstad, A. A., . . . Speel, E.-J. M. (2005). Chromosomal instability predicts metastatic disease in patients with insulinomas. *Endocrine-Related Cancer, 12*(2), 435-447. doi:10.1677/erc.1.00960

Jonkers, Y. M. H., Ramaekers, F. C. S., & Speel E.-J. M. (2007). Molecular alterations during insulinoma tumorigenesis. *Biochimica Et Biophysica Acta*, 1775(2), 313-332. doi:10.1016/j.bbcan.2007.05.004

Jyotsna, V. P., Malik, E., Birla, S., & Sharma, A. (2015). Novel MEN 1 gene findings in rare sporadic insulinoma--a case control study. *BMC Endocrine Disorders, 15*(1), 44-44. doi:10.1186/s12902-015-0041-2

Kalff, V., Iravani, A., Ackhurst, T., Pattison, D. A., Eu, P., Hofman, M. S., & Hicks, R. J. (2020). Utility of 68Ga-DOTA-exendin-4 PET/CT imaging in distinguishing between insulinoma and nesidioblastosis in patients with confirmed endogenous hyperinsulinaemic hypoglycaemia. *Internal Medicine Journal 2020-12-14*. doi:10.1111/imj.15141

Kallela, M. (2018). Kohtausoireen selvittely. *Lääkärin käsikirja*. Kustannus Oy Duodecim. Updated 6 May, 2020.

Kaltsas, G., Caplin, M., Davies, P., Ferone, D., Garcia-Carbonero, R., Grozinsky-Glasberg, S., . . . de Herder, W. W. & all other Antibes Consensus Conference participants (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Pre- and perioperative therapy in patients with neuroendocrine tumors. *Neuroendocrinology, 105*(3), 245-254. doi:10.1159/000461583

Kang, C., LeRoith, D., & Gallagher, E. J. (2018). Diabetes, obesity, and breast cancer. *Endocrinology, 159*(11), 3801-3812. doi:10.1210/en.2018-00574

Kang, I., Hwang, H. K., Lee, W. J., & Kang, C. M. First experience of pancreaticoduodenectomy using revo-i in a patient with insulinoma. *Annals of Hepato-Biliary-Pancreatic Surgery*, 2020 (24), 104-108. doi:10.14701/ahbps.2020.24.1.104.

Karppinen, A., Ritvonen, E., Roine, R., Sintonen, H., Vehkavaara, S., Kivipelto, L., . . . Schalin-Jäntti, C. (2016). Health-related quality of life in patients treated for nonfunctioning pituitary adenomas during the years 2000-2010. *Clinical Endocrinology, 84*(4), 532-539. doi:10.1111/cen.12967

Karppinen, N., Linden, R., Sintonen, H., Tarkkanen, M., Roine, R., Heiskanen, I., . . . Schalin-Jäntti, C. (2018). Health-related quality of life in patients with small intestine neuroendocrine tumors. *Neuroendocrinology, 107*(4), 366-374. doi:10.1159/000494293

Kauhanen, S., Seppänen, M., Minn, H., Gullichsen, R., Salonen, A., Alanen, K., . . . Nuutila, P. (2007). Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients. *Journal of Clinical Endocrinology & Metabolism, 92*(4), 1237-1244. doi:10.1210/jc.2006-1479

Keutgen, X. M., Nilubol, N., & Kebebew, E. (2016). Malignant-functioning neuroendocrine tumors of the pancreas: A survival analysis. *Surgery, 159*(5), 1382-1389. doi:10.1016/j.surg.2015.11.010

Kierszenbaum, A. L., & Tres, L. L. (2016). *Histology and cell biology: An introduction to pathology*. Philadelphia, PA: Elsevier/Saunders.

Kluz, M., Staron, R., Krupa, L., Partyka, M., Polkowski, M., & Gutkowski, K. (2020). Successful endoscopic ultrasound-guided radiofrequency ablation of a pancreatic insulinoma. *Polish Archives of Internal Medicine, 130*(2), 145-146. doi:10.20452/pamw.15100

Knigge, U., Capdevila, J., Bartsch, D. K., Baudin, E., Falkerby, J., Kianmanesh, R., . . . Vullierme, M.-P., & all other Antibes Consensus Conference participants (2017). ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms: Follow-up and documentation. *Neuroendocrinology, 105*(3), 310-319. doi:10.1159/000458155

Ko, S., Park, Y., Yun, J., Cha, S., Choi, E., Han, K., . . . Ahn, Y. (2018). Severe hypoglycemia is a risk factor for atrial fibrillation in type 2 diabetes mellitus: Nationwide population-based cohort study. *Journal of Diabetes and its Complications*, 32(2), 157-163. doi:10.1016/j.jdiacomp.2017.09.009

Koskinen, S., Lundqvist, A., & Ristiluoma, N., eds. (2012). *Health, functional capacity and welfare in Finland in 2011*. National Institute for Health and Welfare (THL). Report 68/2012. Helsinki 2012. http://urn.fi/URN:ISBN:978-952-245-769-1. Accessed Jul 2020.

Krampitz, G. W., & Norton, J. A. (2013). Pancreatic neuroendocrine tumors. *Current Problems in Surgery*, 50(11), 509-545. doi:10.1067/j.cpsurg.2013.08.001

Kriger, A. G., Berelavichus, S. V., Kaldarov, A. R., Panteleev, V. I., Gorin, D. S., Dugarova, R. S., & Yukina, M. Y. (2019). Proinsulin-secreting neuroendocrine tumors of the pancreas: A single-centre experience. *Gastrointestinal Tumors, 6*(3-4), 64-70. doi:10.1159/000501455

Kuo, E. J., & Salem, R. R. (2013). Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. *Annals of Surgical Oncology, 20*(9), 2815-2821. doi:10.1245/s10434-013-3005-7

Larouche, V., Akirov, A., Thain, E., Kim, R. H., & Ezzat, S. (2019). Co-occurrence of breast cancer and neuroendocrine tumours: New genetic insights beyond multiple endocrine neoplasia syndromes. *Endocrinology, and Diabetes & Metabolism, 2*(4), e00092. doi:10.1002/edm2.92

Lega, I. C., & Lipscombe, L. L. (2020). Review: Diabetes, obesity, and cancer-pathophysiology and clinical implications. *Endocrine Reviews, 41*(1), bnz014. doi:10.1210/endrev/bnz014

Leoncini, E., Boffetta, P., Shafir, M., Aleksovska, K., Boccia, S., & Rindi, G. (2017). Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine, 58*(2), 368-379. doi:10.1007/s12020-017-1273-x

Leonetti, F., Iozzo, P., Giaccari, A., Sbraccia, P., Buongiorno, A., Tamburrano, G., & Andreani, D. (1993). Absence of clinically overt atherosclerotic vascular disease and adverse changes in cardiovascular risk factors in 70 patients with insulinoma. *Journal of Endocrinological Investigation, 16*(11), 875-880. doi:10.1007/BF03348949

Li, J., Chen, X., Xu, K., Zhu, L., He, M., Sun, T., . . . Xue, H. (2020). Detection of insulinoma: One-stop pancreatic perfusion CT with calculated mean temporal images can replace the combination of bi-phasic plus perfusion scan. *European Radiology, 30*(8), 4164-4174. doi:10.1007/s00330-020-06657-4

Li, X., Zhang, F., Chen, H., Yu, H., Zhou, J., Li, M., . . . Jia, W. (2017). Diagnosis of insulinoma using the ratios of serum concentrations of insulin and C-peptide to glucose during a 5-hour oral glucose tolerance test. *Endocrine Journal, 64*(1), 49-57. doi:10.1507/endocrj.EJ16-0292

Liao, J., Ding, F., Luo, W., Nie, X., He, Y., & Li, G. (2021). Using the secretion ratios of insulin and C-peptide during the 2-h oral glucose tolerance test to diagnose insulinoma. *Digestive Diseases & Sciences, 66*(5), 1533-1539. doi:10.1007/s10620-020-06379-z

Liu, Q., Duan, J., Zheng, Y., Luo, J., Cai, X., & Tan, H. (2018). Rare malignant insulinoma with multiple liver metastases derived from ectopic pancreas: 3-year follow-up and literature review. *OncoTargets and Therapy, 11*, 1813-1819. doi:10.2147/OTT.S154991

Lopez, C. L., Albers, M. B., Bollmann, C., Manoharan, J., Waldmann, J., Fendrich, V., & Bartsch, D. K. (2016). Minimally invasive versus open pancreatic surgery in patients with multiple endocrine neoplasia type 1. *World Journal of Surgery, 40*(7), 1729-1736. doi:10.1007/s00268-016-3456-7

Magalhães, D., Sampaio, I. L., Ferreira, G., Bogalho, P., Martins-Branco, D., Santos, R., & Duarte, H. (2019). Peptide receptor radionuclide therapy with 177Lu-DOTA-TATE as a promising treatment of malignant insulinoma: A series of case reports and literature review. *Journal of Endocrinological Investigation, 42*(3), 249-260. doi:10.1007/s40618-018-0911-3

Maggio, I., Mollica, V., Brighi, N., Lamberti, G., Manuzzi, L., Ricci, A. D., & Campana, D. (2020). The functioning side of the pancreas: A review on insulinomas. *Journal of Endocrinological Investigation, 43*(2), 139-148. doi:10.1007/s40618-019-01091-w

Martini, C., Gamper, E., Wintner, L., Nilica, B., Sperner-Unterweger, B., Holzner, B., & Virgolini, I. (2016). Systematic review reveals lack of quality in reporting health-related quality of life in patients with gastroenteropancreatic neuroendocrine tumours. *Health & Quality of Life Outcomes, 14*(1), 127. doi:10.1186/s12955-016-0527-2

Marx, S. J. (2018). Recent topics around multiple endocrine neoplasia type 1. *The Journal of Clinical Endocrinology and Metabolism, 103*(4), 1296-1301. doi:10.1210/jc.2017-02340

Matsubayashi, H., Niwakawa, M., Uesaka, K., Sasaki, K., Kiyozumi, Y., Ishiwatari, H., . . . Ono, H. (2017). Renal cell carcinoma and a pancreatic neuroendocrine tumor: A coincidence or instance of von Hippel-Lindau disease? *Internal Medicine, 56*(17), 2281-2284. doi:10.2169/internalmedicine.8347-16

Mehrabi A., Fischer L., Hafezi M., Dirlewanger A., Grenacher L., Diener M. K., . . . Buchler M. W. (2014). A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas, 43*(5), 675-686. doi:10.1097/MPA.0000000000000110

Mele, C., Brunani, A., Damascelli, B., Ticha, V., Castello, L., Aimaretti, G., . . . Marzullo, P. (2018). Non-surgical ablative therapies for inoperable benign insulinoma. *Journal of Endocrinological Investigation, 41*(2), 153-162. doi:10.1007/s40618-017-0738-3

Mikkola, K., Yim, C., Lehtiniemi, P., Kauhanen, S., Tarkia, M., Tolvanen, T., . . . Solin, O. (2016). Low kidney uptake of GLP-1R-targeting, beta cell-specific PET tracer, 18F-labeled [Nle14,Lys40]exendin-4 analog, shows promise for clinical imaging. *EJNMMI Research, 6*(1), 1-11. doi:10.1186/s13550-016-0243-2

Minn, A. H., Kayton, M., Lorang, D., Hoffmann, S. C., Harlan, D. M., Libutti, S. K., & Shalev, A. (2004). Insulinomas and expression of an insulin splice variant. *Lancet, 363*(9406), 363-367. doi:10.1016/S0140-6736(04)15438-X

Modlin, I. M., Öberg, K., Chung, D. C., Jensen, R. T., de Herder, W. W., Thakker, R. V., . . . Sundin, A. (2008). Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology, 9*(1), 61-72. doi:10.1016/S1470-2045(07)70410-2

Moock, J., & Kohlmann, T. (2008). Comparing preference-based quality-of-life measures: Results from rehabilitation patients with musculoskeletal, cardiovascular, or psychosomatic disorders. *Quality of Life Research, 17*(3), 485-495. doi:10.1007/s11136-008-9317-6

Munir, A., Choudhary, P., Harrison, B., Heller, S., & Newell-Price, J. (2008). Continuous glucose monitoring in patients with insulinoma. *Clinical Endocrinology, 68*(6), 912-918. doi:10.1111/j.1365-2265.2007.03161.x

Murtha, T. D., Lupsa, B. C., Majumdar, S., Jain, D., & Salem, R. R. (2017). A systematic review of proinsulin-secreting pancreatic neuroendocrine tumors. *Journal of Gastrointestinal Surgery, 21*(8), 1335-1341. doi:10.1007/s11605-017-3428-8

Nagtegaal, I. D., Odze, R. D., Klimstra, D., Paradis, V., Rugge, M., Schirmacher, P., . . . WHO Classification of Tumours Editorial Board. (2020). The 2019 WHO classification of tumours of the digestive system. *Histopathology, 76*(2), 182-188. doi:10.1111/his.13975

Neves, J. S., Teles, L., Guerreiro, V., Lau, E., Oliveira, A. I., Graça, L., . . . Carvalho, D. (2021). Clinical characteristics and incidence of glucose metabolism disorders during the follow-up of surgically treated insulinoma. *Endocrine, 71*(2), 351-356. doi:10.1007/s12020-020-02520-0

Nikfarjam M., Warshaw A. L., Axelrod L., Deshpande V., Thayer S. P., Ferrone C. R., & Fernandez-del Castillo C. (2008). Improved contemporary surgical management of insulinomas: A 25-year Experience at the Massachusetts General Hospital. *Annals of Surgery, 247*(1), 165-172. doi:10.1097/SLA.0b013e31815792ed

Nockel, P., Babic, B., Millo, C., Herscovitch, P., Patel, D., Nilubol, N., . . . Kebebew, E. (2017). Localization of insulinoma using 68Ga-DOTATATE PET/CT scan. *Journal of Clinical Endocrinology & Metabolism, 102*(1), 195-199. doi:10.1210/jc.2016-3445

Norrbom, C., Steding-Jessen, M., Agger, C. T., Osler, M., Krabbe-Sorensen, M., Settnes, A., . . . Loekkegaard, E. C. L. (2019). Risk of adhesive bowel obstruction after abdominal surgery. A national cohort study of 665,423 Danish women. *American Journal of Surgery, 217*(4), 694-703. doi:10.1016/j.amjsurg.2018.10.035

O'Shea, T., & Druce, M. (2017). When should genetic testing be performed in patients with neuroendocrine tumours? *Reviews in Endocrine and Metabolic Disorders, 18*(4), 499-515. doi:10.1007/s11154-017-9430-3

O'Brien T., Young W. F. Jr, Palumbo P. J., O'Brien P. C., & Service F. J. (1993). Hypertension and dyslipidemia in patients with insulinoma. *Mayo Clinic Proceedings, 68*(2), 141-146. doi:10.1016/s0025-6196(12)60161-x

Oronsky, B., Ma, P. C., Morgensztern, D., & Carter, C. A. (2017). Nothing but NET: A review of neuroendocrine tumors and carcinomas. *Neoplasia (New York), 19*(12), 991-1002. doi:10.1016/j.neo.2017.09.002

Ovalle, W. K., Nahirney, P. C., & Netter, F. H. (2013). *Netter's essential histology*. Philadelphia, PA: Elsevier/Saunders.

Partelli, S., Bartsch, D. K., Capdevila, J., Chen, J., Knigge, U., Niederle, B., . . . Falconi, M., & all other Antibes Consensus Conference participants. (2017). ENETS consensus guidelines for standard of care in neuroendocrine tumours: Surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology, 105*(3), 255-265. doi:10.1159/000464292

Pavel, M., & de Herder, W. W. (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors. *Neuroendocrinology, 105*(3), 193-195. doi:10.1159/000457957

Pavel, M., Öberg, K., Falconi, M., Krenning, E., Sundin, A., Perren, A., & Berruti, A. (2020). Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology, 31*(7), 844-860. doi:10.1016/j.annonc.2020.03.304

Pavel, M., Valle, J. W., Eriksson, B., Rinke, A., Caplin, M., Chen, J., . . . Garcia-Carbonero, R., & all other Antibes Consensus Conference participants (2017). ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: Systemic therapy - biotherapy and novel targeted agents. *Neuroendocrinology, 105*(3), 266-280. doi:10.1159/000471880

Pelkonen, R., Taskinen, M. R., & Rauste, J. (1974). Insulooma--diagnostisia näkökohtia. *Duodecim, 90*(1), 22-33.

Peltola, E., Hannula, P., Huhtala, H., Metso, S., Kiviniemi, U., Vornanen, M., . . . Jaatinen, P. (2018). Characteristics and outcomes of 79 patients with an insulinoma: A nationwide retrospective study in Finland. *International Journal of Endocrinology*, Article ID 2059481, 10 pages. doi:10.1155/2018/2059481

Peltola, E., Hannula, P., Huhtala, H., Sintonen, H., Metso, S., Sand, J., . . . Jaatinen, P. (2021a). Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010. *Clinical Endocrinology, 94*(2), 250-257. doi:10.1111/cen.14336

Peltola, E., Hannula, P., Huhtala, H., Metso, S., Sand, J., Laukkarinen J., . . . Jaatinen, P (2021b). Accepted manuscript: Long-term morbidity and mortality in patients diagnosed with an insulinoma. Accepted for publication in European Journal of Endocrinology. doi:10.1530/EJE-21-0230

Pelttari, H., Sintonen, H., Schalin-Jäntti, C., & Välimäki, M. J. (2009). Health-related quality of life in long-term follow-up of patients with cured TNM stage I or II differentiated thyroid carcinoma. *Clinical Endocrinology, 70*(3), 493-497. doi:10.1111/j.1365-2265.2008.03366.x

Perren, A., Couvelard, A., Scoazec, J.-Y., Costa, F., Borbath, I., Delle Fave, G., . . . Welin, S, & all other Antibes Consensus Conference participants. (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Pathology: Diagnosis and prognostic stratification. *Neuroendocrinology, 105*(3), 196-200. doi:10.1159/000457956

Placzkowski, K. A., Vella, A., Thompson, G. B., Grant, C. S., Reading, C. C., Charboneau, J. W., . . . Service, F. J. (2009). Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. *Journal of Clinical Endocrinology & Metabolism, 94*(4), 1069-1073. doi:10.1210/jc.2008-2031

Portela-Gomes, G., Stridsberg, M., Grimelius, L., Rorstad, O., & Janson, E. T. (2007). Differential expression of the five somatostatin receptor subtypes in human benign and malignant insulinomas – predominance of receptor subtype 4. *Endocrine Pathology, 18*(2), 79-85. doi:10.1007/s12022-007-0014-8

Qi, Z., Li, D., Ma, J., Xu, P., Hao, Y., & Zhang, A. (2019). Insulinoma presenting as a complex partial seizure: Still a possible misleading factor. *Frontiers in Neuroscience, 13*, 1388. doi:10.3389/fnins.2019.01388

Queiroz Almeida, M., Machado, M. C., Correa-Giannella, M. L., Giannella-Neto, D., & Albergaria Pereira, M. A. (2006). Endogenous hyperinsulinemic hypoglycemia: Diagnostic strategies, predictive features of malignancy and long-term survival. *Journal of Endocrinological Investigation, 29*(8), 679-687. doi:10.1007/BF03344176

Raffel A., Eisenberger C. F., Cupisti K., Schott M., Baldus S. E., Hoffmann I., . . . Stoecklein N. H. (2010). Increased EpCAM expression in malignant insulinoma: Potential clinical implications. *European Journal of Endocrinology, 162*(2), 391-398. doi:10.1530/EJE-08-0916

Ramkumar, S., Dhingra, A., Jyotsna, V. P., Ganie, M. A., Das, C. J., Seth, A., . . . Bal, C. S. (2014). Ectopic insulin secreting neuroendocrine tumor of kidney with recurrent hypoglycemia: A diagnostic dilemma. *BMC Endocrine Disorders, 14*(1), 36-36. doi:10.1186/1472-6823-14-36

Rariy, C. M., Rometo, D., & Korytkowski, M. (2016). Post–gastric bypass hypoglycemia. *Current Diabetes Reports, 16*(2), 1-9. doi:10.1007/s11892-015-0711-5

Richards, M. L., Thompson, G. B., Farley, D. R., Kendrick, M. L., Service, J. F., Vella, A., & Grant, C. S. (2011). Setting the bar for laparoscopic resection of sporadic insulinoma. *World Journal of Surgery, 35*(4), 785-789. doi:10.1007/s00268-011-0970-5

Rindi, G., Klöppel, G., Alhman, H., Caplin, M., Couvelard, A., de Herder, W. W., . . . Wiedenmann, B. (2006). TNM staging of foregut (neuro)endocrine tumors: A consensus proposal including a grading system. *Virchows Archiv: An International Journal of Pathology, 449*(4), 395-401. doi:10.1007/s00428-006-0250-1

Rindi, G., & Wiedenmann, B. (2011). Neuroendocrine neoplasms of the gut and pancreas: New insights. *Nature Reviews Endocrinology, 8*(1), 54-64. doi:10.1038/nrendo.2011.120

Ritvonen, E., Karppinen, A., Sintonen, H., Vehkavaara, S., Kivipelto, L., Roine, R. P., . . . Schalin-Jäntti, C. (2015). Normal long-term health-related quality of life can be achieved in patients with functional pituitary adenomas having surgery as primary treatment. *Clinical Endocrinology, 82*(3), 412-421. doi:10.1111/cen.12550

Roland, C. L., Bian, A., Mansour, J. C., Yopp, A. C., Balch, G. C., Sharma, R., . . . Schwarz, R. E. (2012). Survival impact of malignant pancreatic neuroendocrine and islet cell neoplasm phenotypes. *Journal of Surgical Oncology, 105*(6), 595-600. doi:10.1002/jso.22118

Roland, C. L., Lo, C.-Y., Miller, B. S., Holt, S., & Nwariaku, F. E. (2008). Surgical approach and perioperative complications determine short-term outcomes in patients with

insulinoma: Results of a bi-institutional study. *Annals of Surgical Oncology, 15*(12), 3532-3537. doi:10.1245/s10434-008-0157-y

Ross, M. H., & Pawlina, W. (2011). *Histology: A text and atlas: With correlated cell and molecular biology* (6th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Rumilla, K. M., Erickson, L. A., Service, F. J., Vella, A., Thompson, G. B., Grant, C. S., & Lloyd, R. V. (2009). Hyperinsulinemic hypoglycemia with nesidioblastosis: Histologic features and growth factor expression. *Modern Pathology, 22*(2), 239-245. doi:10.1038/modpathol.2008.169

Ryhänen, E. M., Heiskanen, I., Sintonen, H., Välimäki, M. J., Roine, R. P., & Schalin-Jäntti, C. (2015). Health-related quality of life is impaired in primary hyperparathyroidism and significantly improves after surgery: A prospective study using the 15D instrument. *Endocrine Connections, 4*(3), 179-186. doi:10.1530/EC-15-0053

Röder, P.V., Wu, B., Liu, Y., & Han, W. (2016). Pancreatic regulation of glucose homeostasis. *Experimental & Molecular Medicine, 48*(3), e219-e219. doi:10.1038/emm.2016.6

Sada, A., Glasgow, A. E., Vella, A., Thompson, G. B., McKenzie, T. J., & Habermann, E. B. (2020). Malignant insulinoma: A rare form of neuroendocrine tumor. *World Journal of Surgery, 44*(7), 2288-2294. doi:10.1007/s00268-020-05445-x

Sada, A., Yamashita, T. S., Glasgow, A. E., Habermann, E. B., Thompson, G. B., Lyden, M. L., . . . McKenzie, T. J. (2021). Comparison of benign and malignant insulinoma. *American Journal of Surgery, 221*(2), 437-447. doi:10.1016/j.amjsurg.2020.08.003

Sadanandam, A., Wullschleger, S., Lyssiotis, C. A., Grötzinger, C., Barbi, S., Bersani, S., . . . Hanahan, D. (2015). A cross-species analysis in pancreatic neuroendocrine tumors reveals molecular subtypes with distinctive clinical, metastatic, developmental, and metabolic characteristics. *Cancer Discovery, 5*(12), 1296-1313. doi:10.1158/2159-8290.CD-15-0068

Sakurai, A., Yamazaki, M., Suzuki, S., Fukushima, T., Imai, T., Kikumori, T., . . . Imamura, M. (2012). Clinical features of insulinoma in patients with multiple endocrine neoplasia type 1: Analysis of the database of the MEN consortium of Japan. *Endocrine Journal, 59*(10), 859-866. doi:10.1507/endocrj.EJ12-0173

Seckl, M. J., Seckl, J. R., Mulholland, P. J., Bishop, A. E., Teale, J. D., Hales, C. N., . . . Watkins, S. (1999). Hypoglycemia due to an insulin-secreting small-cell carcinoma of the cervix. *The New England Journal of Medicine, 341*(10), 733-736. doi:10.1056/NEJM199909023411004

Service, F. J., McMahon, M. M., O'Brien, P. C., & Ballard, D. J. (1991). Functioning insulinoma--incidence, recurrence, and long-term survival of patients: A 60-year study. *Mayo Clinic Proceedings, 66*(7), 711-719. doi:10.1016/s0025-6196(12)62083-7

Service, F. J., & Natt, N. (2000). The prolonged fast. *Journal of Clinical Endocrinology & Metabolism, 85*(11), 3973-3974. doi:10.1210/jcem.85.11.6934

Service, F. J. (1995). Hypoglycemic disorders. *The New England Journal of Medicine, 332*(17), 1144-1152. doi:10.1056/NEJM199504273321707

Service, G. J., Thompson, G. B., Service, F. J., Andrews, J. C., Collazo-Clavell, M. L., & Lloyd, R. V. (2005). Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *New England Journal of Medicine, 353*(3), 249-254. doi:10.1056/NEJMoa043690

Shah, R., Garg, R., Majmundar, M., Purandare, N., Malhotra, G., Patil, V., . . . Bandgar, T (2021). Exendin-4-based imaging in insulinoma localization: Systematic review and meta-analysis. *Clinical Endocrinology (Oxford), 2021 Jan 1*: 1-11. doi:10.1111/cen.14406

Shantavasinkul, P. C., Torquati, A., & Corsino, L. (2016). Post-gastric bypass hypoglycaemia: A review. *Clinical Endocrinology (Oxford), 85*(1), 3-9. doi:10.1111/cen.13033

Sheen, Y., & Sheu, W. H. H. (2016). Association between hypoglycemia and dementia in patients with type 2 diabetes. *Diabetes Research & Clinical Practice, 116*, 279-287. doi:10.1016/j.diabres.2016.04.004

Shin, J. J., Gorden, P., & Libutti, S. K. (2010). Insulinoma: Pathophysiology, localization and management. *Future Oncology (London, England), 6*(2), 229-237. doi:10.2217/fon.09.165

Siddiqui, M., Vora, A., Ali, S., Abramowitz, J., & Mirfakhraee, S (2021). Pasireotide: A novel treatment for tumor-induced hypoglycemia due to insulinoma and non-islet cell tumor hypoglycemia. *Journal of the Endocrine Society, 5*(1), 1-7. doi:10.1210/jendso/bvaa171

Sintonen, H. (2001). The 15D instrument of health-related quality of life: Properties and applications. *Annals of Medicine, 33*(5), 328-336. doi:10.3109/07853890109002086

Solarek, W., Czarnecka, A. M., Escudier, B., Bielecka, Z. F., Lian, F., & Szczylik, C. (2015). Insulin and IGFs in renal cancer risk and progression. *Endocrine-Related Cancer, 22*(5), R253-64. doi:10.1530/ERC-15-0135

Sorbye, H., Meyer, L. S., Mordal, K. E., Myhre, S., & Thiis-Evensen, E. (2020). Patient reported symptoms, coping and quality of life during somatostatin analogue treatment for metastatic small- intestinal neuroendocrine tumours. *Health & Quality of Life Outcomes, 18*(1), 188. doi:10.1186/s12955-020-01452-7

Sotoudehmanesh, R., Hedayat, A., Shirazian, N., Shahraeeni, S., Ainechi, S., Zeinali, F., & Kolahdoozan, S. (2007). Endoscopic ultrasonography (EUS) in the localization of insulinoma. *Endocrine, 31*(3), 238-241. doi:10.1007/s12020-007-0045-4

Sowa-Staszczak, A., Pach, D., Mikolajczak, R., Macke, H., Jabrocka-Hybel, A., Stefanska, A., . . . Hubalewska-Dydejczyk, A. (2013). Glucagon-like peptide-1 receptor imaging with [Lys40(ahx-HYNIC- 99mTc/EDDA)NH2]-exendin-4 for the detection of insulinoma. *European Journal of Nuclear Medicine & Molecular Imaging, 40*(4), 524-531. doi:10.1007/s00259-012-2299-1

Starke A, Saddig C, Mansfeld L, Koester R, Tschahargane C, Czygan P, & Goretzki P. (2005). Malignant metastatic insulinoma-postoperative treatment and follow-up. *World Journal of Surgery, 29*(6), 789-793. doi:10.1007/s00268-005-7743-y

Statistics Finland. Statistics Finland's PxWeb databases: Population according to age (1-year 0-112) and sex, 1972-2019. Retrieved from http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__vaerak/statfin_vaerak_pxt_11rd.px/table/tableViewLayout1/

Statistics Finland (2017). Official Statistics of Finland (OSF): Causes of death [e-publication]. Retrieved from https://www.stat.fi/meta/til/ksyyt_en.html. Accessed Sep 2020.

Su, A.-P., Ke, N.-W., Zhang, Y., Liu, X.-B., Hu, W.-M., Tian, B.-L., & Zhang, Z.-D. (2014). Is laparoscopic approach for pancreatic insulinomas safe? Results of a systematic review and meta-analysis. *Journal of Surgical Research, 186*(1), 126-134. doi:10.1016/j.jss.2013.07.051

Suminaga, K., Murakami, T., Yabe, D., Sone, M., Sugawa, T., Masui, T., . . . Inagaki, N. (2020). Factory-calibrated continuous glucose monitoring and capillary blood glucose monitoring in a case with insulinoma: Usefulness and possible pitfall under chronic hyperinsulinemic hypoglycemia. *Endocrine Journal, 67*(3), 361-366. doi:10.1507/endocrj.EJ19-0339

Sund, R. (2012). Quality of the Finnish hospital discharge register: A systematic review. *Scandinavian Journal of Public Health, 40*(6), 505-515. doi:10.1177/1403494812456637

Sundin, A., Arnold, R., Baudin, E., Cwikla, J. B., Eriksson, B., Fanti, S., . . . Vullierme, M.-P. & all other Antibes Consensus Conference participants (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Radiological, nuclear medicine and hybrid imaging. *Neuroendocrinology, 105*(3), 212-244. doi:10.1159/000471879

Taskin, O. C., Clarke, C. N., Erkan, M., Tsai, S., Evans, D. B., & Adsay, V. (2020). Pancreatic neuroendocrine neoplasms: Current state and ongoing controversies on terminology, classification and prognostication. *Journal of Gastrointestinal Oncology, 11*(3), 548-558. doi:10.21037/jgo.2020.03.07

ten Broek, R. P. G., Issa, Y., van Santbrink, E. J. P., Bouvy, N. D., Kruitwagen, R. F. P. M., Jeekel, J., . . . van Goor, H. (2013). Burden of adhesions in abdominal and pelvic surgery: Systematic review and met-analysis. *BMJ, 347*, f5588. doi:10.1136/bmj.f5588

Thompson, G. B., Service, F. J., Andrews, J. C., Lloyd, R. V., Natt, N., van Heerden, J. A., & Grant, C. S. (2000). Noninsulinoma pancreatogenous hypoglycemia syndrome: An update in 10 surgically treated patients. *Surgery, 128*(6), 937-945. doi:10.1067/msy.2000.110243

Tiensuu Janson, E., Sorbye, H., Welin, S., Federspiel, B., Grønbaek, H., Hellman, P., . . . Knigge, U. (2014). Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncologica, 53*(10), 1284-1297. doi:10.3109/0284186X.2014.941999

Tiensuu Janson, E., Knigge, U., Dam, G., Federspiel, B., Grønbaek, H., Stålberg, P., . . . Sorbye, H (2021). Nordic guidelines 2021 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncologica, 60*(7), 931-941. doi:10.1080/0284186X.2021.1921262

Tirosh, A., Stemmer, S. M., Solomonov, E., Elnekave, E., Saeger, W., Ravkin, Y., . . . Shimon, I. (2016). Pasireotide for malignant insulinoma. *Hormones, 15*(2), 271-276. doi:10.14310/horm.2002.1639

Toaiari, M., Davì, M. V., Dalle Carbonare, L., Boninsegna, L., Castellani, C., Falconi, M., & Francia, G. (2013). Presentation, diagnostic features and glucose handling in a monocentric series of insulinomas. *Journal of Endocrinological Investigation, 36*(9), 753-758. doi:10.3275/8942

Topping, M., Gray, D., Friend, E., Davies, A., & Ramage, J. (2017). A systematic review of symptoms and quality of life issues in pancreatic neuroendocrine tumours. *Neuroendocrinology, 105*(3), 320-330. doi:10.1159/000475793

Torimoto, K., Okada, Y., Tanaka, Y., Matsuoka, A., Hirota, Y., Ogawa, W., . . . Koga, M. (2019). Usefulness of hemoglobin A1c and glycated albumin measurements for insulinoma screening: An observational case-control study. *BMC Cancer, 19*(1), 174. doi:10.1186/s12885-019-5389-7

Uitto, E., Hannula, P., Metso, S., Vornanen, M., Sand, J., & Jaatinen, P. (2015). Insulinomas in Tampere University Hospital Special Responsibility Area in 1980-2010 (in Finnish). *Duodecim, 131*(17), 1598-1604.

Vagefi, P. A., Razo, O., Deshpande, V., McGrath, D. J., Lauwers, G. Y., Thayer, S. P., . . . Fernandez-Del Castillo, C. (2007). Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: The Massachusetts General Hospital Experience from 1977 to 2005. *Archives of Surgery, 142*(4), 347-354. doi:10.1001/archsurg.142.4.347

van Beek, D. J., Nell, S., Verkooijen, H. M., Borel Rinkes, I. H. M., Valk, G. D., Vriens, M. R., . . . Dejong, C. H. C. (2020). Surgery for multiple endocrine neoplasia type 1-related insulinoma: Long-term outcomes in a large international cohort. *British Journal of Surgery, 107*(11), 1489-1499. doi:10.1002/bjs.11632

van Leeuwaarde, R. S., Dreijerink, K. M., Ausems, M. G., Beijers, H. J., Dekkers, O. M., de Herder, W. W., . . . Valk, G. D. (2017). MEN1-dependent breast cancer: Indication for early screening? Results from the Dutch MEN1 study group. *Journal of Clinical Endocrinology & Metabolism, 102*(6), 2083-2090. doi:10.1210/jc.2016-3690

van Schaik, E., van Vliet, E. I., Feelders, R. A., Krenning, E. P., Khan, S., Kamp, K., . . . de Herder, W. W. (2011). Improved control of severe hypoglycemia in patients with malignant insulinomas by peptide receptor radionuclide therapy. *The Journal of Clinical Endocrinology and Metabolism, 96*(11), 3381-3389. doi:10.1210/jc.2011-1563

Varshney, N., Kebede, A. A., Owusu-Dapaah, H., Lather, J., Kaushik, M., & Bhullar, J. S. (2017). A review of von Hippel-Lindau syndrome. *Journal of Kidney Cancer and VHL, 4*(3), 20-29. doi:10.15586/jkcvhl.2017.88

Veltroni, A., Cosaro, E., Spada, F., Fazio, N., Faggiano, A., Colao, A., . . . Davì, M. V. (2020). Clinico-pathological features, treatments and survival of malignant insulinomas: A multicenter study. *European Journal of Endocrinology, 182*(4), 439-446. doi:10.1530/EJE-19-0989

Vezzosi, D., Bennet, A., Courbon, F., & Caron, P. (2008). Short- and long-term somatostatin analogue treatment in patients with hypoglycaemia related to endogenous hyperinsulinism. *Clinical Endocrinology, 68*(6), 904-911. doi:10.1111/j.1365-2265.2007.03136.x

Vezzosi D., Bennet A., Fauvel J., & Caron P. (2007). Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. *European Journal of Endocrinology, 157*(1), 75-83. doi:10.1530/EJE-07-0109

Vezzosi, D., Bennet, A., Rochaix, P., Courbon, F., Selves, J., Pradere, B., . . . Caron, P. (2005). Octreotide in insulinoma patients: Efficacy on hypoglycemia, relationships with octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. *European Journal of Endocrinology, 152*(5), 757-767. doi:10.1530/eje.1.01901

Wang, L., Yang, M., Zhang, Y., Xu, S., & Tian, B. L. (2015). Prognostic validation of the WHO 2010 grading system in pancreatic insulinoma patients. *Neoplasma, 62*(3), 484-490. doi:10.4149/neo_2015_058

Waser, B., Blank, A., Karamitopoulou, E., Perren, A., & Reubi, J. C. (2015). Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. *Modern Pathology, 28*(3), 391-402. doi:10.1038/modpathol.2014.113

Whipple, A. (1938). The surgical therapy of hyperinsulinism. *Journal International de Chirurgie,* (3), 237-276.

WHO Classification of Tumours Editorial Board (Eds.) (2019). *Digestive system tumours. WHO classification of tumours* (5th ed.). Lyon: IARC Press.

Wild, D., Christ, E., Caplin, M. E., Kurzawinski, T. R., Forrer, F., Brändle, M., . . . Reubi, J. C. (2011). Glucagon-like peptide-1 versus somatostatin receptor targeting reveals 2 distinct forms of malignant insulinomas. *The Journal of Nuclear Medicine (1978), 52*(7), 1073-1078. doi:10.2967/jnumed.110.085142

Wilder, R. M., Allan, F. N., Power, M. H., & Robertson, H. E. (1927). Carcinoma of the islands of the pancreas: hyperinsulinism and hypoglycemia. *Journal of the American Medical Association, 89*(5), 348-355. doi:10.1001/jama.1927.02690050014007

Wolf, P., Winhofer, Y., Smajis, S., Anderwald, C.-H., Scheuba, C., Niederle, B., . . . Koperek, O. (2015). Clinical presentation in insulinoma predicts histopathological tumour characteristics. *Clinical Endocrinology, 83*(1), 67-71. doi:10.1111/cen.12777

Yao, C., Wang, X., Zhang, Y., Kong, J., Gao, J., Ke, S., . . . Sun, W. (2020). Treatment of insulinomas by laparoscopic radiofrequency ablation: Case reports and literature review. *Open Medicine, 15*, 84-91. doi:10.1515/med-2020-0013.

Yao, J. C., Hassan, M., Phan, A., Dagohoy, C., Leary, C., Mares, J. E., . . . Evans, D. B. (2008). One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology, 26*(18), 3063-3072. doi:10.1200/JCO.2007.15.4377

Yao, J. C., Bergsland, E. K., & Kulke, M. H. (2009). Glycemic control in patients with insulinoma treated with everolimus. *The New England Journal of Medicine, 360*(2), 195-197. doi:10.1056/NEJMc0806740

Yu, R. (2020). Malignant insulinoma is largely derived from nonfunctioning pancreatic neuroendocrine tumors: A contemporary view. *Pancreas, 49*(6), 733-736. doi:10.1097/MPA.0000000000001562

Zhao, Y.-P., Zhan, H.-X., Cong, L., Zhang, T.-P., Liao, Q., Dai, M.-H., . . . Zhu Y. (2012). Risk factors for postoperative pancreatic fistula in patients with insulinomas: Analysis of 292 consecutive cases. *Hepatobiliary & Pancreatic Diseases International, 11*(1), 102-106. doi:10.1016/s1499-3872(11)60132-x

Zhao, Y.-P., Zhan, H.-X., Zhangm T.-P., Cong, L., Dai, M.-H., Liao, Q., & Cai L.-X. (2011). Surgical management of patients with insulinomas: Result of 292 cases in a single institution. *Journal of Surgical Oncology, 103*(2), 169-174. doi:10.1002/jso.21773

Zhao, K., Patel, N., Kulkarni, K., Gross, J. S., & Taslakian, B. (2020). Essentials of insulinoma localization with selective arterial calcium stimulation and hepatic venous sampling. *Journal of Clinical Medicine, 9*(10), 3091. doi:10.3390/jcm9103091

Zhu, L., Xue, H., Sun, H., Wang, X., Wu, W., Jin, Z., & Zhao, Y. (2017). Insulinoma detection with MDCT: Is there a role for whole-pancreas perfusion? *American Journal of Roentgenology (1976), 208*(2), 306-314. doi:10.2214/AJR.16.16351

Zhu, L., Tang, L., Qiao, X., Wolin, E., Nissen, N. N., Dhall, D., . . . Chen, Y. (2016). Differences and similarities in the clinicopathological features of pancreatic neuroendocrine tumors in China and the United States: A multicenter study. *Medicine, 95*(7), e2836. doi:10.1097/MD.0000000000002836

Znaor, A., Lortet-Tieulent, J., Laversanne, M., Jemal, A., & Bray, F. (2014). International variations and trends in renal cell carcinoma incidence and mortality. *European Urology, 67*(3), 519-530. doi:10.1016/j.eururo.2014.10.002

Öberg, K., Åkerstrom, G., Rindi, G., & Jelic, S., on behalf of the ESMO Guidelines Working Group. (2010). Neuroendocrine gastroenteropancreatic tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology, 21*(Suppl 5), 223-227. doi:10.1093/annonc/mdq192

Öberg, K., Couvelard, A., Delle Fave, G., Gross, D., Grossman, A., Jensen, R. T., . . . Ferone, D & all other Antibes Consensus Conference participants. (2017). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Biochemical markers. *Neuroendocrinology, 105*(3), 201-211. doi:10.1159/000472254

9 APPENDIX 1: THE 15D INSTRUMENT

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY

1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

10 APPENDIX 2: THE HEALTH QUESTIONNAIRE

Health Questionnaire (Peltola et al., 2021a)

Question 1. Gender[a]

- ☐ male
- ☐ female

Question 2. What is your marital status?[a]

- ☐ married
- ☐ cohabiting
- ☐ single
- ☐ separated or divorced
- ☐ widowed
- ☐ registered partnership

Question 3. What is your education? Mark your highest educational degree[a]

- ☐ elementary school, basic education
- ☐ lower secondary education
- ☐ vocational school/equivalent
- ☐ upper secondary education/high school
- ☐ non-university lower education
- ☐ non-university higher education
- ☐ university education

Question 4. How do you find your current health status? Is it[a]

- ☐ excellent
- ☐ quite good
- ☐ average
- ☐ quite poor
- ☐ very poor

Question 5. Do you still have regular follow-up visits to a doctor due to insulinoma?

- ☐ yes, in primary health care
- ☐ yes, in regional hospital
- ☐ yes, in university hospital
- ☐ no, the follow-up has been ended in the year _____

Question 6. What is your current height and weight?

Height _____ cm Weight _____ kg

Question 7. When was the last time you had your blood sugar measured?[a]

- ☐ during the last 6 months
- ☐ 6 months – 1 year ago
- ☐ 1 year – 5 years ago
- ☐ over 5 years ago
- ☐ never (proceed to question 11)
- ☐ I do not know (proceed to question 11)

Question 8. Have you ever been diagnosed with diabetes?[a]

- ☐ no (proceed to question 11)
- ☐ no, but I have been diagnosed with elevated blood glucose levels or prediabetes
- ☐ yes, type 1 diabetes (childhood-onset diabetes), in the year _____
- ☐ yes, type 2 diabetes (adult-onset diabetes), in the year _____
- ☐ yes, but I don't know which type, in the year _____
- ☐ yes, gestational diabetes, in the year _____

Question 9. When diagnosed with diabetes, were you given one of the following treatments?[a]

- ☐ dietary counseling only
- ☐ tablet treatment
- ☐ insulin treatment
- ☐ none of the above

Question 10. What prescription medicines do you now use for diabetes?[a]

- ☐ none
- ☐ insulin
- ☐ tablets
- ☐ both insulin and tablets
- ☐ other injectable medicine together with tablets and/or insulin

Question 11. Has a doctor diagnosed or treated you for any of the following diseases during the past 12 months?[a]

	no	yes
Increased blood pressure, hypertension	☐	☐
High cholesterol	☐	☐
Heart failure	☐	☐
Effort angina (Angina pectoris)	☐	☐
Diabetes	☐	☐
Cancer	☐	☐
Asthma	☐	☐
Chronic obstructive pulmonary disease (COPD)	☐	☐
Gallstones, gall bladder inflammation	☐	☐
Rheumatoid arthritis (rheumatism)	☐	☐
Other disease of the joints	☐	☐
Degenerative arthritis of the back, other illness of the back	☐	☐
Depression	☐	☐
Other psychological illness	☐	☐
Renal failure	☐	☐
Proteinuria (excessive protein in urine)	☐	☐
Other chronic illness, which disease: _____	☐	☐

Question 12. Has a doctor ever diagnosed you with myocardial infarction?[a]

☐ no

☐ yes, in the year_____

Question 13. Has a doctor ever diagnosed you with stroke, cerebral (brain) hemorrhage or obstruction of a blood vessel in brain?[a]

☐ no

☐ yes, in the year_____

Question 14. Have you ever had coronary (heart) bypass surgery?[a]

☐ no

☐ yes, in the year_____

Question 15. Have you ever had coronary (heart) angioplasty?[a]

☐ no

☐ yes, in the year_____

Please, list all your daily medicines and their doses here:

_____

_____

_____

_____

_____

_____

_____

_____

_____

Thank you for the answers!

[a] indicates questions adapted and modified from Questionnaire 1 in the National FINRISK Study 2012 (Borodulin et al., 2013a; Borodulin et al., 2013b; FINRISKI 2012 National Health Study)

ORIGINAL PUBLICATIONS

I Peltola, E., Hannula, P., Huhtala, H., Metso, S., Kiviniemi, U., Vornanen, M., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Arola, J., Sirén, J., Piiroinen, A., Soinio, M., Nuutila, P., Söderström, M., Hämäläinen, H., Moilanen, L., Laaksonen, D., Pirinen, E., Sundelin, F., Ebeling, T., Salmela, P., Mäkinen, M. J., and Jaatinen, P. (2018). Characteristics and outcomes of 79 patients with an insulinoma: A nationwide retrospective study in Finland. International Journal of Endocrinology, Article ID 2059481, 10 pages. doi:10.1155/2018/2059481

II Peltola, E., Hannula, P., Huhtala, H., Sintonen, H., Metso, S., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Ebeling, T., and Jaatinen, P. (2021). Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010. Clinical Endocrinology, 94(2), 250-257. doi:10.1111/cen.14336

III Accepted manuscript: Peltola, E., Hannula, P., Huhtala, H., Metso, S., Sand, J., Laukkarinen J., Tiikkainen, M., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Laaksonen, D. E., Ebeling, T., Arola, J., Schalin-Jäntti, C., and Jaatinen, P. (2021). Long-term morbidity and mortality in patients diagnosed with an insulinoma. Accepted for publication in European Journal of Endocrinology. doi:10.1530/EJE-21-0230

PUBLICATION I

Characteristics and Outcomes of 79 patients with an Insulinoma: A Nationwide Retrospective Study in Finland

Peltola, E., Hannula, P., Huhtala, H., Metso, S., Kiviniemi, U., Vornanen, M., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Arola, J., Sirén, J., Piiroinen, A., Soinio, M., Nuutila, P., Söderström, M., Hämäläinen, H., Moilanen, L., Laaksonen, D., Pirinen, E., Sundelin, F., Ebeling, T., Salmela, P., Mäkinen, M. J., and Jaatinen, P.

International Journal of Endocrinology, Article ID 2059481, 10 pages.
doi:10.1155/2018/2059481

Hindawi
International Journal of Endocrinology
Volume 2018, Article ID 2059481, 10 pages
https://doi.org/10.1155/2018/2059481

Research Article

Characteristics and Outcomes of 79 Patients with an Insulinoma: A Nationwide Retrospective Study in Finland

Elina Peltola,[1,2] Päivi Hannula,[3] Heini Huhtala,[4] Saara Metso,[3] Ulla Kiviniemi,[3] Martine Vornanen,[5] Juhani Sand,[6] Johanna Laukkarinen,[1,7] Mirja Tiikkainen,[8] Camilla Schalin-Jäntti,[8,9] Johanna Arola,[10,11] Jukka Sirén,[12] Antti Piiroinen,[13] Minna Soinio,[14] Pirjo Nuutila,[13,14] Mirva Söderström,[15] Hanna Hämäläinen,[16] Leena Moilanen,[17] David Laaksonen,[17] Elina Pirinen,[18] Fia Sundelin,[19] Tapani Ebeling,[19,20] Pasi Salmela,[20] Markus J. Mäkinen,[21,22] and Pia Jaatinen[1,2,3]

[1]*Faculty of Medicine and Life Sciences, University of Tampere, Finland*
[2]*Division of Internal Medicine, Seinäjoki Central Hospital, Finland*
[3]*Endocrinology, Department of Internal Medicine, Tampere University Hospital, Finland*
[4]*Faculty of Social Sciences, University of Tampere, Finland*
[5]*Fimlab Laboratories, Pathology Department, Tampere University Hospital, Finland*
[6]*Päijät-Häme Joint Authority for Health and Wellbeing, Finland*
[7]*Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Finland*
[8]*Endocrinology, Abdominal Center, Helsinki University Hospital, Finland*
[9]*Endocrinology, Abdominal Center, University of Helsinki, Finland*
[10]*Pathology, HUSLAB Helsinki University Hospital, Finland*
[11]*Pathology, University of Helsinki, Finland*
[12]*Abdominal Center, Helsinki University Hospital, Finland*
[13]*Faculty of Medicine, University of Turku, Finland*
[14]*Endocrinology, Department of Internal Medicine, Turku University Hospital, Finland*
[15]*Department of Pathology, Turku University Hospital, Finland*
[16]*Faculty of Health Sciences, School of Medicine, University of Eastern Finland, Finland*
[17]*Department of Medicine, Kuopio University Hospital, Finland*
[18]*Department of Clinical Pathology, Kuopio University Hospital, Finland*
[19]*Faculty of Medicine, University of Oulu, Finland*
[20]*Endocrinology, Oulu University Hospital, Finland*
[21]*Research Unit of Cancer and Translational Medicine, Department of Pathology, University of Oulu, Finland*
[22]*Department of Pathology, Oulu University Hospital, Finland*

Correspondence should be addressed to Pia Jaatinen; pia.jaatinen@uta.fi

Received 6 May 2018; Accepted 9 September 2018; Published 23 October 2018

Academic Editor: Thomas J. Fahey

Objective. Insulinomas are rare pancreatic tumours. Population-based data on their incidence, clinical picture, diagnosis, and treatment are almost nonexistent. The aim of this study was to clarify these aspects in a nationwide cohort of insulinoma patients diagnosed during three decades. *Design and Methods*. Retrospective analysis on all adult patients diagnosed with insulinoma in Finland during 1980–2010. *Results*. Seventy-nine patients were diagnosed with insulinoma over the research period. The median follow-up from diagnosis to last control visit was one (min 0, max 31) year. The incidence increased from 0.5/million/year in the 1980s to 0.9/million/year in the 2000s ($p = 0.002$). The median diagnostic delay was 13 months and did not change over the study period. The mean age at diagnosis was 52 (SD 16) years. The overall imaging sensitivity improved

from 39% in the 1980s to 98% in the 2000s ($p < 0.001$). Seventy-one (90%) of the patients underwent surgery with a curative aim, two (3%) had palliative surgery, and 6 (8%) were inoperable. There were no significant differences in the types of surgical procedures between the 1980s, 1990s, and 2000s; tumour enucleations comprised 43% of the operations, distal pancreatic resections 45%, and pancreaticoduodenectomies 12%, over the whole study period. Of the patients who underwent surgery with a curative aim, 89% had a full recovery. Postoperative complications occurred in half of the patients, but postoperative mortality was rare. *Conclusions*. The incidence of insulinomas has increased during the past three decades. Despite the improved diagnostic options, diagnostic delay has remained unchanged. To shorten the delay, clinicians should be informed and alert to consider the possibility of hypoglycemia and insulinoma, when symptomatic attacks are investigated in different sectors of the healthcare system. Developing the surgical treatment is another major target, in order to lower the overall complication rate, without compromising the high cure rate of insulinomas.

1. Introduction

Insulinomas are the most common functioning endocrine neoplasms of the pancreas with an estimated incidence of 1–4 per million per year. Less than 10% are reported to metastasize [1, 2]. During the past few decades, the incidence of all neuroendocrine neoplasms (NENs) has increased rapidly compared with the general incidence of cancers [3, 4]. The increase may in part be explained by improved diagnostics, including more sensitive imaging methods [4, 5]. Whether the incidence of insulinomas has followed the increasing trend of NENs in general is presently unknown.

In patients with insulinoma, episodes of hyperinsulinemic hypoglycemia cause various autonomic and neuroglycopenic symptoms, which usually emerge in the fasting state. Documentation of the so-called Whipple's triad, i.e., symptoms consistent with hypoglycemia, a low plasma glucose measured at the time of the symptoms, and immediate relief of the symptoms after administration of glucose, is the cornerstone of insulinoma diagnostics [6–8]. Demonstration of a low plasma glucose concomitant with inappropriately high serum insulin and C-peptide levels in a symptomatic patient constitutes the basis for the biochemical diagnosis, with the exclusion of other causes of hyperinsulinemic hypoglycemia [7]. β-Hydroxybutyrate levels of 2.7 mmol/liter or less, an increase in plasma glucose of at least 1.4 mmol/liter after iv glucagon, and a negative screen for oral hypoglycemic agents distinguish endogenous hyperinsulinemic hypoglycemia from that caused by other mechanisms [7]. A 72-hour fasting test with plasma glucose, insulin, and C-peptide measurements is considered the gold standard for the biochemical diagnosis of insulinoma [7]. Gadolinium-enhanced dynamic magnetic resonance imaging (MRI), 3-phase computed tomography (CT), and endoscopic ultrasonography (EUS) have been regarded as the most useful imaging modalities for insulinoma evaluation [8]. In experienced hands, the sensitivity of EUS is 70–95%, and combined with 3-phase CT, sensitivities up to 100% have been reported [8, 9]. Conventional US, CT, and MRI are widely available and thus often applied as the first-line imaging methods, but their success rates remain at 10–40% in many studies [9]. During the past 10 years, new functional nuclear imaging methods (such as ^{18}F-DOPA-PET/CT, ^{68}Ga-DOTA-NOC-PET/CT, and recently, GLP-1-analogue-PET/CT) have also become available, and promising results have been reported with sensitivities exceeding 90% [10–13]. These functional imaging methods have largely replaced the previously more commonly used diagnostic angiography (based on detection of a hypervascular lesion consistent with an insulinoma) and octreotide scintigraphy, with general sensitivities of 60 and 50%, respectively [9]. Laparoscopic surgery has developed, and pancreas-preserving surgical methods have become more common in many centers, to avoid the adverse effects of extensive pancreatic resections, such as exocrine dysfunction and insulin-dependent diabetes [14].

Because previous reports on single-center cohorts have suggested changes in the clinical picture, diagnostics, and treatment of insulinoma [10, 15–18], we wanted to clarify these aspects in an unselected, nationwide cohort of patients with insulinomas, diagnosed over a 3-decade period. Moreover, no previous population-based data exist on changes in the incidence of insulinomas, although an increase in the overall incidence of NENs has been noted worldwide. We have previously reported a pilot study of 23 insulinoma patients included in the present study, diagnosed at one of the participating centers (Tampere University Hospital, Finland) [19].

2. Subjects and Methods

2.1. Patient Population. A retrospective analysis was performed on adult (≥18 years) patients diagnosed with an insulinoma in Finland during 1980–2010. To find all the Finnish insulinoma patients, a comprehensive search was carried out in the patient record and pathology registries in all the five university hospitals, as well as at the Finnish Cancer Registry. In Finland, the diagnostics and treatment of insulinomas are centralized in the University Hospitals. Diagnosis codes for benign and malignant pancreatic tumours, as well as hypoglycemia, were searched for in the patient records of all the five Finnish University Hospitals (detailed search strategy in Supplementary Materials (available here)). To double-check the search results of surgically managed insulinomas, pathology registries of the University Hospitals were searched for the term *insulinoma**. In addition, a search in the Finnish Cancer Registry, a nationwide database on all cancers diagnosed in Finland, was performed with ICD-O-3 morphological codes *8150 Pancreatic endocrine tumour* and *8151 Insulinoma*. The case histories of all the patients identified by the searches described above were reviewed to verify if the inclusion criteria of the present study were fulfilled.

2.2. Inclusion Criteria. The diagnosis of insulinoma was based on documentation of the Whipple's triad and/or

hyperinsulinemic hypoglycemia together with histopathological verification of an insulinoma. Histopathology was regarded as positive, if the diagnosis was pancreatic neuroendocrine tumour and insulin staining (if performed) was positive. In patients without histopathological verification, the diagnosis required documentation of the Whipple's triad or hyperinsulinemic hypoglycemia, as well as imaging findings of a pancreatic tumour compatible with an insulinoma.

2.3. Data Collection. Data was collected on the clinical picture, laboratory findings, imaging, pathology, treatment, and follow-up of insulinomas. The symptoms were classified as neuroglycopenic and autonomic. Laboratory findings registered were the lowest incidental blood glucose concentration, measurements of glycated hemoglobin (HbA1c), and the results of fasting tests and prolonged (5-hour) OGTTs. The fasting tests were analysed according to the Endocrine Society 2009 Guideline criteria for hyperinsulinemic hypoglycemia [7] (Table 1). The blood glucose values were multiplied by 1.15, to be comparable with the plasma glucose measurements. Any medication potentially affecting insulin secretion or insulin sensitivity was documented. The number and the size of insulinomas, the type of operation, surgical complications, and the histopathological diagnosis were registered. Postoperative hospital mortality was recorded. Postoperative surgical complications were classified according to the Clavien-Dindo (CD) classification [20, 21]. The incidence of insulinoma was calculated according to the population statistics provided by Statistics Finland [22].

The ethical committee of Tampere University Hospital and the National Institute for Health and Welfare approved the study protocol.

2.4. Statistical Analysis. The statistical analysis was conducted with the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The numerical results are presented as mean (standard deviation, SD) for normally distributed variables, median (minimum, maximum) for other continuous variables, and number (%) for categorical variables. Diagnostic delay was calculated from the first presentation of hypoglycemic symptoms up to the clinical diagnosis of insulinoma, as documented in the patient records. Differences were analysed between insulinomas diagnosed in the 1980s, 1990s, and 2000s. Categorical variables were analysed by the chi-square test or the Fisher exact test, as appropriate. Numerical variables were assessed by the Mann-Whitney U test, Student t-test, or Kruskal-Wallis test, as appropriate. A two-sided p value below 0.05 was considered statistically significant. The changes in the incidence of insulinomas were assessed with Poisson regression, conducted with STATA Statistical Software: Release 13 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Patient Characteristics and Incidence of Insulinomas. Altogether, 79 insulinoma patients were identified, 55 (70%) of them female. In 73 patients, the diagnosis was confirmed histopathologically, whereas in 6 patients, the diagnosis was based on documentation of the Whipple's triad or hyperinsulinemic hypoglycemia and imaging findings compatible with an insulinoma. Of these 6 patients without histopathologic verification, 4 were inoperable (2 malignant insulinomas with distant metastases and 2 clinically classified as benign but inoperable due to other diseases). One patient with hypoglycemic symptoms, confirmed hyperinsulinemic hypoglycemia, and imaging results consistent with an insulinoma died of bleeding complicating the pancreatic surgery, and histopathological verification of the insulinoma was not obtained. In one patient, diagnosed in the 1980s, no insulinoma could be localized in the primary surgery, despite the preoperative transhepatic portovenous sampling (THPVS) findings compatible with an insulinoma located in the body of the pancreas. As the hypoglycemic symptoms progressed, a diagnostic angiography was performed to localize the tumour. As a complication of this angiography, lethal intraabdominal bleeding developed, and no histopathological verification of the tumour was obtained.

Table 1: The criteria for endogenous hyperinsulinemic hypoglycemia according to the Endocrine Society Guideline 2009 [7].

Symptoms and signs, or both, consistent with hypoglycemia with concomitant plasma concentrations of	
Glucose	<3.0 mmol/l
Insulin	≥18 pmol/l
C-Peptide	≥0.2 nmol/l
Proinsulin	≥5.0 pmol/l

The median length of follow-up from the clinical diagnosis of insulinoma up to the last control visit at the University Hospital was one (0, 31) year. MEN1 syndrome was diagnosed in two patients, both of them associated with a solitary insulinoma. The mean age at the time of diagnosis was 52 (SD 16) years. The MEN1 patients were younger at the diagnosis (mean age 42 years in MEN1 vs. 52 years in sporadic cases), but the difference was not statistically significant ($p = 0.368$). The median age at the time of diagnosis did not differ between malignant [55 (39, 76) years] and nonmalignant (insulinomas classified as benign or undetermined) insulinomas [51 (21, 84) years, $p = 0.098$]. The median BMI at diagnosis was 27 (20, 51) kg/m^2.

The incidence of insulinoma over the whole research period was 0.6 per million adults per year and increased remarkably during the study period (0.5, 0.4, and 0.9/million/year in the 1980s, 1990s, and 2000s, respectively). In Poisson regression analysis, the yearly incidence rate ratio was 1.043, and the increase in incidence was statistically significant ($p = 0.002$). The increasing incidence of insulinomas is presented in Figure 1. The median diagnostic delay was 13 months (17, 11, and 17 months in the 1980s, 1990s, and 2000s, respectively). Thirty-one of 79 patients were first examined for their symptoms by specialities other than endocrinology, most often by neurology, neurosurgery, or cardiology.

3.2. Symptoms. All but two patients had hypoglycemic symptoms before the insulinoma diagnosis (Table 2). The

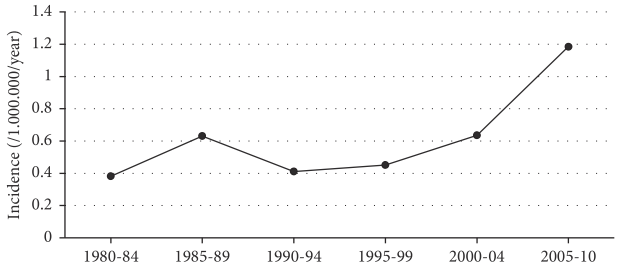


Figure 1: The incidence of insulinomas in Finland 1980–2010. In Poisson regression analysis, the yearly incidence rate ratio was 1.043, and the increase in incidence was statistically significant ($p = 0.002$).

Table 2: The presenting symptoms of the 79 patients diagnosed with an insulinoma in Finland 1980–2010.

Symptom	*n*	%
Autonomic symptoms	61	77
Sweating/diaphoresis	45	57
Tremor	21	27
Anxiety, aggressiveness	16	20
Palpitations	14	18
Neuroglycopenic symptoms	76	96
Confusion	68	86
Drowsiness	46	58
Visual disturbances	41	52
Amnesia	35	44
Unconsciousness	36	46
Lightheadedness	26	33
Hunger	24	30
Paresthesias	20	25
Headache	16	20
Seizures	15	19

symptoms were usually progressive, provoked by fasting, and at worst, occurred daily or weekly. 96% of the patients had neuroglycopenic symptoms, and 77% had autonomic symptoms. The most common presenting symptoms were confusion (86%), drowsiness (58%), and excessive sweating (57%). Weight gain was documented in 56% of the patients, of whom one-third gained weight more than 10 kilograms.

Of the two patients without hypoglycemic symptoms prior to the diagnosis of insulinoma, one was found in connection with the MEN1-investigations of the patient's sibling, and the symptoms related to hypoglycemia first appeared 3 years after the diagnosis. The other patient presented with jaundice and diarrhea related to a pancreatic tumour. The tumour was operated on, and hypoglycemic symptoms and verified hyperinsulinemic hypoglycemia did not occur until 8 months after the primary operation, when liver metastases were detected.

3.3. Laboratory Findings. In all except the two patients described above, hypoglycemia had been detected, either spontaneously or in a fasting test, prior to the insulinoma diagnosis. The median lowest spontaneous plasma glucose was 2.0 (1.3, 4.9) mmol/l ($n = 62$). The median glycated hemoglobin (HbA1c) value at diagnosis was 4.9% (3.7, 5.7; $n = 31$). Hyperinsulinemic hypoglycemia was verified in 65 (82%) of the patients, either spontaneously, during a fasting test, or during a prolonged OGTT.

Sixty-five patients underwent a fasting test, aiming at a 24, 36, or 72-hour fasting time. Data for analysis was available on 64 patients. In the fasting test, the median plasma glucose nadir was 2.2 (0.8, 4.5) mmol/l ($n = 64$), and the corresponding serum insulin 16 (1.5, 154) mU/l ($n = 55$) and C-peptide 0.9 (0.3, 4.4) nmol/l ($n = 44$). The criteria for endogeneous hyperinsulinemic hypoglycemia by the Endocrine Society [7] were met in 92% of the tests, after a median fasting time of 14 (0, 36) hours. In 5 patients, the criteria were not met, but in three of them, the test was interrupted prematurely. Eleven (14%) patients underwent a prolonged OGTT, and three of these tests verified hyperinsulinemic hypoglycemia.

3.4. Imaging Methods. The tumour was localized preoperatively in 59 (75%) of the patients. In 9 (11%) of the patients, the imaging results were indefinite, and in 11 (14%) negative. A median of 3 imaging modalities was used per patient (1, 7). The most frequently used imaging modalities were CT scan, angiography, MRI, EUS, and ^{18}F-DOPA-PET/CT, of which EUS, ^{18}F-DOPA-PET/CT, and MRI were the most successful ones, with overall sensitivities of 78, 55, and 50%, respectively. A CT scan was performed on 90% of the patients, and the sensitivity of CT scanning improved remarkably under the study period, from 6% in the 1980s to 51% in the 2000s ($p = 0.001$). The overall imaging sensitivity improved during the study period from 39% in the 1980s to 98% in the 2000s ($p < 0.001$) (Table 3). EUS had the best sensitivity (78%) for detecting small tumours (diameter of 1 cm or less), while the sensitivities of other modalities were 43% for ^{18}F-DOPA-PET/CT, 40% for MRI, 33% for octreotide scintigraphy, 23% for CT, and 0% for transabdominal US. Intraoperative US was performed in 19 patients, with an overall success rate of 79%.

3.5. Medical Treatment. Fifty-five (70%) of the patients used preoperative medication: 47 (59%) used diazoxide, 10 (13%)

Table 3: The imaging methods used and their sensitivities in the localization of insulinomas in Finland 1980–2010.

Localizing method	1980–1989 ($n = 18$)		1990–1999 ($n = 18$)		2000–2010 ($n = 43$)	
	Ratio[a]	%	Ratio	%	Ratio	%
Abdominal US	1/12	8	1/12	8	4/11	36
Angiography	3/14	21	3/9	33	7/11	64
CT scan	1/17	6	3/17	17	19/37	51
EUS	NA		4/6	67	14/17	82
ERCP	0	0	0/2	0	NA	
MRCP	NA		NA		1/1	100
MRI	NA		2/6	33	12/22	55
Octreotide scintigraphy	NA		2/6	33	1/9	11
THPVS	3/4	75	NA		NA	
^{18}F-DOPA-PET/CT	NA		0/1	0	11/19	58
^{18}F-FDG-PET/CT	NA		NA		0/1	0
Overall detection	7/18	39	10/18	56	42/43	98

[a]Ratio indicates the proportion of patients in whom the imaging method was successful in localizing the insulinoma. US indicates ultrasonography; CT: computed tomography; EUS: endoscopic ultrasonography; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; THPVS: transhepatic portovenous sampling; ^{18}F-DOPA-PET: ^{18}F-dihydroxyphenylalanine positron emission tomography; ^{18}F-FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography; NA: not applicable.

Table 4: Surgical treatment of insulinoma patients in Finland 1980–2010.

Surgical procedure	1980–1989 ($n = 13$)		1990–1999 ($n = 19$)		2000–2010 ($n = 41$)		Total ($n = 73$)	
	n	%	n	%	n	%	n	%
Tumour enucleation	4	31	11	58	16	39	31	43
Distal resection	8	61	5	26	20	49	33	45
Pancreaticoduodenectomy	1	8	3	16	5	12	9	12

used a somatostatin analogue, and 4 (5%) used both compounds. The median maintenance dose of diazoxide was 150 (25, 600) mg/day, and a favorable response (relief of symptoms and/or improvement of plasma glucose levels) to diazoxide was documented in 19 (63%) of the 30 patients with data available.

3.6. Surgery. Seventy-one of the 79 (90%) patients underwent pancreatic surgery with a curative aim, two (3%) had palliative surgery of the primary tumour, and six cases (8%) were inoperable. The operations included 31 enucleations (43%), 33 distal resections (45%), and 9 pancreticoduodenectomies (PDs; 12%). In one of the two patients with palliative pancreatic surgery, also liver resections were performed, to reduce the tumour load.

The median tumour diameter for enucleations tended to be smaller [10 (5, 28) mm] than for distal resections [15 (7, 60) mm] or PDs [15 (5, 26) mm], ($p = 0.073$). Enucleations became slightly more common during the study period, but there was no statistically significant difference in the distribution of surgical procedures between the 1980s, 1990s, and 2000s in the whole cohort (Table 4, $p = 0.355$). In Helsinki University Hospital, where most of the insulinoma operations were performed, the enucleation rate increased from 0 in the 1980s to 44% in the 2000s, and the distal resection rate decreased from 100 to 56%, respectively ($p = 0.021$).

Postoperative hospital mortality was 3% (2/73). Postoperative complications, graded according to the Clavien-Dindo classification [20, 21], occurred in 51% of the patients (Figure 2); CD grade I in 3% and significant CD grades II–IV complications in 45%. The most common postoperative complications were pancreatic fistula (19%), pancreatitis (10%), intra-abdominal abscess (14%), and wound infection (10%). Pancreatic fistulas occurred in 19% of the patients (23% after tumour enucleations, 12% after distal resections, and 33% after PDs, without a significant difference between the surgical methods (ns; $p = 0.293$)). Overall major complications (CD grades III–V) occurred in 16% of enucleations, 24% of distal resections, and 56% of PDs ($p = 0.062$). There was no difference in the Clavien-Dindo grade between the 1980s, 1990s, and 2000s ($p = 0.894$), between the surgical centers ($p = 0.079$) or between the insulinomas classified as malignant and those classified as nonmalignant ($p = 0.488$). The postoperative mortality for insulinoma enucleation was 3%, for distal resection 3%, and for PD 0% ($p = 1.00$). Two patients died during the postoperative hospitalization, both because of surgical complications. One patient with a single insulinoma located in the pancreatic tail died because of bleeding during tail resection. One patient died during a reoperation because of a pancreatic fistula, severe pancreatitis, and sepsis after primary enucleation of a benign insulinoma in the head of the pancreas.

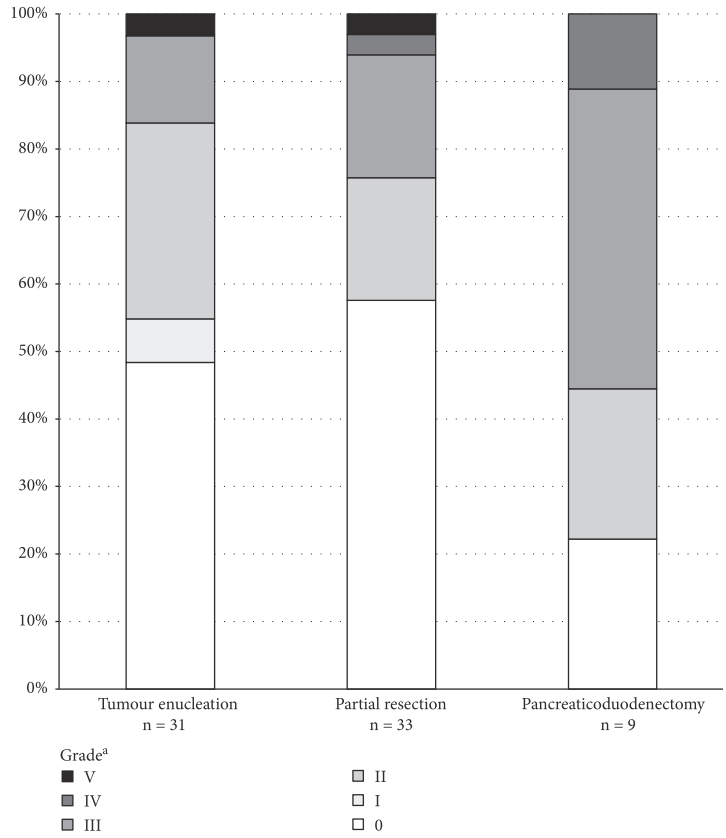


Figure 2: Postoperative overall complications graded according to the Clavien-Dindo classification [20, 21] in the 73 insulinoma patients operated in Finland 1980–2010. [a]Complication grade (0–V) according to the Clavien-Dindo classification, where 0 indicates no complications and V indicates death of the patient. There was no statistically significant difference in the Clavien-Dindo grades between the surgical methods ($p = 0.218$, Fisher exact test).

3.7. Tumour Characteristics. Seventy-three of the 79 patients had a solitary insulinoma, and 5 had multiple tumours (data not available for one patient). In 44% of the patients, the tumour was located in the head of the pancreas, while tumours in the pancreatic tail and body accounted for 27% and 18%, respectively. In 8 patients, the localization of the insulinoma was not documented. The median tumour diameter was 14 (5, 60) mm.

In the patient record and pathology registry data, the insulinomas were classified as benign in 58 (73%), malignant in 11 (14%), and undetermined in 6 (8%) patients, using the contemporary classifications of PNENs. Distant metastases were documented in 9 (11%) patients. In the two patients without distant metastases, the malignant classification was based on a locally invasive growth of the tumour and a relatively high Ki-67 labeling index (9%). Insulin staining was performed in 59 specimens and was positive in all of them. The tumours were also stained positively with other neuroendocrine markers, e.g., chromogranin A (39 positive/42 tested) and synaptophysin (32/35). Ki-67/MIB-1 staining was performed in 29 specimens and was ≤2% in 20 (69%) and ≥5% in 7 (24%) of the tested specimens (min < 1%, max 50%).

3.8. Management and Outcome of Insulinomas Classified as Benign or Undetermined. The median length of follow-up of insulinomas classified as benign was 0.7 (0.1, 26) years and 1.6 (0.2, 31) years for those classified as undetermined. A total of 66 of the 68 patients with nonmalignant insulinomas underwent surgery, and 62 of them had a full recovery. Two patients, as described above, died of surgical complications and one of complications in a diagnostic angiography. In one patient, tumour recurrence was detected 10 years after the primary enucleation of a single benign tumour, located in the head of the pancreas. This patient was treated with somatostatin analogues and a reoperation, and no recurrence was detected during 7.5 years of follow-up after the reoperation. Two patients with benign insulinomas were inoperable

due to other diseases: one of them was treated with diazoxide, and the symptoms did not progress during the 6-year follow-up. The other patient was treated by frequent meals only, during 13 years of follow-up.

3.9. Management and Outcome of Insulinomas Classified as Malignant. The median length of follow-up of the insulinomas classified as malignant was 3 (1, 27) years. Of the 11 patients with a malignant insulinoma, 5 underwent surgery with a curative aim. Two of them had immediate disease progression due to distant metastases (liver and lung, liver and jejunal mesentery): one of them was treated with a somatostatin analogue and the other one with diazoxide, prednisolone, and streptozotocin. Two patients had relapses, 1 year and 5 years after the primary surgery. The first one was operated on the liver metastases, as well as treated with diazoxide, somatostatin analogues, 5-fluorouracil-streptozotocin, epirubicin, and interferon alpha, and the other one was treated with diazoxide, low-dose interferon, and chemoembolization of the liver metastases. One of the insulinomas classified as malignant was cured by surgery. This insulinoma had no distant metastases, but the histopathologic diagnosis of malignancy was based on the local invasion and the relatively high Ki-67 index (9%) of the tumour.

In two patients with malignant insulinoma, distal pancreatic resections were performed as palliative surgery. In both of them, the disease progressed, and the patients died 1.3 years and 4.2 years after surgery. Of the four inoperable malignant insulinomas, all progressed. Medical treatment of these inoperable patients and the patients with palliative surgery included diazoxide ($n = 4$), somatostatin analogues ($n = 5$), radiation therapy of metastases ($n = 2$), 5-fluorouracil-streptozotocin ($n = 3$), sunitinib ($n = 1$), doxorubicin ($n = 1$), doxorubicin-dacarbazine ($n = 1$), interferon alpha ($n = 3$), peroral corticosteroids ($n = 4$), dearterialization and embolization of liver arteries ($n = 1$), chemoembolization of liver metastases ($n = 1$), resection and thermoablation of liver metastases ($n = 1$), and superselective embolization of a branch of the gastroduodenal artery ($n = 1$).

4. Discussion

In this study, we demonstrate an almost two-fold increase in the incidence of insulinomas in Finland, from 0.5/million/year in the 1980s and 0.4/million/year in the 1990s to 0.9/million/year in the 2000s. In spite of the improved diagnostic methods available, the delay from the first symptoms to the diagnosis has remained unchanged over the last three decades (median delay ca. 13 months). Preoperative imaging has improved remarkably, and in the 2000s, all the insulinomas except for one were localized preoperatively. Eighty-nine percent of the patients who underwent surgery with a curative aim had a full recovery, but postoperative complications occurred in half of the patients.

The observed incidence of 0.4–0.9/million adults/year is slightly lower than the estimated incidence of 1–4/million/year suggested in earlier studies [1, 2]. Earlier estimates of the incidence of insulinoma might be incorrectly high because of the selected data of single-center cohorts or data from a limited area. For example, in the large Mayo Clinic study of 224 insulinoma patients treated between 1927 and 1986, the incidence of insulinoma was calculated based on eight detected insulinomas among the residents of Olmsted County [2]. In our study, the incidence of insulinoma increased approximately two-fold during the study period, being 0.9/million adults/year in the 2000s. This may be explained by improved diagnostic methods, especially imaging. An actual increase in the incidence of insulinomas, however, cannot be excluded.

In this cohort, all except two patients had symptomatic hypoglycemia before the diagnosis of insulinoma; in the remaining two patients, the symptoms emerged only after the diagnosis. The median duration of hypoglycemic symptoms before the diagnosis was 13 months, which is slightly shorter than the 18 months reported in previous studies [2, 16]. Thirty-one (39%) of the patients were first examined by other specialities, reflecting the diverse symptoms associated with insulinomas. The episodic symptoms were often interpreted as cerebrovascular disorders, epilepsy, or psychiatric disorders.

In the present cohort, the criteria for hyperinsulinemic hypoglycemia were met in 91% of the fasting tests, and all the positive findings were detected within a 36-hour fast. Our results support the suggestion that the diagnosis of endogeneous hyperinsulinemic hypoglycemia can be achieved in over 90% of cases within 48 hours, and a 48-hour fast could replace the current 72-hour fast as the diagnostic standard [23]. According to a Mayo clinic study, 20% of insulinoma patients have additionally and 6% exclusively postprandial symptoms [24]. In patients with postprandial symptoms only, the corresponding plasma measurements can be performed postprandially or during a prolonged oral glucose tolerance test (OGTT) [1, 7, 25]. In the present cohort, postprandial symptoms were documented in 6 (8%) patients, but all of them had also symptoms provoked by fasting.

In the preoperative localization of insulinomas, noninvasive imaging methods, primarily CT and MRI, are preferred. The lower sensitivity and limited utility in providing additional information have reduced the use of transabdominal US as a diagnostic modality [14]. Invasive localizing methods, including selective angiography, EUS, and selective arterial calcium stimulation (SACS) test, are applied when the noninvasive studies fail to localize an insulinoma. Blind pancreatic resection is not recommended because of a low cure rate and a high risk of complications [26]. In this study cohort, all the aforementioned localizing methods were applied, except for the SACS test, which has also proved to be a sensitive method for localizing insulinoma [27]. During the study period, the preoperative localization of insulinomas improved remarkably, and in the 2000s, up to 98% of the tumours were localized preoperatively. In the 2000s, the most sensitive imaging methods were EUS (sensitivity 82%), selective angiography (64%), ^{18}F-DOPA-PET/CT (58%), MRI (55%), and CT (51%), in accordance with the sensitivities reported in a recent systematic review [14]. ^{68}Ga-NOTA-Exendin-4 PET/CT, a novel technique for localizing insulinomas with a reported sensitivity of 97%, was not available during the study period [28].

Most patients underwent surgery with a curative aim, and 3% had palliative surgery. Typical complications in pancreatic surgery are fistulas, hemorrhages and, delayed gastric emptying [29–31]. Clavien-Dindo classified overall postoperative complications occurred in 51% of the patients, which is slightly more than the complication rate of 33–35% presented in a recent systematic review [14], but similar to the overall complication rates in pancreatic surgery. Postoperative mortality was 3%, which is acceptable and similar to the percentages reported in the systematic review (3.7% for open approach and 0% for laparoscopic approach) [14]. Eighty-nine percent of the patients who underwent curative surgery had a full recovery. The recurrence rate (8%) was comparable to the previously reported 7.2% [14]. Of note, current guidelines suggest enucleation of sporadic small insulinomas (<2 cm), if structural integrity of the pancreatic duct can be maintained [32]. Laparoscopic enucleation is currently considered feasible even in challenging locations, such as the posterior surface of the pancreatic neck [33, 34]. The complication risk associated with enucleations is comparable or even higher than with distal resections and PDs [35, 36]. For MEN1 patients, distal or subtotal pancreatectomy must be considered in multifocal disease, when other pancreatic NENs are present, and in cases with potentially malignant disease.

A major strength of this study is the nationwide data including all insulinomas diagnosed in Finland over three decades. In contrast to many previous studies, we also included inoperable cases, which constituted 6% of the cohort. Collecting nationwide data enabled us to assess the incidence, as well as the evolving methods of diagnostics and treatment of insulinomas, in an unselected cohort of patients.

There are, however, some limitations to this study. Due to the retrospective, register-based design of the study, there was incompleteness in the data, regarding, e.g., the clinical picture and the response to the medical treatment of insulinomas. As the search for insulinomas was carried out on patient and pathology registries and thus depends on correct enrolling of the diagnoses, we may not have found all the insulinomas, especially from the earlier years of the study period. To minimize the loss of cases, a comprehensive search was performed on three separate databases, and all the potential cases found were reviewed. Another limitation is the short follow-up, as patients with a benign insulinoma are followed up at the University Hospitals only for a short time after a successful operation. In case of a possible relapse or disease progression, however, an insulinoma patient would most likely have ended up at one of the five Finnish University Hospitals with a new referral, and the relapse/progression would have been registered in our study. Thirdly, as patient record data from primary health care was not available, we could not distinguish the health care system delay (time from the first consultation of health care providers to the diagnosis) from the total diagnostic delay (from the onset of symptoms) calculated in this study.

5. Conclusions

The incidence of insulinomas has increased during the past three decades. The diagnostic delay has remained unchanged since the 1980s, despite improved imaging. To shorten the diagnostic delay, clinicians should be informed to consider the possibility of hypoglycemia and insulinoma, when symptomatic attacks are investigated in any health care unit. Developing the surgical treatment is another major target in the management of insulinomas, to lower the overall complication rate, while ensuring the high cure rate.

Data Availability

The datasets generated and analysed during the current study are not publicly available, in order to protect patient privacy, as it might be possible to identify the results of an individual patient from this limited group of patients.

Disclosure

The funding organizations had no role in the design, conduct, reporting, or publishing of this research. The research was performed as part of the employment of the first author Elina Peltola as a doctoral (Ph.D.) student at the University of Tampere, Faculty of Medicine and Life Sciences.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the study or its publication.

Acknowledgments

The authors thank Esko Väyrynen, M.A., for revising the language of the manuscript. This work was financially supported by the Competitive Research Funding of the Special Responsibility Area of Tampere University Hospital (9U012) and by the Finnish Medical Foundation.

Supplementary Materials

Diagnosis-based search strategy on patient records 1980–2010. *(Supplementary Materials)*

References

[1] M. Falconi, B. Eriksson, G. Kaltsas et al., "ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors," *Neuroendocrinology*, vol. 103, no. 2, pp. 153–171, 2016.

[2] F. J. Service, M. M. McMahon, P. C. O'Brien, and D. J. Ballard, "Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study," *Mayo Clinic Proceedings*, vol. 66, no. 7, pp. 711–719, 1991.

[3] J. C. Yao, M. Hassan, A. Phan et al., "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States," *Journal of Clinical Oncology*, vol. 26, no. 18, pp. 3063–3072, 2008.

[4] I. M. Modlin, K. Oberg, D. C. Chung et al., "Gastroenteropancreatic neuroendocrine tumours," *The Lancet Oncology*, vol. 9, no. 1, pp. 61–72, 2008.

[5] J. Hallet, C. H. L. Law, M. Cukier, R. Saskin, N. Liu, and S. Singh, "Exploring the rising incidence of neuroendocrine

tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes," *Cancer*, vol. 121, no. 4, pp. 589–597, 2015.

[6] A. Whipple, "The surgical therapy of hyperinsulinism," *Journal International De Chirurgie*, vol. 3, pp. 237–276, 1938.

[7] P. E. Cryer, L. Axelrod, A. B. Grossman et al., "Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline," *The Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 3, pp. 709–728, 2009.

[8] W. W. de Herder, B. Niederle, J. Y. Scoazec et al., "Well-differentiated pancreatic tumor/carcinoma: insulinoma," *Neuroendocrinology*, vol. 84, no. 3, pp. 183–188, 2007.

[9] R. T. Jensen, G. Cadiot, M. L. Brandi et al., "ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes," *Neuroendocrinology*, vol. 95, no. 2, pp. 98–119, 2012.

[10] S. Kauhanen, M. Seppänen, H. Minn et al., "Fluorine-18-l-dihydroxyphenylalanine (^{18}F-DOPA) positron emission tomography as a tool to localize an insulinoma or β-cell hyperplasia in adult patients," *The Journal of Clinical Endocrinology & Metabolism*, vol. 92, no. 4, pp. 1237–1244, 2007.

[11] E. Christ, D. Wild, F. Forrer et al., "Glucagon-like peptide-1 receptor imaging for localization of insulinomas," *The Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 11, pp. 4398–4405, 2009.

[12] O. Eriksson, I. Velikyan, R. K. Selvaraju et al., "Detection of metastatic insulinoma by positron emission tomography with [^{68}ga]exendin-4—a case report," *The Journal of Clinical Endocrinology & Metabolism*, vol. 99, no. 5, pp. 1519–1524, 2014.

[13] P. Nockel, B. Babic, C. Millo et al., "Localization of insulinoma using ^{68}Ga-DOTATATE PET/CT scan," *The Journal of Clinical Endocrinology & Metabolism*, vol. 102, no. 1, pp. 195–199, 2016.

[14] A. Mehrabi, L. Fischer, M. Hafezi et al., "A systematic review of localization, surgical treatment options, and outcome of insulinoma," *Pancreas*, vol. 43, no. 5, pp. 675–686, 2014.

[15] Y. P. Zhao, H. X. Zhan, T. P. Zhang et al., "Surgical management of patients with insulinomas: result of 292 cases in a single institution," *Journal of Surgical Oncology*, vol. 103, no. 2, pp. 169–174, 2011.

[16] M. Nikfarjam, A. L. Warshaw, L. Axelrod et al., "Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital," *Annals of Surgery*, vol. 247, no. 1, pp. 165–172, 2008.

[17] M. Q. de Almeida, M. C. C. Machado, M. L. Correa-Giannella, D. Giannella-Neto, and M. A. A. Pereira, "Endogenous hyperinsulinemic hypoglycemia: diagnostic strategies, predictive features of malignancy and long-term survival," *Journal of Endocrinological Investigation*, vol. 29, no. 8, pp. 679–687, 2006.

[18] M. L. Richards, G. B. Thompson, D. R. Farley et al., "Setting the bar for laparoscopic resection of sporadic insulinoma," *World Journal of Surgery*, vol. 35, no. 4, pp. 785–789, 2011.

[19] E. Uitto, P. Hannula, S. Metso, M. Vornanen, J. Sand, and P. Jaatinen, "Insulinomas in Tampere University Hospital special responsibility area in 1980–2010," *Duodecim*, vol. 131, no. 17, pp. 1598–1604, 2015.

[20] D. Dindo, N. Demartines, and P. A. Clavien, "Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey," *Annals of Surgery*, vol. 240, no. 2, pp. 205–213, 2004.

[21] P. A. Clavien, J. Barkun, M. L. de Oliveira et al., "The Clavien-Dindo classification of surgical complications: five-year experience," *Annals of Surgery*, vol. 250, no. 2, pp. 187–196, 2009.

[22] "Statistics Finland's PX-web databases: population according to age (1-year) and sex in 1970 to 2017," October 2017 http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__vaerak/statfin_vaerak_pxt_001.px/?rxid=cf6d9aa1-91d8-4ea6-8878-f595f6754be5.

[23] B. Hirshberg, A. Livi, D. L. Bartlett et al., "Forty-eight-hour fast: the diagnostic test for insulinoma," *The Journal of Clinical Endocrinology & Metabolism*, vol. 85, no. 9, pp. 3222–3226, 2000.

[24] K. A. Placzkowski, A. Vella, G. B. Thompson et al., "Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007," *The Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 4, pp. 1069–1073, 2009.

[25] X. Li, F. Zhang, H. Chen et al., "Diagnosis of insulinoma using the ratios of serum concentrations of insulin and C-peptide to glucose during a 5-hour oral glucose tolerance test," *Endocrine Journal*, vol. 64, no. 1, pp. 49–57, 2017.

[26] B. Hirshberg, S. K. Libutti, H. R. Alexander et al., "Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure," *Journal of the American College of Surgeons*, vol. 194, no. 6, pp. 761–764, 2002.

[27] G. Braatvedt, E. Jennison, and I. M. Holdaway, "Comparison of two low-dose calcium infusion schedules for localization of insulinomas by selective pancreatic arterial injection with hepatic venous sampling for insulin," *Clinical Endocrinology*, vol. 80, no. 1, pp. 80–84, 2014.

[28] Y. Luo, Q. Pan, S. Yao et al., "Glucagon-like peptide-1 receptor PET/CT with 68Ga-NOTA-exendin-4 for detecting localized insulinoma: a prospective cohort study," *Journal of Nuclear Medicine*, vol. 57, no. 5, pp. 715–720, 2016.

[29] C. Bassi, G. Marchegiani, C. Dervenis et al., "The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after," *Surgery*, vol. 161, no. 3, pp. 584–591, 2017.

[30] M. N. Wente, C. Bassi, C. Dervenis et al., "Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS)," *Surgery*, vol. 142, no. 5, pp. 761–768, 2007.

[31] M. N. Wente, J. A. Veit, C. Bassi et al., "Postpancreatectomy hemorrhage (PPH)—an International Study Group of Pancreatic Surgery (ISGPS) definition," *Surgery*, vol. 142, no. 1, pp. 20–25, 2007.

[32] S. Partelli, D. K. Bartsch, J. Capdevila et al., "ENETS consensus guidelines for the standards of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours," *Neuroendocrinology*, vol. 105, no. 3, pp. 255–265, 2017.

[33] C. Conrad, G. Passot, M. H. G. Katz et al., "Laparoscopic insulinoma enucleation from the retro-pancreatic neck: a stepwise approach," *Annals of Surgical Oncology*, vol. 23, no. 6, p. 2001, 2016.

[34] P. Drymousis, D. A. Raptis, D. Spalding et al., "Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis," *HPB*, vol. 16, no. 5, pp. 397–406, 2014.

[35] S. Crippa, C. Bassi, R. Salvia, M. Falconi, G. Butturini, and P. Pederzoli, "Enucleation of pancreatic neoplasms," *British Journal of Surgery*, vol. 94, no. 10, pp. 1254–1259, 2007.

[36] J. M. Kiely, A. Nakeeb, R. A. Komorowski, S. D. Wilson, and H. A. Pitt, "Cystic pancreatic neoplasms: enucleate or resect?," *Journal of Gastrointestinal Surgery*, vol. 7, no. 7, pp. 890–897, 2003.

SUPPLEMENTARY MATERIAL

Diagnosis-based search strategy on patient records 1980–2010

ICD 8th revision (from 1 January 1980 to 31 December 1986):

- 211,6 Benign neoplasm of other parts of digestive system: pancreas OR
- 251 Disorders of pancreatic internal secretion other than diabetes mellitus (including 251,0 Insuloma and 251,02 Insuloma)

ICD 9th revision (from 1 January 1987 to 31 December 1995):

- 1574 Malignant neoplasm of islets of Langerhans OR
- 2117 Benign neoplasm of islets of Langerhans OR
- 2511 Other specified hypoglycemia (including 2511A Hyperinsulinism)

ICD 10th revision (from 1 January 1996 to 31 December 2010):

- C25.4 Malignant neoplasm of endocrine pancreas OR
- D13.6 Benign neoplasm of pancreas OR
- D13.7 Benign neoplasm of endocrine pancreas OR
- E16.1 Other hypoglycemia (including E16.10 Hyperinsulinism)

The case histories of all the patients identified by the searches on patient records, pathology registries and the Finnish Cancer Registry were reviewed, and only cases fulfilling the inclusion criteria of the present study were analysed (see Inclusion Criteria in Subjects and Methods).

PUBLICATION II

Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010

Peltola, E., Hannula, P., Huhtala, H., Sintonen, H., Metso, S., Sand, J., Laukkarinen, J., Tiikkainen, M., Schalin-Jäntti, C., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Ebeling, T., and Jaatinen, P.

Clinical Endocrinology, 94(2), 250-257
doi:10.1111/cen.14336

Received: 9 June 2020 | Revised: 18 August 2020 | Accepted: 10 September 2020

DOI: 10.1111/cen.14336

ORIGINAL ARTICLE

WILEY

Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010

Elina Peltola[1,2] | Päivi Hannula[1,3] | Heini Huhtala[4] | Harri Sintonen[5] | Saara Metso[1,3] | Juhani Sand[6] | Johanna Laukkarinen[1,6] | Mirja Tiikkainen[7] | Camilla Schalin-Jäntti[7,8] | Jukka Sirén[9] | Minna Soinio[10] | Pirjo Nuutila[10,11] | Leena Moilanen[12] | Tapani Ebeling[13,14] | Pia Jaatinen[1,2,3]

[1]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[2]Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

[3]Endocrinology, Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

[4]Faculty of Social Sciences, Tampere University, Tampere, Finland

[5]Department of Public Health, University of Helsinki, Helsinki, Finland

[6]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland

[7]Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

[8]Endocrinology, Abdominal Center, University of Helsinki, Helsinki, Finland

[9]Surgery, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

[10]Endocrinology, Department of Internal Medicine, Turku University Hospital, Turku, Finland

[11]Faculty of Medicine, University of Turku, Turku, Finland

[12]Department of Medicine, Kuopio University Hospital, Kuopio, Finland

[13]Faculty of Medicine, University of Oulu, Oulu, Finland

[14]Endocrinology, Department of Medicine, Oulu University Hospital, Oulu, Finland

Correspondence
Elina Peltola, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.
Email: elina.peltola@tuni.fi

Funding information
Helsinki University Hospital Research Funds, Grant/Award Number: TYH2019254; Medical Research Fund of Seinäjoki Central Hospital, Grant/Award Number: 1717/6043 and 1717/6080; Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, Grant/Award Number: 9U012 and 5900/3225; Finska Läkaresällskapet

Abstract

Objective: Insulinomas are rare pancreatic neoplasms, which can usually be cured by surgery. As the diagnostic delay is often long and the prolonged hyperinsulinemia may have long-term effects on health and the quality of life, we studied the long-term health-related quality of life (HRQoL) in insulinoma patients.

Design, patients and measurements: The HRQoL of adults diagnosed with an insulinoma in Finland in 1980-2010 was studied with the 15D instrument, and the results were compared to those of an age- and gender-matched sample of the general population. The minimum clinically important difference in the total 15D score has been defined as ±0.015. The clinical characteristics, details of insulinoma diagnosis and treatment, and the current health status of the subjects were examined to specify the possible determinants of long-term HRQoL.

Results: Thirty-eight insulinoma patients participated in the HRQoL survey (response rate 75%). All had undergone surgery with a curative aim, a median of 13 (min 7, max 34) years before the survey. The insulinoma patients had a clinically importantly

and statistically significantly better mean 15D score compared with the controls (0.930 ± 0.072 vs 0.903 ± 0.039, $P = .046$) and were significantly better off regarding mobility, usual activities and eating. Among the insulinoma patients, younger age at the time of survey, higher level of education and smaller number of chronic diseases were associated with better overall HRQoL.

Conclusions: In the long term, the overall HRQoL of insulinoma patients is slightly better than that of the general population.

KEYWORDS

hyperinsulinism, hypoglycaemia, insulin, insulinoma, neuroendocrine tumors, pancreas, quality of life

1 | INTRODUCTION

Insulinomas are the most common functioning endocrine neoplasms of the pancreas, with an estimated incidence of 1-3 per million per year. Over 90% of insulinomas are benign, and a vast majority of them are completely cured by surgery.[1-3] Patients with a malignant insulinoma have a median survival of less than 2 years.[2] Despite the improved diagnostic options, the diagnostic delay has remained long,[4] and little is known about the long-term prognosis of patients with an insulinoma.

Studies on the health-related quality of life (HRQoL) of patients with gastroenteropancreatic neuroendocrine neoplasms or tumours (GEP-NENs, GEP-NETs) are scarce. In the existing studies, the methods and the quality of processing and reporting the HRQoL data vary.[5] According to a recent review, despite the generally good HRQoL, patients with metastatic well-differentiated GEP-NETs have specific psychological and physical complaints.[6] Impairments in multiple domains of HRQoL, such as emotional, role and social functioning, as well as impaired excretion have been reported in GEP-NET patients, compared to the general population.[5,7-9] The HRQoL of insulinoma patients has not been studied before. The aim of this study was to evaluate the long-term HRQoL in a nationwide Finnish insulinoma cohort,[4] and to investigate the factors determining the HRQoL of patients with a previously treated insulinoma.

2 | SUBJECTS AND METHODS

2.1 | Study populations and protocol

In our previous retrospective study on insulinoma, we described the incidence, clinical picture, diagnostics and treatment of all adult Finnish patients diagnosed with an insulinoma in 1980-2010.[4] The research register includes data on the clinical picture, laboratory findings, imaging, pathology, surgical and medical treatment, and the follow-up of the patients with an insulinoma. The decisions on the treatment and follow-up of insulinoma patients were made by a multidisciplinary expert team in one of the five University Hospitals in Finland. After curative resection of a sporadic insulinoma, usually no long-term follow-up investigations were organized, whereas patients with a syndromic, advanced or unresectable insulinoma were actively followed up at the University Hospital, usually every 3 to 12 months. Postoperative dietetic consultation was offered to patients with secondary diabetes and/or exocrine pancreatic insufficiency.

In the present study, the HRQoL of the Finnish insulinoma cohort was assessed with a self-administered 15D instrument, as well as a questionnaire on current health and medication. The questionnaires were sent by mail to all living insulinoma patients of the cohort in September 2017. A second letter was sent to all nonrespondents in October 2017. Address information of the study population was obtained from the Population Register Centre. Each participant of the study gave written informed consent and a permission to combine the information received from the questionnaires with the data in the previously created register. Participation was voluntary, free of charge and uncompensated.

The results obtained from the participants with the 15D instrument were compared to those of an age- and gender-matched sample of the general population from the National Health 2011 Health Examination survey (controls, n = 4692).[10] After obtaining the questionnaires from the participants, the Finnish insulinoma cohort was divided into the groups of participants, nonparticipants and those deceased before the survey, for demographic and insulinoma-specific descriptions. The regional Ethics Committee of the Tampere University Hospital catchment area and the Finnish Institute for Health and Welfare reviewed and approved the study protocol. Research data are not shared for ethical reasons, in order to protect the anonymity of the patients with a rare endocrine disease.

2.2 | HRQoL and health questionnaires

2.2.1 | The 15D instrument

The 15D instrument is a generic, validated instrument for measuring self-reported HRQoL among adults.[11] It can be used both as a profile and a single index instrument and consists of 15 dimensions

(mobility/moving, vision/seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity), each divided into five grades of severity. For each dimension, the patient chooses the level best describing his or her present health status. To create the 15D profile, within-dimension level values are calculated from the questionnaire on a scale of 0-1, a higher score reflecting better HRQoL on each dimension. The single index 15D score, representing the overall HRQoL, is generated from the dimension level values using a set of population-based preference or utility weights, the maximum 15D score being 1 (no problems on any dimension) and minimum score 0 (equivalent to being dead). The 15D instrument has a high discriminatory power and responsiveness to change.[12,13] The minimum important difference in the 15D score in a cross-sectional setting has been estimated to be ±0.015.[14]

2.2.2 | Health questionnaire

In addition to the 15D instrument, the current state of health of the insulinoma patients was assessed by a health questionnaire. The questionnaire included 14 multiple choice questions concerning demographic characteristics, self-assessed health, follow-up for the insulinoma, glucose metabolism and any chronic diseases the patient has been diagnosed with (Appendix S1: Health Questionnaire). Thirteen of the questions were adapted or modified from questionnaire 1[15] in the National FINRISK 2012 study.[16,17] The participants were also asked about their current height and weight, and their regular medications. The information obtained from the questionnaires was combined with the clinical data of the insulinoma register,[4] to evaluate factors associated with the HRQoL of insulinoma patients.

2.3 | Statistical analysis

The statistical analysis was conducted with IBM SPSS Statistics for Windows, Versions 23.0, and 25.0 (IBM Corp). The data are presented as mean ± standard deviation for 15D scores, median (minimum–maximum) for other numerical variables and number (%) for categorical variables. The characteristics of the participants, the nonparticipants (alive at the time of mailing the questionnaires) and the deceased patients were compared, using the Mann-Whitney *U* test for numerical variables and the Fisher exact test for categorical variables. Body mass indexes (BMI) were calculated, and the weight and BMI at the time of the HRQoL survey were compared with those at clinical insulinoma diagnosis, using the Wilcoxon signed rank test. The mean 15D scores and the 15D profiles between the patients and the controls were compared with the independent samples *t* test. The mean difference in the total 15D score between the patients and the controls was calculated and compared to the minimum clinically important difference, previously defined as ± 0.015.[14] Because of the non-normal distribution of the 15D variables, the analyses were repeated with the Mann-Whitney *U* test.

To examine the factors associated with the HRQoL in insulinoma patients, correlations between demographic and clinical characteristics (acquired from medical reports and the Health Questionnaire) and the 15D scores were analysed. Spearman correlation coefficients were calculated for numerical variables. For binary variables, differences in the 15D scores were analysed with the Mann-Whitney *U* test. Differences in the 15D scores between different surgical methods were analysed with the Kruskal-Wallis test. A two-sided *P* value of <.05 was considered statistically significant.

3 | RESULTS

Of the 51 insulinoma cohort patients alive at time of the HRQoL survey, 38 returned the questionnaires (response rate 75%). The patient characteristics are summarized in Table 1. All the 38 patients participating in the HRQoL study had undergone insulinoma surgery with a curative aim, a median of 13 (7–34) years before the HRQoL survey. The surgical methods included 16 (42%) tumour enucleations, 16 (42%) partial pancreatic resections and 6 (16%) pancreaticoduodenectomies. During the study period, only one laparoscopic operation of insulinoma was performed (data missing for two patients). In 36 of the participants, the insulinoma was regarded as benign, and completely cured by surgery. In one participant, the insulinoma was associated with MEN1 syndrome, but other hereditary tumour syndromes were not diagnosed in any of the participants. Malignant, metastatic insulinomas were detected in two patients. The patients were followed up at the University Hospital for a median of 2 (0-374) months after the surgery, and after that the follow-up was either discontinued or transferred to primary or secondary health care. In the majority (76%) of the participants, the follow-up due to insulinoma had ended by the time of the survey (Table 2).

The demographic and clinical characteristics of the participants, nonparticipants and those deceased before the survey are shown in Table 1. There were no significant differences in any of these characteristics between the participants and the nonparticipants. Among the patients deceased before the survey (n = 28), metastatic disease was significantly more common compared to the participants and nonparticipants (25% vs 5% and 0%, respectively; $P = .026$) and surgery with a curative aim was less common (71% vs 100% and 100%, respectively, $P = .001$).

In the health questionnaire, 74% of the study participants reported that their health was very good or quite good, 24% average, 3% quite bad and none very bad. The median weight 70 (48-147) kg and BMI 25 (19-51) kg/m^2 at the time of the survey were significantly lower than the weight 77 (55-125) kg and BMI 26 (21-39) kg/m^2 at the time of insulinoma diagnosis, $P = .011$ and .014, respectively. Twenty-seven (71%) respondents reported having at least one chronic disease, of which hypertension was the most common one, with a prevalence of 47% (Table 2). There was no significant difference between males and females in the prevalence of any chronic disease. In women, however, the overall number of chronic diseases [2 (0-7) vs 0 (0-3), $P = .031$] and the number of medications in regular use [2 (0-18) vs 0 (0-5), $P = .011$] were significantly higher than in men. One participant (3%) was using

TABLE 1 Characteristics of the patients diagnosed with an insulinoma in Finland during 1980 - 2010

	Participants (n = 38)		Nonparticipants (n = 13)		Deceased patients (n = 28)		Significance
	n/median	%/min–max	n/median	%/min–max	n/median	%/min–max	
Median age, years	64.1	30.9-85.4	72.0	39.1-94.1			
Median age at diagnosis, years	46.4	20.8-75.9	45.6	26.8-83.8	57.2	29.3-79.9	0.462
Median time since diagnosis, years	13.9	6.9-34.4	12.5	7.0-30.4			
Gender (% of all)							
Female	28	74	10	77	17	61	0.516
Male	10	26	3	23	11	39	
Type of surgery (% of all)							
Surgery with a curative aim	38	100	13	100	20	71	0.001*
Palliative surgery	0	0	0	0	2	7	
No surgery	0	0	0	0	6	21	
Surgical method (% of surgically treated)							
Tumour enucleation	16	42	8	62	7	32	0.400
Distal pancreatic resection	16	42	5	38	12	55	
Pancreaticoduodenectomy	6	16	0	0	3	14	
Period of surgery (% of surgically treated)							
1980s	4	11	1	8	8	36	0.092
1990s	9	24	4	31	6	27	
2000s	25	66	8	62	8	36	
Major surgical complications[a] (% of surgically treated)	7	18	3	23	8	36	0.275
Metastasized disease (% of all)	2	5	0	0	7	25	0.026*

Note: Comparison between the participants of the HRQoL survey, the nonparticipants and the deceased patients. The characteristics were compared using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables.

[a]The number of patients with major surgical complications (grades III-V of the Clavien-Dindo classification[18,19]).

*Indicates a statistically significant difference ($P < .05$) between the three groups. Comparison between the participants and the nonparticipants did not show statistically significant differences in any of these characteristics.

combination therapy with metformin and rapid-acting insulin for a suspected secondary diabetes. None of the participants had insulin-dependent diabetes requiring multiple daily injections. Three participants (8%) reported daily use of pancreatic enzyme supplementation, most probably for postoperative exocrine pancreatic insufficiency.

3.1 | HRQoL in insulinoma patients compared with the general population

The patients with a previously treated insulinoma had a higher mean 15D score compared with the age- and gender-matched sample of the general population (0.930 ± 0.072 vs 0.903 ± 0.039, $P = .046$, Figure 1). The mean 15D difference (0.027) exceeded the limit of 0.015 for a minimum clinically important difference,[14] indicating a slightly better HRQoL of the insulinoma patients. Of the individual dimensions, mobility (0.977 ± 0.078 vs 0.911 ± 0.072, $P < .001$), usual activities (0.963 ± 0.096 vs 0.899 ± 0.077, $P = .002$) and eating (1.000 ± 0.000 vs 0.994 ± 0.010, $P = .001$) showed a statistically significant difference between the groups, indicating better self-reported quality of life among the insulinoma patients, compared to the age- and gender-matched control group. Six patients (16%) reported full health on every 15 dimensions. There was no statistically significant impairment on any of the dimensions compared to the general population (Figure 1). The nonparametric tests confirmed the statistically significant differences in the total 15D score 0.956 (0.690-1.000) vs 0.914 (0.780-0.960) and in the dimensions of mobility 1.000 (0.710-1.000) vs 0.932 (0.670-0.990), usual activities 1.000 (0.720-1.000) vs 0.918 (0.620-0.970) and eating 1.000 (1.000-1.000) vs 0.998 (0.950-1.000), $P < .001$ for all comparisons, between the insulinoma patients and the general population.

3.2 | Determinants of the HRQoL in insulinoma patients

Among the patients with a previously treated insulinoma, younger age at the time of survey was associated with a better total 15D score ($r = -0.414$, $P = .010$), as well as with better scores on the dimensions of breathing ($r = -0.409$, $P = .011$), and discomfort

TABLE 2 Demographic data and self-reported chronic diseases of the 38 insulinoma patients participating in the HRQoL survey

	n	%
Marital status		
Married or cohabiting	26	68
Single	3	8
Divorced	4	11
Widowed	5	13
Education		
Lower education	7	18
High school or above	31	82
Follow-up for insulinoma		
Primary healthcare	3	8
Regional hospital	3	8
University hospital	2	5
No follow-up	29	76
Data missing	1	3
Chronic diseases		
Hypertension	18	47
Peripheral joint disease	6	16
Hypercholesterolemia	5	13
Spondyloarthrosis	5	13
Diabetes[a]	4	11
Asthma	4	11
Depression	3	8
Other psychiatric disorder	1	3
Heart failure	1	3
Stroke	1	3
Other chronic diseases[b]	8	21

[a]Including one patient with suspected postoperative secondary diabetes and three patients with type 2 diabetes.

[b]Other chronic diseases included other cardiovascular diseases (n = 3), gastroesophageal reflux disease (n = 2), osteoporosis (n = 2), anaemia, goitre, pain syndrome and diverticulosis (n = 1 each).

and symptoms ($r = -0.327$, $P = .045$). Age at diagnosis, time since diagnosis, time since surgery or diagnostic delay (from the first symptoms up to the clinical diagnosis) had no statistically significant correlation with the total 15D score ($r = -0.246$, $P = .137$; $r = -0.131$, $P = .432$; $r = -0.148$, $P = .375$ and $r = -0.123$, $P = .468$, respectively). BMI correlated negatively with scores on the dimensions of moving ($r = -0.343$, $P = .038$) and breathing ($r = -0.366$, $P = .026$), but not with the total 15D score. Both the number of chronic diseases and the number of medications reported in the health questionnaire negatively correlated with the total 15D score ($r = -0.550$, $P < .001$; $r = -0.573$, $P < .001$, respectively), as well as with HRQoL on the dimensions of moving, seeing, breathing, mental function, discomfort and symptoms, depression and vitality.

There was no significant difference in the mean 15D scores between the patients treated with pancreaticoduodenectomy (0.973 ± 0.033), tumour enucleation (0.932 ± 0.073) and partial pancreatic resection (0.913 ± 0.077, $P = .092$), nor between the patients with or without major surgical complications, classified as grades III-V of the Clavien-Dindo classification[18,19] (0.927 ± 0.075 vs 0.931 ± 0.072, $P = .685$). Likewise, no statistically significant difference was found in the total 15D scores between the patients requiring pancreatic enzyme supplementation and those not using enzyme supplementation (mean 15D score 0.864 ± 0.152 vs 0.936 ± 0.062, $P = .405$). Among the insulinoma patients, there was no significant difference in the total 15D score by gender, cohabiting status or follow-up status (ie whether the follow-up of the insulinoma still continued or not). A higher level of education was associated with a better total 15D score (0.950 ± 0.054 vs 0.844 ± 0.081, $P < .001$), and better scores in breathing (0.961 ± 0.103 vs 0.741 ± 0.114, $P = .002$), discomfort and symptoms (0.865 ± 0.170 vs 0.631 ± 0.255, $P = .027$) and vitality (0.956 ± 0.092 vs 0.769 ± 0.235, $P = .024$). In the patients with hypertension (n = 18), the total 15D score was lower (0.898 ± 0.088) than in the patients without hypertension (0.959 ± 0.036, $P = .017$), and statistically significant impairment was detected on the dimensions of breathing (0.849 ± 0.156 vs 0.985 ± 0.068, $P = .017$), discomfort and symptoms (0.740 ± 0.235 vs 0.896 ± 0.146, $P = .048$) and depression (0.869 ± 0.147 vs 0.977 ± 0.072, $P = .033$). Two of the study participants had a metastatic insulinoma and were followed up after surgical treatment performed with a curative aim several years before the survey. The mean total 15D score of the participants with a metastatic insulinoma was 0.895, and the patients reported impairment on several dimensions of the HRQoL.

4 | DISCUSSION

In the present study, the long-term overall HRQoL of insulinoma patients was slightly better than the HRQoL of the age- and gender-adjusted sample of the general population. Insulinoma patients were doing better with regard to mobility, usual activities and eating and were not inferior to the controls on any dimension of the HRQoL. However, among the insulinoma patients, older age, a lower educational level and a larger number of chronic diseases and medications were associated with impaired HRQoL.

The insulinomas were benign and completely cured by the surgery in 95% of the HRQoL survey respondents, which may explain the good self-reported HRQoL of insulinoma patients in this study. The reason for the better HRQoL of insulinoma patients compared to the general population in this study remains unclear. Our hypothesis is that being cured of a potentially life-threatening disease may have a positive influence on the subjective quality of life of persons with a previous insulinoma in the long term. Similarly to our findings, patients with a curatively treated NEN (n = 83) had a HRQoL similar to or better than the general population, in a previous study of 663 NEN patients.[20] In another study of 217 surgically cured, recurrence-free patients with a pancreatic or periampullary neoplasm, including 68 pancreatic NENs (panNEN), the QoL outcomes were

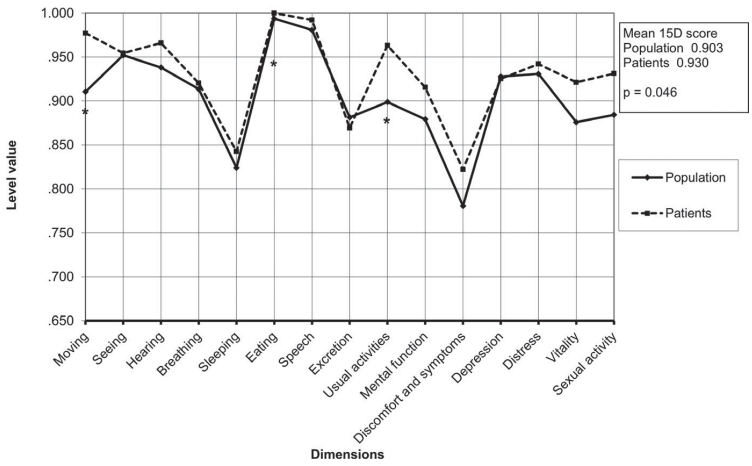


FIGURE 1 The mean 15D HRQoL profiles and the mean total 15D score of persons with a previously treated insulinoma (n = 38) and an age- and gender-matched cohort of the Finnish general population (n = 4692).[10] * indicates a statistically significant difference ($P < .05$) between the groups

comparable to the general population, and the incidence of clinically significant anxiety and depression was low after a median of 53.3 (7.6-214.8) months following the surgery.[21] In subsequent analyses, distal pancreatectomy was an independent predictor of poorer HRQoL and increased anxiety and depression, compared to patients treated with pancreaticoduodenectomy.[21] In our study, no significant difference on HRQoL was found between patients treated with different surgical methods, but the statistical power was limited, as only 38 persons with a previously surgically treated insulinoma participated in the HRQoL survey.

The median weight and BMI of insulinoma patients at the time of survey were significantly lower than at diagnosis, a median of 13.9 years earlier. As weight loss and a lower BMI have been shown to be associated with improved HRQoL,[22] it is possible that the favourable postoperative weight development of insulinoma patients may have contributed to the good overall and physical HRQoL in the long term. Among insulinoma patients, there was a negative correlation between BMI and scores on the dimensions of moving and breathing. The confounding effect of a possible difference in weight between the patients and the controls on HRQoL, however, could not be assessed, as we had no data on the weight or BMI of the controls.

Significantly worse HRQoL scores (especially regarding physical functioning, physical role limitation, general health and vitality) have been reported in patients with a current, not cured NEN compared to the general population.[20,23,24] These studies, however, have not specifically addressed insulinoma or panNEN patients. In our study, only two participants had a metastatic insulinoma, and both of them reported impairment on several dimensions of the HRQoL. Among the deceased patients of the insulinoma cohort, the prevalence of metastatic disease was significantly higher (25%) than in the participants of the HRQoL survey, reflecting the poor survival of patients with a metastatic insulinoma. It is not possible to draw conclusions regarding the impact of malignant insulinomas on HRQoL in the present study, due to the paucity of malignant cases in the long-term survey.

In line with previous studies, age at the time of survey correlated negatively with HRQoL in the present study, especially regarding physical health (dimensions of breathing and discomfort and symptoms).[20,23,24] Similar to some previous studies on NETs,[20,23] we found no clear relationship between HRQoL and time after the insulinoma diagnosis. In our study, the minimum time since diagnosis was relatively long, 6.9 years. We found no correlation between HRQoL and the gender or the cohabiting status of the patients. Similar to our findings, these factors have been unrelated to the HRQoL in a previous study on patients with a NET.[24]

The major strengths of this study are the nationwide data and the high response rate of a rare patient group, with no HRQoL data reported previously. The survey participants were similar to the nonparticipants regarding demographic and insulinoma-specific features. Therefore, the results are likely to represent well the long-term HRQoL of typical insulinoma patients. The HRQoL in this study was assessed with the generic 15D instrument, with a good reliability, validity and sensitivity,[11,14] as well as age- and gender-adjusted reference values from a large, representative sample of the Finnish general population.[10] The 15D has previously proved to be a sensitive instrument for investigating the HRQoL in other endocrine tumour diseases, such as small intestine NENs,[8] thyroid carcinomas,[25] pituitary adenomas[26,27] and primary hyperparathyroidism.[28] The use of validated disease-specific tools in assessing the HRQoL of patients with a GEP-NET has been recommended in recent reviews.[5,6] To date, two GEP-NET-specific HRQoL questionnaires have been introduced: the QLQ-GINET21 applied together with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),[29,30] and the Norfolk QOL-NET.[31] Neither instrument, however, is fully applicable to patients with an insulinoma, as the questionnaires do not address the specific symptoms of insulinoma patients (eg fear of collapses and other hypoglycaemic symptoms).[29-31]

There are also some limitations to this study. Due to the rarity of the disease, the sample size is relatively small. With the small number of malignant cases and only one case associated with the

MEN1 syndrome, we were not able to evaluate comprehensively the HRQoL of patients with a metastatic insulinoma or with a hereditary tumour syndrome. Likewise, the effect of the different pharmacological treatment options of insulinoma, or the effect of complications such as postoperative secondary diabetes or exocrine pancreatic insufficiency, on HRQoL could not be definitively assessed. A larger study population might be needed to detect possible differences in the HRQoL of insulinoma patients treated with different surgical methods. We could not assess the efficacy of the treatment on patients' HRQoL, as we did not measure the HRQoL before surgery. In addition, the confounding effect of other factors, for example a possible difference in weight between the patients and the controls, on HRQoL could not be ruled out. Finally, as the study population consisted of Finnish subjects only, the results might not be directly generalizable to other populations.

In conclusion, the long-term HRQoL of patients with a previously treated insulinoma in Finland was slightly better than that of the general population. No significant difference was found in the long-term HRQoL between the surgical methods used. In the long-term follow-up of patients with a previously treated insulinoma, the prevention and treatment of comorbidities is essential, as the number of chronic diseases and medications are the most important determinants of HRQoL in insulinoma patients.

ACKNOWLEDGEMENTS

The authors thank Antti Piiroinen, MD, Fia Sundelin, MD, and Hanna Hämäläinen, MD, for collecting the insulinoma register data from the patient records in Turku, Oulu and Kuopio University Hospital catchment areas, respectively, and Esko Väyrynen, MA, for revising the language of the manuscript. This work was financially supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (9U012, 5900/3225; EP, PJ), the Medical Research Fund of Seinäjoki Central Hospital (1717/6043, 1717/6080; EP, PJ), the Helsinki University Hospital Research Funds (TYH2019254; CS-J) and Finska Läkaresällskapet (not numbered; CS-J). Harri Sintonen is the developer of the 15D instrument and obtains royalties from its electronic versions. The other authors have stated explicitly that there are no conflicts of interest in connection with this article. The funders had no role in study design, data collection or analysis, decision to publish, or preparation of the manuscript. Research data are not shared for ethical reasons, in order to protect the anonymity of the patients with a rare endocrine disease.

ORCID

Elina Peltola https://orcid.org/0000-0003-3359-7109
Päivi Hannula https://orcid.org/0000-0003-3172-9331
Camilla Schalin-Jäntti https://orcid.org/0000-0002-2428-0161
Pia Jaatinen https://orcid.org/0000-0002-8693-3498

REFERENCES

1. Falconi M, Eriksson B, Kaltsas G, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2016;103(2):153-171.
2. Jensen RT, Cadiot G, Brandi ML, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes. *Neuroendocrinology*. 2012;95(2):98-119.
3. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma–incidence, recurrence, and long-term survival of patients: A 60-year study. *Mayo Clin Proc*. 1991;66(7):711-719.
4. Peltola E, Hannula P, Huhtala H, et al. Characteristics and outcomes of 79 patients with an insulinoma: A nationwide retrospective study in Finland. *Int J Endocrinol*. 2018;2018:1-10.
5. Martini C, Gamper E, Wintner L, et al. Systematic review reveals lack of quality in reporting health-related quality of life in patients with gastroenteropancreatic neuroendocrine tumours. *Health Qual Life Outcomes*. 2016;14(1):127.
6. Jimenez-Fonseca P, Carmona-Bayonas A, Martin-Perez E, et al. Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. *Cancer Metastasis Rev*. 2015;34(3):381-400.
7. Chau I, Casciano R, Willet J, Wang X, Yao JC. Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: A systematic review. *Eur J Cancer Care*. 2013;22(6):714-725.
8. Karppinen N, Linden R, Sintonen H, et al. Health-related quality of life in patients with small intestine neuroendocrine tumors. *Neuroendocrinology*. 2018;107(4):366-374.
9. Sorbye H, Meyer LS, Mordal KE, Myhre S, Thiis-Evensen E. Patient reported symptoms, coping and quality of life during somatostatin analogue treatment for metastatic small-intestinal neuroendocrine tumours. *Health Qual Life Outcomes*. 2020;18(1):188.
10. Koskinen S, Lundqvist A, Ristiluoma N, eds. Health, functional capacity and welfare in Finland in 2011. National Institute for Health and Welfare (THL), Report 68/2012. Helsinki 2012. http://urn.fi/URN:ISBN:978-952-245-769-1. Accessed Jul 2020
11. Sintonen H. The 15D instrument of health-related quality of life: Properties and applications. *Ann Med*. 2001;33(5):328-336.
12. Hawthorne G, Richardson J, Day NA. A comparison of the assessment of quality of life (AQoL) with four other generic utility instruments. *Ann Med*. 2001;33(5):358-370.
13. Moock J, Kohlmann T. Comparing preference-based quality-of-life measures: Results from rehabilitation patients with musculoskeletal, cardiovascular, or psychosomatic disorders. *Qual Life Res*. 2008;17(3):485-495.
14. Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. *Qual Life Res*. 2015;24(3):599-606.
15. The National FINRISK 2012 Study: Questionnaire 1. https://thl.fi/en/web/thlfi-en/research-and-expertwork/population-studies/the-national-finrisk-study/questionnaires. Updated 8 Oct 2019. Accessed Jul 2020
16. Borodulin K, Saarikoski L, Lund L, et al. The National FINRISK 2012 Study - part 1: Study protocol and methods. Raport 22/2013, part I. The National Institute for Health and Welfare (THL). http://urn.fi/URN:ISBN:978-952-302-053-5. Accessed Jul 2020
17. Borodulin K, Levälahti E, Saarikoski L, et al. The National FINRISK 2012 Study - part 2: Tables. Raport 22/2013, part II. The National Institute for Health and Welfare (THL). http://urn.fi/URN:ISBN:978-952-302-054-2. Accessed Jul 2020
18. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. *Ann Surg*. 2009;250(2):187-196.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.

20. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas*. 2012;41(3):461-466.
21. Cloyd JM, Tran Cao HS, Petzel MQB, et al. Impact of pancreatectomy on long-term patient-reported symptoms and quality of life in recurrence-free survivors of pancreatic and periampullary neoplasms. *J Surg Oncol*. 2017;115(2):144-150.
22. Kolotkin RL, Andersen JR. A systematic review of reviews: Exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes*. 2017;7(5):273-289.
23. Haugland T, Vatn MH, Veenstra M, Wahl AK, Natvig GK. Health related quality of life in patients with neuroendocrine tumors compared with the general Norwegian population. *Qual Life Res*. 2009;18(6):719-726.
24. Haugland T, Wahl AK, Hofoss D, DeVon HA. Association between general self-efficacy, social support, cancer-related stress and physical health-related quality of life: A path model study in patients with neuroendocrine tumors. *Health Qual Life Outcomes*. 2016;14:11.
25. Pelttari H, Sintonen H, Schalin-Jäntti C, Välimäki MJ. Health-related quality of life in long-term follow-up of patients with cured TNM stage I or II differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)*. 2009;70(3):493-497.
26. Karppinen A, Ritvonen E, Roine R, et al. Health-related quality of life in patients treated for nonfunctioning pituitary adenomas during the years 2000–2010. *Clin Endocrinol (Oxf)*. 2016;84(4):532-539.
27. Ritvonen E, Karppinen A, Sintonen H, et al. Normal long-term health-related quality of life can be achieved in patients with functional pituitary adenomas having surgery as primary treatment. *Clin Endocrinol (Oxf)*. 2015;82(3):412-421.
28. Ryhänen EM, Heiskanen I, Sintonen H, Välimäki MJ, Roine RP, Schalin-Jäntti C. Health-related quality of life is impaired in primary hyperparathyroidism and significantly improves after surgery: A prospective study using the 15D instrument. *Endocr Connect*. 2015;4(3):179-186.
29. Davies AHG, Larsson G, Ardill J, et al. Development of a disease-specific quality of life questionnaire module for patients with gastrointestinal neuroendocrine tumours. *Eur J Cancer*. 2006;42(4):477-484.
30. Yadegarfar G, Friend L, Jones L, et al. Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. *Br J Cancer*. 2013;108(2):301-310.
31. Vinik E, Carlton CA, Silva MP, Vinik AI. Development of the Norfolk quality of life tool for assessing patients with neuroendocrine tumors. *Pancreas*. 2009;38(3):e87-95.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Peltola E, Hannula P, Huhtala H, et al. Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010. *Clin Endocrinol (Oxf)* 2021;94:250–257. https://doi.org/10.1111/cen.14336

PUBLICATION III

Long-term morbidity and mortality in patients diagnosed with an insulinoma

Peltola, E., Hannula, P., Huhtala, H., Metso, S., Sand, J., Laukkarinen J., Tiikkainen, M., Sirén, J., Soinio, M., Nuutila, P., Moilanen, L., Laaksonen, D. E., Ebeling, T., Arola, J., Schalin-Jäntti, C., and Jaatinen, P.

European Journal of Endocrinology, 185(4), 577-586
doi:10.1530/EJE-21-0230

Long-term morbidity and mortality in patients diagnosed with an insulinoma

Elina Peltola[1,2], **Päivi Hannula**[1,3], **Heini Huhtala**[4], **Saara Metso**[1,3], **Juhani Sand**[5], **Johanna Laukkarinen**[1,5], **Mirja Tiikkainen**[6], **Jukka Sirén**[7,8], **Minna Soinio**[9], **Pirjo Nuutila**[10,11], **Leena Moilanen**[12], **David E Laaksonen**[12], **Tapani Ebeling**[13,14], **Johanna Arola**[15,16], **Camilla Schalin-Jäntti**[6,17] and **Pia Jaatinen**[1,2,3]

[1]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, [2]Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland, [3]Endocrinology, Department of Internal Medicine, Tampere University Hospital, Tampere, Finland, [4]Faculty of Social Sciences, Tampere University, Tampere, Finland, [5]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland, [6]Endocrinology, Abdominal Center, [7]Surgery, Abdominal Center, Helsinki University Hospital, Helsinki, Finland, [8]Surgery, Abdominal Center, University of Helsinki, Helsinki, Finland, [9]Department of Endocrinology, [10]Department of Endocrinology, Division of Medicine, Turku University Hospital, Turku, Finland, [11]Turku PET Centre, University of Turku, Turku, Finland, [12]Department of Medicine, Kuopio University Hospital, Kuopio, Finland, [13]Faculty of Medicine, University of Oulu, Oulu, Finland, [14]Endocrinology, Department of Medicine, Oulu University Hospital, Oulu, Finland, [15]Pathology, HUSLAB, Helsinki University Hospital, Helsinki, Finland, [16]Pathology, University of Helsinki, Helsinki, Finland, and [17]Endocrinology, Abdominal Center, University of Helsinki, Helsinki, Finland

Correspondence should be addressed to E Peltola
Email
elina.peltola@tuni.fi

European Journal of Endocrinology

Abstract

Objective: Insulinomas are rare functional pancreatic neuroendocrine tumours. As previous data on the long-term prognosis of insulinoma patients are scarce, we studied the morbidity and mortality in the Finnish insulinoma cohort.
Design: Retrospective cohort study.
Methods: Incidence of endocrine, cardiovascular, gastrointestinal and psychiatric disorders, and cancers was compared in all the patients diagnosed with an insulinoma in Finland during 1980–2010 ($n = 79$, including two patients with multiple endocrine neoplasia type 1 syndrome), vs 316 matched controls, using the Mantel–Haenszel method. Overall survival was analysed with Kaplan–Meier and Cox regression analyses.
Results: The median length of follow-up was 10.7 years for the patients and 12.2 years for the controls. The long-term incidence of atrial fibrillation (rate ratio (RR): 2.07 (95% CI: 1.02–4.22)), intestinal obstruction (18.65 (2.09–166.86)), and possibly breast (4.46 (1.29–15.39) and kidney cancers (RR not applicable) was increased among insulinoma patients vs controls, $P < 0.05$ for all comparisons. Endocrine disorders and pancreatic diseases were more frequent in the patients during the first year after insulinoma diagnosis, but not later on. The survival of patients with a non-metastatic insulinoma ($n = 70$) was similar to that of controls, but for patients with distant metastases ($n = 9$), the survival was significantly impaired (median 3.4 years).
Conclusions: The long-term prognosis of patients with a non-metastatic insulinoma is similar to the general population, except for an increased incidence of atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers. These results need to be confirmed in future studies. Metastatic insulinomas entail a markedly decreased survival.

European Journal of Endocrinology
(2021) **185**, 577–586

Introduction

Insulinomas are rare insulin-secreting functional pancreatic neuroendocrine tumours, with an estimated incidence of 1–4 per million per year (1, 2, 3, 4). They usually do not show metastatic behaviour and are considered cured after complete surgical removal of the tumour (3, 4, 5). On the other hand, disease recurrence occurs in 7% of the

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-21-0230

surgically treated patients (4), and in patients with distant metastases, the median survival has been reported to be less than 2 years (2).

Despite the improved diagnostic options, the diagnostic delay of insulinomas has remained long, presumably due to the rarity of the disease and the nonspecific clinical picture, as we have shown in our previous study on all adult patients diagnosed with an insulinoma in Finland during 1980–2010 (6). Because previous data on the long-term prognosis of insulinoma patients are scarce, we wanted to study the long-term morbidity and mortality in the Finnish insulinoma cohort (6).

Subjects and methods

The Finnish insulinoma register consists of all adult patients (≥18 years of age) diagnosed with an insulinoma in Finland during 1980–2010 ($n=79$) (6). For each patient, four controls were chosen from the Finnish Population Register Centre. The controls had to be equal by age (±6 months), gender, and the place of residence, and alive at the diagnosis of the corresponding patient. The dates of death or emigration were provided by the Finnish Population Register Centre. Personal identification numbers assigned to all Finnish residents were used to link the information from the separate registers described below. The register-based follow-up began on 1 January 1980 and lasted until 31 December 2015, unless death or emigration occurred first.

The morbidity of insulinoma patients vs controls was analysed before and after the diagnosis of insulinoma, focusing on five distinct disease groups: endocrine, gastrointestinal, cardiovascular, cancer, and psychiatric diseases, to evaluate the potential comorbidity and long-term effects of insulinoma on the development of these diseases. Cancer morbidity was evaluated based on the cancer diagnoses registered at the Finnish Cancer Registry, where Finnish health care organizations statutorily provide information on all new cancer cases. Insulinoma-related notifications were excluded from the analyses.

Morbidity due to endocrine, cardiovascular, gastrointestinal, and psychiatric disorders was evaluated on the basis of the diagnoses registered at the National Hospital Discharge Register, the Care Register for Health Care. This register, maintained by the Finnish Institute of Health and Welfare, collects the statutory data on all Finnish residents discharged from inpatient care in any Finnish hospital since 1969 and on outpatient visits in specialized health care since 1998. The diagnoses are coded according to the Finnish version of the 10th revision of the International Classification of Diseases (ICD-10) since 1996, ICD-9 during 1987–1995, and ICD-8 during 1980–1986. These classifications were reviewed, and the diagnoses of interest were grouped into corresponding disease categories and subcategories (Supplementary Table 1, see section on supplementary materials given at the end of this article). Both the primary and the secondary diagnoses were included in the analyses, and the diagnosis codes for hyperinsulinism and hypoglycaemia were excluded from the analysis of endocrine disorders.

For the mortality analyses, the causes of death were obtained from Statistics Finland, which collects the dates and causes of death of all Finnish citizens deceased since 1971. The causes of death are classified according to the ICD, as well as with a national time series classification, including 54 categories. In the analyses, we used the underlying cause of death, defined as the disease that has initiated the series of illnesses directly leading to death.

This study was conducted in accordance with the Declaration of Helsinki. The Regional Ethics Committee of the Tampere University Hospital catchment area reviewed and approved the study protocol. Informed consent was waived because of the retrospective, register-based nature of the study, and the fact that many of the study subjects died before data collection for the study. The Finnish Institute for Health and Welfare, the University Hospitals of Tampere, Helsinki, Kuopio, Oulu and Turku, Statistics Finland, and the Finnish Population Register Centre yielded permission for the use of data from their registers. Research data are not shared for ethical reasons, to protect the anonymity of patients with a rare disease.

Statistical analysis

The analyses were conducted with the IBM SPSS Statistics for Windows, Versions 25.0 and 27.0 (IBM Corp.), the STATA Statistical Software, Release 13 (StataCorp LP), and the OpenEPI Collection of Epidemiologic Calculators, Version 3.01. The data are presented as mean (S.D.) for normally distributed variables, median (minimum–maximum) for other numerical variables, and number (%) for categorical variables.

In the morbidity analyses, the prevalence of diseases diagnosed before the diagnosis of insulinoma was first compared between the patients and the controls with the Fisher's exact test and conditional logistic regression. Then, the incidence rates of these disease groups after the diagnosis of insulinoma were compared by analysing the incidence rate ratios (RR) and 95% CIs, using the Mantel–Haenszel method. Because only the first notification of each

disease category per person was included in the analyses, the patients with a disease registered before the diagnosis of insulinoma were excluded from the incidence calculations of that disease category, together with their controls. The controls with a given disease diagnosed before the index date were excluded from the analyses individually. For diseases with a statistically significant difference in the patients vs controls, a sensitivity analysis was performed, excluding the MEN1 patients and their controls, as well as the persons with each disease diagnosed within the first year after insulinoma diagnosis, to eliminate detection bias. The Bonferroni correction was applied to define the level of significance for multiple comparisons.

The overall survival of the patients vs controls was compared using Kaplan–Meier analysis with the log-rank test. Insulinomas were retrospectively classified according to their highest diameter (≥ vs <2 cm) and staged according to the most recent TNM classification system (7). Cox regression analyses were used to calculate the hazard ratios (HR), to identify factors associated with mortality among the patients. The distribution of the causes of death was compared with the Fisher's exact test. For the patients who underwent curative-intent surgery, disease-free survival was calculated from the date of primary surgery to the date of disease progression or relapse. In the survival analyses, a two-sided *P* value below 0.05 was considered statistically significant.

Results

Follow-up data of all the 79 patients and their 316 controls were included in the study. The mean age at the insulinoma diagnosis was 51.7 (15.6) years in the patients and 51.7 (15.5) years in the controls. The median duration of symptoms before the diagnosis was 13.0 (0.1–243.5) months. The median duration of the register-based follow-up between 1 January 1980, and the date of diagnosis of insulinoma was 22.7 (0.5–30.8) years for both the patients and the controls, and the median duration of follow-up after the diagnosis of insulinoma was 10.7 (0.2–32.6) years for the patients and 12.2 (1.2–35.5) years for the controls. A metastatic insulinoma was detected in nine (11%) patients. Multiple endocrine neoplasia type 1 (MEN1) syndrome was diagnosed in two patients, both associated with a non-metastatic, solitary insulinoma.

Long-term morbidity

Before the diagnosis of insulinoma, there was no statistically significant difference in morbidity between the patients and the controls (Supplementary Table 2). After the diagnosis of insulinoma, the overall incidence of any cardiovascular disease and the incidence of atrial fibrillation were increased in the patients vs controls, although the increase was not significant after the Bonferroni correction (Fig. 1A and Table 1). In the Kaplan–Meier analysis, the difference in the cumulative incidence of atrial fibrillation in the patients vs controls increased gradually after the diagnosis of insulinoma (Fig. 1B). A sensitivity analysis excluding the first year after insulinoma diagnosis showed a trend towards an increased incidence of atrial fibrillation in the insulinoma patients, but this difference was not statistically significant (Table 2).

Regarding endocrine morbidity (Fig. 1C), the overall incidence of endocrine and thyroid disorders was higher in the patients than in the controls (Fig. 1C and Table 1). The thyroid diagnoses included hypothyroidism in three (4%), hyperthyroidism in two (3%), and goitre in one (1%) of the patients, compared to six (2%), two (1%), and two (1%) of the controls, respectively. In the Kaplan–Meier analysis, the cumulative incidence of thyroid disorders in the patients vs controls started to increase right from the diagnosis of insulinoma (Fig. 1D). After excluding the

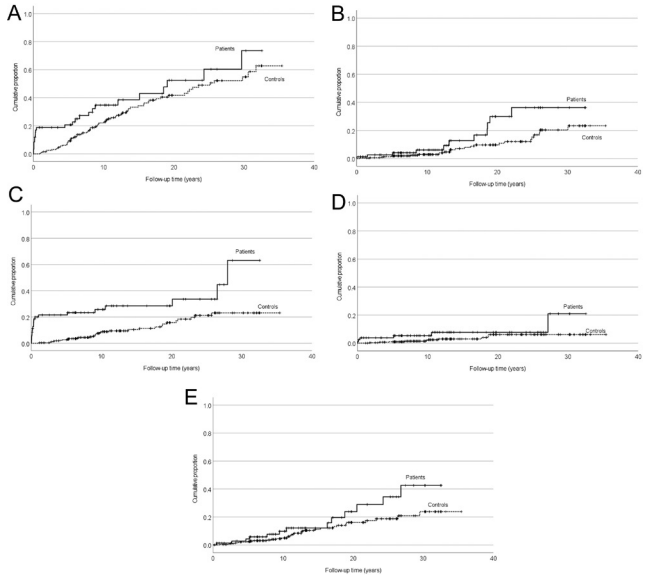


Figure 1
(A, B, C, D and E) Cumulative incidence of cardiovascular, endocrine, and cancer diseases in the patients (solid line) diagnosed with an insulinoma Finland during 1980–2010, compared with controls (dashed line) matched for age, gender, and the place of residence (log-rank test). (A) Cardiovascular diseases ($P = 0.048$), (B) atrial fibrillation ($P = 0.024$), (C) endocrine disorders ($P < 0.001$), (D) thyroid disorders ($P = 0.047$), (E) cancers ($P = 0.061$).

Table 1 Incidence of endocrine, cardiovascular, gastrointestinal, and psychiatric disorders in the 79 patients diagnosed with an insulinoma in Finland during 1980–2010, and in 316 matched controls, after the diagnosis of insulinoma.

	Patients			Controls			Patients vs controls		
Disease	*n*/*n* at risk	Incidence rate/ 10 000/year	95% CI	*n*/*n* at risk	Incidence rate/ 10 000/year	95% CI	Rate ratio	95% CI	*P* value
Endocrine disorders[a]	21/72	295.37	192.58–453.01	32/273	84.58	59.81–119.60	3.49	2.01–6.06	**<0.001**
Diabetes	8/75	89.05	44.53–178.07	22/294	53.36	35.14–81.04	1.67	0.74–3.75	0.210
Thyroid disorders	6/79	61.72	27.73–137.39	10/311	22.35	12.02–41.55	2.76	1.00–7.60	**0.040**
Parathyroid disorders	2/79	20.16	5.04–80.61	0/315	0.00	0.00–7.97	NA		
Other endocrine disorders[b]	11/76	130.00	70.65–230.00	1/301	2.27	0.32–16.14	56.12	7.25–434.67	**<0.001**
Cardiovascular diseases	24/59	423.26	283.70–631.47	70/196	265.79	210.28–335.95	1.59	1.00–2.53	**0.047**
Cerebrovascular diseases	7/78	74.27	35.41–155.79	29/305	67.92	47.20–97.73	1.09	0.48–2.50	0.832
Hypertension	15/70	189.95	114.51–315.07	47/265	123.68	92.93–164.61	1.54	0.86–2.75	0.145
Arrhythmias and conduction disorders	15/77	166.75	100.53–276.59	40/299	93.64	68.69–127.65	1.78	0.98–3.22	0.053
Atrial fibrillation and flutter	11/78	117.74	65.20–212.60	25/307	56.75	38.35–83.99	2.07	1.02–4.22	**0.039**
Coronary artery disease	11/77	119.17	66.00–215.19	36/297	87.03	62.77–120.65	1.37	0.70–2.69	0.360
Diseases of the arteries and veins	7/73	78.92	37.62–165.54	30/259	81.56	57.02–116.64	0.97	0.43–2.20	0.938
Valvular diseases and cardiomyopathies	4/76	42.12	15.81–112.23	12/302	27.24	15.47–47.96	1.55	0.50–4.80	0.447
Heart failure	4/77	40.03	15.02–106.66	19/304	42.87	27.34–67.21	0.93	0.32–2.75	0.901
Diseases of the pulmonary circulation	2/79	19.72	4.93–78.84	4/316	8.77	3.29–23.36	2.25	0.41–12.28	0.336
Gastrointestinal diseases	27/67	463.70	318.00–676.16	55/233	175.53	134.76–228.63	2.64	1.67–4.19	**<0.001**
Diseases of the oesophagus, stomach, and duodenum	6/76	63.83	28.68–142.07	22/298	51.70	34.04–78.52	1.24	0.50–3.05	0.647
Abdominal hernias[c]	8/73	91.32	45.67–182.61	19/282	45.96	29.31–72.05	1.99	0.87–4.54	0.097
Chronic inflammatory bowel diseases	0/79	0.00	0.00–35.85	3/315	6.58	2.12–20.39	0.00		0.412
Diseases of the appendix	2/78	20.46	5.12–81.79	8/304	18.32	9.16–36.63	1.12	0.24–5.26	0.889
Other bowel diseases	14/77	156.41	92.63–264.09	30/296	71.68	50.11–102.51	2.18	1.16–4.12	**0.013**
Diseases of the liver, biliary tract, and gallbladder	6/77	65.02	29.21–144.72	20/292	48.18	31.08–74.68	1.35	0.54–3.36	0.518
Diseases of the pancreas[d]	8/78	85.62	42.82–171.20	3/311	6.66	2.15–20.64	12.86	3.41–48.49	**<0.001**
Mental and behavioural disorders	12/71	148.85	84.54–262.11	36/265	98.09	70.76–135.99	1.52	0.79–2.92	0.208
Dementia	4/79	39.64	14.88–105.61	14/312	30.86	18.28–52.11	1.28	0.42–3.90	0.658

Bold values indicate a statistically significant difference between the patients and the controls ($P < 0.05$, Mantel–Haenszel method). When the Bonferroni correction for multiple comparisons is applied, a P value < 0.002 (<0.05/25) is considered statistically significant.

[a]Excluding hyperinsulinism and hypoglycaemia; [b]Other endocrine disorders in the patients included a polyglandular endocrine disorder ($n = 1$) and other or unspecified endocrine disorders ($n = 10$); [c]Abdominal hernias in the patients included seven ventral hernias and one inguinal hernia; [d]Pancreatic diseases in the patients included acute pancreatitis ($n = 6$), pancreatic pseudocyst ($n = 1$), and other/undefined pancreatic disease ($n = 1$).

NA, not applicable.

Table 2 Sensitivity analysis of the incidence of endocrine, cardiovascular, gastrointestinal, and psychiatric disorders in the 77 patients diagnosed with a sporadic insulinoma in Finland during 1980–2010, and in 308 matched controls, after the diagnosis of insulinoma, excluding the first year after diagnosis.

	Patients[a]			Controls			Patients vs controls		
Disease	*n*/*n* at risk[b]	Incidence rate/ 10 000/year	95% CI	*n*/*n* at risk[b]	Incidence rate/ 10 000/year	95% CI	Rate ratio	95% CI	***P*-value**
Endocrine disorders[c]	7/52	107.19	51.10–224.85	27/219	91.76	62.93–133.80	1.17	0.51–2.68	0.714
Thyroid disorders	3/69	34.88	11.25–108.13	9/296	22.87	11.90–43.96	1.53	0.41–5.63	0.524
Parathyroid disorders	1/72	11.07	1.56–78.59	0/308	0.00		NA		
Other endocrine disorders	1/61	12.56	1.77–89.13	1/262	2.74	0.39–19.43	4.59	0.29–73.34	0.236
Cardiovascular diseases	12/44	220.51	125.23–388.29	44/147	227.49	169.29–305.69	0.97	0.51–1.84	0.924
Atrial fibrillation and flutter	10/70	121.66	65.46–226.11	20/274	58.34	37.64–90.42	2.09	0.98–4.46	0.052
Gastrointestinal diseases	13/46	262.06	152.16–451.31	38/175	169.19	123.11–232.51	1.55	0.83–2.91	0.170
Other bowel diseases	11/68	138.54	76.72–250.16	26/279	70.39	47.93–103.38	1.97	0.97–3.98	0.055
Intestinal obstruction	4/72	46.07	17.29–120.00	1/307	2.43	0.34–17.25	18.96	2.12–169.64	**<0.001**
Diseases of the pancreas	1/66	11.99	1.69–85.09	3/263	9.04	2.91–28.02	1.33	0.14–12.75	0.806

Bold value indicates a statistically significant difference between the patients and the controls ($P < 0.05$, Mantel–Haenszel method). When the Bonferroni correction for multiple comparisons is applied, a *P* value <0.005 (<0.05/10) is considered statistically significant.

[a]Two patients with MEN1 syndrome were excluded from the analyses, together with their corresponding controls; [b]Patients with a disease diagnosed before or within 1 year after the diagnosis of insulinoma were excluded from the incidence calculations of that disease category, together with their corresponding controls. Controls with a given disease diagnosed before or within 1 year after the diagnosis of insulinoma of the corresponding patient, as well as patients and controls with an insufficient follow-up time (less than a year after the diagnosis of insulinoma) were excluded individually; [c]Excluding hyperinsulinism and hypoglycaemia.

NA, not applicable.

first post-diagnostic year, no difference was found in the incidence of endocrine or thyroid disorders between the patients and the controls (Table 2). A parathyroid disorder (hyperparathyroidism) was diagnosed in only two (3%) patients, one of them having a confirmed MEN1 syndrome.

As for gastrointestinal diagnoses, the incidence of pancreatic diseases, and bowel diseases other than IBD, hernias, and appendiceal diseases, was increased among the insulinoma patients (Table 1). The increased incidence of pancreatic diseases was explained by acute pancreatitis, usually diagnosed during the first 2 months after the primary pancreatic surgery. In the subgroup analysis of bowel diseases, the only statistically significant difference was an increased incidence of intestinal obstruction, diagnosed in 5% of the surgically treated patients, a median of 5.9 (2.1–11.3) years after primary pancreatic surgery (RR: 18.7 (95% CI: 2.1–166.9), $P < 0.001$).

The incidence of dementia or all mental and behavioural disorders did not significantly differ between the patients and the controls (Table 1). Regarding cancer morbidity, 14 cancers were diagnosed in the patients and 42 in the controls (Fig. 1E and Table 3), after the diagnosis of insulinoma. Of specific cancer types, the incidence of breast and kidney cancers was increased in insulinoma patients vs controls (Table 3). After the exclusion of the 2 MEN1 patients and their controls, however, no statistically significant increase was found in breast cancer incidence (RR 2.64 (0.63–11.04), $P = 0.167$). The breast cancers occurred 4.7–24.3 years after the diagnosis of insulinoma. The three kidney cancers in the patients were diagnosed 2.7, 16.9, and 20.5 years after the diagnosis of a sporadic, non-metastatic insulinoma. Only one of the kidney cancers was detected before the end of insulinoma follow-up at the University Hospital.

Long-term survival

With the three disease progressions and three recurrences detected in the 71 patients treated with curative-intent surgery (6), the 5-, 10-, and 15-years disease-free survival rates were 94, 93, and 90%, respectively. During the follow-up, 25 (32%) patients and 63 (20%) controls deceased. The Kaplan–Meier survival curves of the patients with a non-metastatic or a metastatic insulinoma and their controls are shown in Fig. 2. In a Cox regression analysis, the median overall survival of 27.5 (95% CI: 24.1–30.8) years in the patients with a non-metastatic insulinoma did not significantly differ from the 33.2 (29.8–36.7) years in their controls (HR: 1.5 (0.9–2.6), $P = 0.128$). In the patients with a metastatic insulinoma, the survival was significantly impaired, with a median of 3.4 (2.9–4.0) years vs not

Table 3 Cancer incidence in the 79 patients diagnosed with an insulinoma in Finland during 1980–2010, and in 316 matched controls, after the diagnosis of insulinoma.

	Patients			Controls		Patients vs controls		
Cancer type	*n*/*n* at risk	Incidence rate/ 10 000/year	95% CI	*n*/*n* at risk	Incidence rate/ 10 000/year	95% CI	Rate ratio	95% CI	*P* value
Any cancer	13/77	135.66	78.77–233.63	32/300	74.59	52.75–105.48	1.82	0.96–3.47	0.065
Breast cancer[a]	5/55	71.99	29.96–172.95	5/216	16.15	6.72–38.81	4.46	1.29–15.39	**0.010**
Kidney cancer	3/79	29.64	9.56–91.90	0/315	0.00	0.00–8.00	NA		**<0.001**
Lymphatic and haematopoietic cancers	2/79	19.74	4.94–78.93	9/315	19.76	10.28–37.97	1.00	0.22–4.62	0.999
Prostate cancer[b]	1/23	32.75	4.61–232.47	6/92	44.36	19.93–98.73	0.74	0.09–6.13	0.778
Colon cancer	0/78	0.00	0.00–36.06	4/312	8.74	3.28–23.28	0.00		0.346
Malignant melanoma	0/79	0.00	0.00–35.85	3/316	6.56	2.12–20.34	0.00		0.413
Gastric cancer	0/79	0.00	0.00–35.85	2/315	4.36	1.09–17.44	0.00		0.504
Lung and tracheal cancers	0/79	0.00	0.00–35.85	2/316	4.34	1.09–17.36	0.00		0.505
Ovarian cancer[a]	0/55	0.00	0.00–51.44	2/220	6.31	1.58–25.21	0.00		0.502
Skin cancer (other than melanoma)	0/79	0.00	0.00–35.85	2/316	4.35	1.09–17.38	0.00		0.505
Other cancers[c]	3/79	29.78	9.60–92.33	6/315	13.12	5.90–29.21	2.27	0.57–9.07	0.233

Bold values indicate a statistically significant difference between the patients and the controls ($P < 0.05$, Mantel–Haenszel method). When the Bonferroni correction for multiple comparisons is applied, a P value < 0.004 (<0.05/12) is considered statistically significant.
[a]Only females included; [b]Only males included; [c]Other cancers in the patients included cancers of the thyroid gland, uterus, and pancreas ($n = 1$ each).
NA, not applicable.

reached in the controls (HR: 5.1 (1.9–13.3), $P = 0.001$). Three of the patients with metastatic insulinoma (33%), however, showed a remarkably long survival time of 6–30 years.

In univariate analyses, older age, distant metastases, tumour size ≥ 2 cm, higher preoperative serum insulin concentration, lack of curative-intent surgery, and the need for postoperative medication for the insulinoma were all associated with a significantly decreased overall survival among insulinoma patients (Supplementary Table 3). The occurrence of major surgical complications, classified as grades III–V of the Clavien–Dindo classification (8, 9), was associated with a decreased survival, due to the early postoperative mortality. After the exclusion of postoperative deaths (grade V complication), no significant difference was found in the survival of patients with major vs no or minor surgical complications (HR 2.28 (0.77–6.71), $P = 0.136$). The association of laparoscopic vs open surgery with survival could not be assessed as only two patients underwent laparoscopic insulinoma surgery. In the multivariate analyses, older age and distant metastases were associated with decreased survival (Table 4 and Supplementary Table 4).

Causes of death

Nine of the 25 insulinoma patients who deceased during the study period (36%) died due to an insulinoma-related cause: 6 patients died of metastatic insulinoma, 2 patients died of surgical complications, and 1 patient died due to complications of invasive diagnostics, as previously described (6). With the two deaths due to surgical complications, the perioperative mortality, defined as any death occurring within 30 days after surgery, was 2.7%. The causes of death of the patients and controls are presented in Table 5. During the follow-up, 16 non-insulinoma-related deaths occurred in the patients and 54 in the controls. Of these 16 deaths among the patients, 8 (50%) were due to diseases of the circulatory system, 4 (25%) due to cancer and 4 (25%) due to other causes, compared to 24 (44%), 12 (22%) and 18 (33%) in the controls, respectively ($P = 0.765$). The distribution of the causes of death did not significantly differ between the patients and the controls ($P = 0.363$), analysed according to the national time-series classification of Statistics Finland.

Discussion

This study suggests an increased long-term morbidity in insulinoma patients, due to atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers.

Endocrine and pancreatic diseases were more frequent within the first year after the diagnosis, likely due to a detection bias and the occurrence of short-term surgical complications, respectively. Despite the increased long-term morbidity, the overall survival of patients with non-metastatic insulinoma is similar to the general population. In patients with metastatic insulinoma, the prognosis is significantly impaired.

The long-term morbidity due to any cardiovascular disease, or due to atrial fibrillation was increased among the patients previously diagnosed with an insulinoma. The reason for the increased cardiovascular morbidity in insulinoma patients is unclear. Previous studies have found no association between insulinoma and hypertension (10, 11), but the incidence of atrial fibrillation in insulinoma patients has, to our knowledge, not been studied before. Hypoglycaemia has been shown to induce cardiac arrhythmias in persons with diabetes, but the potential effect of hypoglycaemia on the cardiovascular morbidity of insulinoma patients is unclear (12, 13). Unfortunately, the total burden of hyperinsulinaemia and hypoglycaemia could not be quantified retrospectively in the present study, nor in the previous ones. In our study, the follow-up due to insulinoma may have contributed to the early diagnoses of atrial fibrillation in the patients as the difference between the patients and the controls was no longer statistically significant after excluding the first year after diagnosis.

Morbidity due to any endocrine or thyroid disorders was increased among the patients during the first year after insulinoma diagnosis, but not later on. Although the diagnosis codes for hyperinsulinism and hypoglycaemia were excluded, the substantial number of other or unspecified endocrine disorders diagnosed near the time of diagnosis of insulinoma indicates that these codes may have been used instead of the specific diagnoses for insulinoma. A possible explanation for the increased thyroid morbidity is the careful examination and follow-up of these patients by endocrinologists, contributing to a prompt diagnosis of disorders that may partly remain undiagnosed in the general population.

The incidence of acute pancreatitis and intestinal obstruction was increased among the insulinoma patients vs controls. Most cases of pancreatitis occurred as early postoperative complications, with a rate of 10% in the surgically treated patients, as described previously (6). Intestinal obstruction occurred in 5% of the surgically treated patients, likely as a late postoperative complication of insulinoma surgery. Previous studies on surgically treated insulinomas have mainly focused on short-term complications and have not reported the incidence of late intestinal obstruction in insulinoma patients. In accordance with this study, previous studies have reported similar rates of intestinal obstruction after pancreatic and other abdominal surgery (14, 15, 16).

Morbidity due to breast and kidney cancers also seemed to increase among insulinoma patients. To our knowledge, increased incidence of breast or kidney cancers in insulinoma patients has not been reported before, apart from an increased risk for breast cancer in MEN1 patients (17). The breast and kidney cancers of the patients were diagnosed 2.7–24.3 years after the diagnosis of insulinoma. The MEN1 syndrome explained at least part of the increased morbidity due to breast cancer, and no statistically significant difference was found in the breast cancer incidence of the patients vs controls after the exclusion of MEN1 patients from the analysis. As renal cancers are often discovered incidentally in abdominal imaging (18, 19), we cannot exclude neither a true association of kidney cancer with insulinoma nor an effect of frequent CT scanning. As these results were based on a small number of patients diagnosed with breast or kidney cancer, larger studies are needed to confirm these preliminary findings.

No significant difference was detected in the incidence of dementia or other psychiatric disorders between insulinoma patients and controls. The sample size and the follow-up time in our study may, however, have been insufficient to detect a possible difference. A recent prospective study reported cognitive impairment in 18 of 34 insulinoma patients, measured with the Montreal Cognitive Assessment questionnaire prior to the pancreatic surgery, with improvement detected in most patients at 1 year after surgery (20).

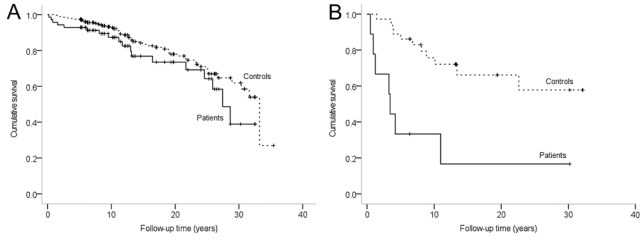


Figure 2

(A and B) Survival of the patients diagnosed with a non-metastatic (A) or a metastatic insulinoma (B) in Finland during 1980–2010, compared with controls matched for age, gender, and the place of residence (log-rank test). (A) Patients with non-metastatic insulinoma vs controls ($P = 0.125$), (B) patients with metastatic insulinoma vs controls ($P < 0.001$).

Table 4 Multivariate analysis of factors associated with mortality among patients diagnosed with an insulinoma in Finland during 1980–2010 ($n = 75$[a]).

Variable	Hazard ratio	95% CI	*P* value
Age at diagnosis	1.05	1.02–1.08	**0.003**
Tumour localization (head/neck vs body/tail)	1.90	0.72–5.03	0.197
Tumour size (≥2 cm vs <2 cm)	2.49	0.93–6.65	0.070
Distant metastases	3.71	1.18–11.67	**0.025**

Bold values indicate a statistically significant hazard ratio ($P < 0.05$, Cox proportional hazards model).
[a]Four of the 79 patients in the total cohort were excluded from this multivariate analysis, due to missing data regarding tumour size ($n = 4$) and localization ($n = 2$).

In the present study, the overall survival of patients with non-metastatic insulinoma did not significantly differ from the general population. The 10-year survival of 87% for non-metastatic and 33% for metastatic insulinomas in this study was similar to the 91 and 29%, respectively, reported previously (1). Similarly to previous studies, older age and metastases were the most important factors associated with an impaired survival (1, 21, 22). In fact, recent evidence suggests that metastatic and non-metastatic insulinomas differ in their origin and pathogenesis and should be regarded as two different diseases (23). An increased risk of insulinoma recurrence and an impaired survival has been reported in MEN1 patients (1). In our study, however, no recurrences were detected during the follow-up of the two MEN1 patients.

Among the surgically treated insulinoma patients, the surgical method or the period of surgery was not associated with the overall survival. The postoperative mortality of 2.7% was slightly lower than the 3.7% reported previously for an open approach (4). Except for the postoperative deaths, no significant association was found between surgical complications and overall survival, which is in line with a recent series of 105 surgically managed pancreatic neuroendocrine tumour patients (24). A recent study of 198 insulinoma patients, however, reported a higher reoperation rate after tumour enucleations compared to pancreatic resections (25). To minimize the complication risks and need for reoperations, the invasive diagnostics and surgical treatment of insulinomas, like all pancreatic tumours, should be performed in centres with adequate expertise (2, 26, 27, 28, 29, 30, 31).

In this study, the median overall survival of 3.4 years in patients with a metastatic insulinoma was similar to the 40 months (3.3 years) reported recently in 31 patients with metastatic insulinomas (32). This is better than the median survival of 29 months (2.4 years) reported earlier (22). Despite the poor overall survival, one-third of the patients with metastatic insulinoma had a remarkably long survival time. Previous studies have shown that palliative debulking surgery, and newer treatment options, such as peptide receptor radionuclide therapy and everolimus, may improve survival and relieve symptoms in patients with metastatic disease (26, 32, 33, 34, 35, 36). Because of the small number of metastatic insulinomas, we were not able to assess the effect of treatment on the survival of patients with metastatic insulinoma.

The major strengths of this study are the nationwide, unselected study cohort, including all the patients diagnosed with an insulinoma in Finland over a 3-decade period, and the long-term follow-up data of the patients and controls, matched for age, gender, and the place of residence. In Finland, it is mandatory to report the underlying causes of death to the Population Information System, and the hospital discharge diagnoses to the National Hospital Discharge Register, contributing to the complete, comprehensive, and high-quality data in these registers (37, 38).

Table 5 Causes of death of the patients diagnosed with an insulinoma in Finland during 1980–2010 and their control group matched for age, gender, and the place of residence. Data are presented as *n* (%).

	Patients ($n = 79$)	**Controls** ($n = 316$)
Deaths related to insulinoma	9 (11.4)	0 (0)
Deaths due to metastatic insulinoma	6 (7.6)	0 (0)
Deaths due to complications of the invasive diagnostics or pancreatic surgery	3 (3.8)	0 (0)
Deaths due to diseases of the circulatory system	8 (10.1)	29 (9.2)
Deaths due to tumours (other than insulinoma)	4 (5.1)	13 (4.1)
Deaths due to other causes	4 (5.1)	21 (6.6)
Alive at the end of follow-up	54 (68.4)	253 (80.1)

The relatively small sample size, due to the rarity of insulinomas, is the major limitation of this study. In addition, the prognosis of the subgroups of patients with metastatic, recurrent, or MEN1-related insulinomas could not be evaluated comprehensively. Due to the retrospective, register-based study design we were not able to specify the causative factors of the long-term morbidity in insulinoma patients. Another limitation is that the National Hospital Discharge Register only includes information on the hospital visits in the specialized health care system, which may lead to underestimation of the incidence of non-severe diseases, treated mainly in the primary health care. On the other hand, detection bias probably contributed to the high incidence of non-severe endocrine disorders near the time of diagnosis of insulinoma in the patients.

In conclusion, the long-term prognosis of patients with a non-metastatic insulinoma seems to be similar to the general population, except for an increased incidence of atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers. Metastatic insulinomas are rare but generally entail a markedly decreased survival. To our knowledge, this is the first study to report findings of increased long-term morbidity in insulinoma patients. In the future, larger studies are needed to confirm these results.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-21-0230.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding
This work was supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grant numbers 9U012, 5900/3225, 6000/3231; to E P, P J), the Medical Research Fund of Seinäjoki Central Hospital (grant numbers 1717/6043, 1717/6080; to E P, P J), the Seinäjoki City and Tampere University Research Funds (not numbered; to E P, P J), the Helsinki University Hospital Research Funds (grant number TYH2019254; to C S-J) and Finska Läkaresällskapet (not numbered; to C S-J). The funders had no role in study design, data collection or analysis, decision to publish, or preparation of the manuscript. Preliminary results of this study have been presented as an e-poster at the eECE2021 congress (39).

Acknowledgements
The authors thank Antti Piiroinen, Fia Sundelin, and Hanna Hämäläinen for collecting the insulinoma register data from the patient records in Turku, Oulu, and Kuopio University Hospital catchment areas, respectively, and Esko Väyrynen for revising the language of the manuscript.

References

1 Service FJ, McMahon MM, O'Brien PC & Ballard DJ. Functioning insulinoma: incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clinic Proceedings* 1991 **66** 711–719. (https://doi.org/10.1016/s0025-6196(12)62083-7)
2 Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012 **95** 98–119. (https://doi.org/10.1159/000335591)
3 Maggio I, Mollica V, Brighi N, Lamberti G, Manuzzi L, Ricci AD & Campana D. The functioning side of the pancreas: a review on insulinomas. *Journal of Endocrinological Investigation* 2020 **43** 139–148. (https://doi.org/10.1007/s40618-019-01091-w)
4 Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, Fonouni H, Golriz M, Garoussi C, Fard N et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas* 2014 **43** 675–686. (https://doi.org/10.1097/MPA.0000000000000110)
5 Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* 2016 **103** 153–171. (https://doi.org/10.1159/000443171)
6 Peltola E, Hannula P, Huhtala H, Metso S, Kiviniemi U, Vornanen M, Sand J, Laukkarinen J, Tiikkainen M, Schalin-Jäntti C et al. Characteristics and outcomes of 79 patients with an insulinoma: a nationwide retrospective study in Finland. *International Journal of Endocrinology* 2018 **2018** 2059481. (https://doi.org/10.1155/2018/2059481)
7 Brierley JD, Gospodarowicz MK, Wittekind C, O'Sullivan B, Mason M, Asamura H, Lee A, Van Eycken E, Denny L, Amin MB et al. *TNM Classification of Malignant Tumours*, 8th ed., pp. 102–103. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc., 2017.
8 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Annals of Surgery* 2009 **250** 187–196. (https://doi.org/10.1097/SLA.0b013e3181b13ca2)
9 Dindo D, Demartines N & Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004 **240** 205–213. (https://doi.org/10.1097/01.sla.0000133083.54934.ae)
10 O'Brien T, Young Jr WF, Palumbo PJ, O'Brien PC & Service FJ. Hypertension and dyslipidemia in patients with insulinoma. *Mayo Clinic Proceedings* 1993 **68** 141–146. (https://doi.org/10.1016/s0025-6196(12)60161-x)
11 Leonetti F, Iozzo P, Giaccari A, Sbraccia P, Buongiorno A, Tamburrano G & Andreani D. Absence of clinically overt atherosclerotic vascular disease and adverse changes in cardiovascular risk factors in 70 patients with insulinoma. *Journal of Endocrinological Investigation* 1993 **16** 875–880. (https://doi.org/10.1007/BF03348949)
12 The International Hypoglycaemia Study Group. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. *Lancet: Diabetes and Endocrinology* 2019 **7** 385–396. (https://doi.org/10.1016/S2213-8587(18)30315-2)
13 Ko SH, Park YM, Yun JS, Cha SA, Choi EK, Han K, Han E, Lee YH & Ahn YB. Severe hypoglycemia is a risk factor for atrial fibrillation in type 2 diabetes mellitus: nationwide population-based cohort study. *Journal of Diabetes and Its Complications* 2018 **32** 157–163. (https://doi.org/10.1016/j.jdiacomp.2017.09.009)
14 ten Broek RPG, Issa Y, van Santbrink EJP, Bouvy ND, Kruitwagen RFPM, Jeekel J, Bakkum EA, Rovers MM & van Goor H. Burden of adhesions

in abdominal and pelvic surgery: systematic review and met-analysis. *BMJ* 2013 **347** f5588. (https://doi.org/10.1136/bmj.f5588)
15 Brown JA, Zenati MS, Simmons RL, Al Abbas AI, Chopra A, Smith K, Lee KKW, Hogg ME, Zeh HJ, Paniccia A et al. Long-term surgical complications after pancreatoduodenectomy: incidence, outcomes, and risk factors. *Journal of Gastrointestinal Surgery* 2020 **24** 1581–1589. (https://doi.org/10.1007/s11605-020-04641-3)
16 Norrbom C, Steding-Jessen M, Agger CT, Osler M, Krabbe-Sorensen M, Settnes A, Nilas L & Loekkegaard ECL. Risk of adhesive bowel obstruction after abdominal surgery: a national cohort study of 665,423 Danish women. *American Journal of Surgery* 2019 **217** 694–703. (https://doi.org/10.1016/j.amjsurg.2018.10.035)
17 van Leeuwaarde RS, Dreijerink KM, Ausems MG, Beijers HJ, Dekkers OM, de Herder WW, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B et al. MEN1-dependent breast cancer: indication for early screening? Results from the Dutch MEN1 Study Group. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 2083–2090. (https://doi.org/10.1210/jc.2016-3690)
18 Barrett TW, Schierling M, Zhou C, Colfax JD, Russ S, Conatser P, Lancaster P & Wrenn K. Prevalence of incidental findings in trauma patients detected by computed tomography imaging. *American Journal of Emergency Medicine* 2009 **27** 428–435. (https://doi.org/10.1016/j.ajem.2008.03.025)
19 Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A & Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *European Urology* 2015 **67** 519–530. (https://doi.org/10.1016/j.eururo.2014.10.002)
20 Dai H, Chen H, Hong X, Han X, Xu Q, Pang H, Yuan J, Wang X, Xu P, Jiang J et al. Early detection of cognitive impairment in patients with insulinoma. *Endocrine* 2019 **65** 524–530. (https://doi.org/10.1007/s12020-019-01994-x)
21 Nikfarjam M, Warshaw AL, Axelrod L, Deshpande V, Thayer SP, Ferrone CR & Fernandez-del Castillo C. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. *Annals of Surgery* 2008 **247** 165–172. (https://doi.org/10.1097/SLA.0b013e31815792ed)
22 Keutgen XM, Nilubol N & Kebebew E. Malignant-functioning neuroendocrine tumors of the pancreas: a survival analysis. *Surgery* 2016 **159** 1382–1389. (https://doi.org/10.1016/j.surg.2015.11.010)
23 Hackeng WM, Schelhaas W, Morsink FHM, Heidsma CM, van Eeden S, Valk GD, Vriens MR, Heaphy CM, Nieveen van Dijkum EJM, Offerhaus GJA et al. Alternative lengthening of telomeres and differential expression of endocrine transcription factors distinguish metastatic and non-metastatic insulinomas. *Endocrine Pathology* 2020 **31** 108–118. (https://doi.org/10.1007/s12022-020-09611-8)
24 Valente R, Lykoudis P, Tamburrino D, Inama M, Passas I, Toumpanakis C, Luong TV, Davidson B, Imber C, Malagò M et al. Major postoperative complications after pancreatic resection for P-NETS are not associated to earlier recurrence. *European Journal of Surgical Oncology* 2017 **43** 2119–2128. (https://doi.org/10.1016/j.ejso.2017.07.012)
25 Crippa S, Zerbi A, Boninsegna L, Capitanio V, Partelli S, Balzano G, Pederzoli P, Di Carlo V & Falconi M. Surgical management of insulinomas: short- and long-term outcomes after enucleations and pancreatic resections. *Archives of Surgery* 2012 **147** 261–266. (https://doi.org/10.1001/archsurg.2011.1843)
26 Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, Nieveen van Dijkum EJM, Pape UF, Pascher A, Ramage J et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology* 2017 **105** 255–265. (https://doi.org/10.1159/000464292)
27 Ahola R, Sand J & Laukkarinen J. Centralization of pancreatic surgery improves results: review. *Scandinavian Journal of Surgery* 2020 **109** 4–10. (https://doi.org/10.1177/1457496919900411)
28 Ahola R, Sand J & Laukkarinen J. Pancreatic resections are not only safest but also most cost-effective when performed in a high-volume centre: a Finnish Register Study. *Pancreatology* 2019 **19** 769–774. (https://doi.org/10.1016/j.pan.2019.06.007)
29 Antila A, Ahola R, Sand J & Laukkarinen J. Management of postoperative complications may favour the centralization of distal pancreatectomies: nationwide data on pancreatic distal resections in Finland 2012–2014. *Pancreatology* 2019 **19** 26–30. (https://doi.org/10.1016/j.pan.2018.11.012)
30 Ahola R, Siiki A, Vasama K, Vornanen M, Sand J & Laukkarinen J. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. *British Journal of Surgery* 2017 **104** 1532–1538. (https://doi.org/10.1002/bjs.10560)
31 de Wilde RF, Besselink MGH, van der Tweel I, de Hingh IHJT, van Eijck CHJ, Dejong CHC, Porte RJ, Gouma DJ, Busch ORC & Molenaar IQ. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *British Journal of Surgery* 2012 **99** 404–410. (https://doi.org/10.1002/bjs.8664)
32 Veltroni A, Cosaro E, Spada F, Fazio N, Faggiano A, Colao A, Pusceddu S, Zatelli MC, Campana D, Piovesan A et al. Clinico-pathological features, treatments and survival of malignant insulinomas: a multicenter study. *European Journal of Endocrinology* 2020 **182** 439–446. (https://doi.org/10.1530/EJE-19-0989)
33 Tiensuu Janson E, Sorbye H, Welin S, Federspiel B, Gronbaek H, Hellman P, Ladekarl M, Langer SW, Mortensen J, Schalin-Jäntti C et al. Nordic guidelines for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncologica* 2014 **53** 1284–1297. (https://doi.org/10.3109/0284186X.2014.941999)
34 Sada A, Glasgow AE, Vella A, Thompson GB, McKenzie TJ & Habermann EB. Malignant insulinoma: a rare form of neuroendocrine tumor. *World Journal of Surgery* 2020 **44** 2288–2294. (https://doi.org/10.1007/s00268-020-05445-x)
35 Bernard V, Lombard-Bohas C, Taquet MC, Caroli-Bosc FX, Ruszniewski P, Niccoli P, Guimbaud R, Chougnet CN, Goichot B, Rohmer V, French Group of Endocrine Tumors et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *European Journal of Endocrinology* 2013 **168** 665–674. (https://doi.org/10.1530/EJE-12-1101)
36 Brown E, Watkin D, Evans J, Yip V & Cuthbertson DJ. Multidisciplinary management of refractory insulinomas. *Clinical Endocrinology* 2018 **88** 615–624. (https://doi.org/10.1111/cen.13528)
37 Official Statistics of Finland. Quality Descriptions, Deaths 2019. Helsinki: Statistics Finland, 2020. (available at: http://www.stat.fi/til/kuol/2019/kuol_2019_2020-04-24_laa_001_en.html). Accessed on 23 September 2020.
38 Sund R. Quality of the Finnish hospital discharge register: a systematic review. *Scandinavian Journal of Public Health* 2012 **40** 505–515. (https://doi.org/10.1177/1403494812456637)
39 Peltola E, Hannula P, Huhtala H, Metso S, Sand J, Laukkarinen J, Tiikkainen M, Sirén J, Soinio M, Nuutila P et al. Long-term prognosis in patients with insulinoma. *Endocrine Abstracts* 2021 **73** PEP9.1. (https://doi.org/10.1530/endoabs.73.PEP9.1)

Received 1 March 2021
Revised version received 9 July 2021
Accepted 6 August 2021