Thesis

NEPHROTIC, WHAT ELSE?

A retrospective kidney biopsy study

submitted by
Jakob Wieser

in partial fulfillment of the requirements for the degree

Doktor der gesamten Heilkunde
(Dr. med. univ.)

at the
Medical University of Graz

executed at the
Department of nephrology

under the supervision of

Univ. Prof. Dr. Alexander Rosenkranz
Dr. Anna Prenner
Dr. Michael Kolland

Graz, date 21.04.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, date 21.04.2023 Jakob Wieser m.p.

Acknowledgement

First of all, I would like to thank my supervisors Prof. Alexander Rosenkranz, Dr. Michael Kolland and Dr. Anna Prenner, whose active support and patience made it possible for me to complete this work. I would also like to thank Dr. Marion Pollheimer for the histological pictures she provided. Finally, I would like to thank all my friends and especially my family for all their support over the past years. Thank you!

Table of contents

Abbreviations and explanation

MCD = minimal change disease
FSGS = focal segmental glomerular sclerosis
MN = membranous nephropathy
HN = hypertensive nephropathy
DKD = diabetic kidney disease
AL = amyloidosis
AKI = acute kidney injury
NKP = normal kidney parenchyma
MD = Malignant disease
TMA = Thrombotic microangiopathy
FGN = Fibrillary glomerulonephritis
IgMN = IgM nephropathy
ATIN = acute tubulointerstitial nephritis
AS = Alport-syndrome
NTX = Nierentransplantation
Crea = creatinine
eGFR = estimated glomerular filtration rate
PCR = protein-creatinine ratio
ACR = albumin-creatinine ratio
NS = nephrotic syndrome
IQR = interquartile ratio
DQ = data quality
ENaC = epithelial sodium channel
uPA = urokinase-type plasminogen activator
IDL = intermediate density lipoprotein
VLDL = very low density lipoprotein
LDL = low-density lipoprotein
LPL = lipoprotein lipase
PCSK9 = proprotein convertase subtilisin/kexin type 9
LM = light microscopy
EM = electron microscopy
IL = inteleukin
Th2 = T helper typ 2
ESRD = end-stage renal disease
HIV = Human Immunodeficiency Virus
HBV = hepatitis B virus
HCV = hepatitis C virus
NOS = not otherwise specified
suPAR = serum urine-type plasminogen activator receptor
GMB = glomerular basement membrane
PLA2R = podocyte membrane antigen M-type phospholipase A2 receptor
THSD7A = thrombospondin type 1 domain containing 7A
BMI = body mass index
DM = diabetes mellitus
eGFR = glomerular filtration rate
ANAs =antinuclear antibodies
ENA = extractable nuclear antigen
ANCAs = antineutrophil cytoplasmic antibodies

dsDNA = double stranded deoxyribonucleic acid
Ig A = immunoglobulin A
KRT = kidney replacement therapy
AKI = acute kidney injury
PCR = protein-creatinine ratio
ACR = albumin-creatinine ratio
NS = nephrotic syndrome
ELISA = Enzyme-linked Immunosorbent Assay
PR3 = proteinase 3
MPO = myeloperoxidase
IF = immunofluorescence
c-ANCA = cytoplasmatic antineutrophil cytoplasmic antibodies
p-ANCA = perinuclear antineutrophil cytoplasmic antibodies
CRP = c-reactive protein
Hb1c = haemoglobin 1c
ATH = antihypertensive
RAAS = renin-angiotensin-aldosterone-system
RAASI = renin-angiotensin-aldosterone-system inhibition
PTH = parathormone
Hb = haemoglobin
HD = haemodialysis
PD = peritoneal dialysis
KTx = kidney transplant
PKTx = pancreas-kidney transplant
AHTD = antihypertensive drugs
DMT1 = diabetes mellitus type 1
DMT2 = diabetes mellitus type 2
CC = correlation coefficient

List of figures

List of tables

Zusammenfassung in Deutsch

Das nephrotische Syndrom, definiert durch Proteinurie, Hypalbuminämie und Ödemen, ist ein Zustandsbild, das bei primären glomerulären oder systemischen Erkrankungen (z.B. Amyloidose) auftreten kann.
Ziel der Studie: epidemiologische Darstellung von Nierenerkrankungen, welche zu einem nephrotischen Syndrom führen. Es wurden Daten von Nierenbiospien gesammelt, welche im Zeitraum von 2007 bis 2017 an der Klinischen Abteilung für Nephrologie der medizinischen Universität Graz durchgeführt wurden. Insgesamt wurden 984 erfasst, davon 243 Patient:Innen (158 Männer) als nephrotisch/other klassifiziert, nephritische und NTX-Patient:Innen wurden exkludiert. Die Patient:Innen wurden bezüglich Krankheitsgruppen, Grunderkrankungen welche bioptische gesichert wurden, sowie nephrotisch und nicht-nephrotisch eingeteilt. Die nachfolgende Auswertung beschränkte sich auf Patient:Innen welche ein nephrotisches Syndrom aufwiesen: Vergleich der Patient:Innencharakteristika, Erfassung renaler und nephrotischer Parameter: Proteinurie, Serumalbumin und Kreatininwerte. Erfassung der Verteilung von renaler Hämaturie, nephritischen Sedimenten, immunologischer Parameter, antihypertensiver Therapie der Krankheitsgruppen, Komplikationen der Nierenbiopsien. Des Weiteren wurden Kennwerte für Chronizität und Daten über Akute Nierenschädigung und Nierenersatztherapie erfasst und auf MCD, FSGS, MN, hypertensive Nephropathie, diabetische Nierenerkrankung sowie Amyloidose eingegangen. Für alle Berechnungen wurde das IBM SPSS Statistics 28.0.1 verwendet.
Insgesamt wurden 119 Patient:Innen (49%) als nephrotisch und 124 Patient:Innen als nicht-nephrotisch (51%) klassifiziert. Für die Krankheitsgruppen wurden folgende Zahlen beobachtet: MCD 34 (14%), FSGS 24 (9,9%), MN 53 (21,8 %), ,HN 46 (18,9%), DN 19 (7,8%), AL 14 (5,8%), akute Nierenschädigung (AKI) 22 (9,1%) und normales Nierenparenchym 12 (4,9%).
Eine renale Hämaturie wurde bei FSGS in 19 (79,2%), bei MN in 43 (81,1%), bei HN in 29 (63,0%), in DN in 17(89,5%), in AL in 10 (71,4%), bei AKI 13 (59,1%) und in 5 (41,7%) der erfolgten Biopsien im normalen Nierenparenchym beobachtet.
Bei MCD Patient:Innen, welche auch die meisten nephrotischen Patient:Innen aufzeigt, wurde in 22 (64,7%) Fällen eine renale Hämaturie und in 17 (50%) Fällen nephritisches Sediment beschrieben. Zudem wurde ein zweiter Gipfel bei den adulten MCD Patient:Innen im Altersbereich zwischen 40 bis 60 beobachtet. In dieser Studie zeigte sich

in einem relativ hohen Prozentsatz der untersuchten PatientInnen mit nephrotischen Syndrom ein nephritisches Sediment, wobei in der Literatur eine einheitliche Definition eines nephritischen Sediments nicht zu finden ist und genauer definiert werden sollte.

Abstract in English

The nephrotic syndrome is defined as the presence of proteinuria, hypalbuminaemia and oedema it is a common condition associated with primary glomerular disease or systemic diseases affecting the kidney.
Goal of this study: display the epidemiology of kidney diseases causing nephrotic syndrome. Between 2007 to 2017 kidney biopsy data of 984 patients was collected at the department of nephrology at the medical university of Graz. 243 (158 male) were included (nephritic/graft excluded) is this study and split into different disease type groups according to their histologically proven disease. Further the patientgroup was divided into nephrotic and non-nephrotic patients. The following evaluation was limited to patients with nephrotic syndrome. Patient characteristics were compared, renal and nephrotic parameters such as proteinuria, serum albumin and creatinine values, distribution of renal haematuria and nephritic sediment analysed, immunological parameters at baseline explored, antihypertensive drug-therapy data and complications of biopsy data collected. Additionally, the outcome was analysed regarding the markers for chronicity, acute-kidney-injury, kidney-replacement-therapy and the disease types MCD, FSGS, MN, hypertensive nephropathy (HN), diabetic kidney disease (DKD) and amyloidosis (AL). For all the statistic calculations program IBM SPSS Statistics 28.0.1 program was used.
In total 119 (49%) patients (78 male) were classified as nephrotic and 124 (51%) as non-nephrotic (80 male). For the other groups the following numbers were observed: MCD 34 (14%), FSGS 24 (9,9%), MN 53 (21,8 %), ,HN 46 (18,9%), DKD 19 (7,8%), AL 14 (5,8%), acute kidney injury (AKI) 22 (9,1%), normal kidney parenchyma (NKP) 12 (4,9%) the remaining groups were sum up under “other”. Renal haematuria was observed: FSGS 19 (79,2%), MN 43 (81,1%), HN 29 (63,0%), DKD 17(89,5%), AL 10 (71,4%), AKI 13 (59,1%) and NKP 5 (41,7%). For MCD, which also displays the most nephrotic patients, renal haematuria 22 (64,7%) and nephritic sediment 17 (50%) was observed. Further a second peak of adult MCD patients was observed between 40 to 60 years. In this study, a relatively high percentage of the patients with nephrotic syndrome examined showed a nephritic sediment, although a uniform definition of nephritic sediment cannot be found in the literature and should be defined more precisely.

1.0 Introduction

1.1 History of the nephrotic syndrome

Defined by a severe proteinuria, hypoalbuminemia and oedema, the nephrotic syndrome is one of the most frequent diseases of the kidney in adults and children. (1) Before clarifying the clinical aspects of the nephrotic syndrome, we first provide the origin of the term itself. The term ‘nephrotic’ which itself is the modified adjectival form of the term ‘nephrosis’, most probably derives from the German adjective ‘nephrotisch’. It had been applied as an adjective to define both oedema (‘nephrotisches Ödem’) and onset (‘nephrotischer Einschlag’). The term ‘syndrome’ as we know is hundreds of years old word and concept, which is utilized widely in medicine. (2)

The term was possibly first mentioned by Henry Christian in 1924, but it took around 30 years until the term found its way into the daily medical use. There was never really a scientific article that could be defined as a ‘milestone’ which was able to evaluate the full situation, defined and displaying the benefit of using the term: it looks like it has diffused gradually into published work and reasoning during the 1940s and 50s. (2)To investigate how the concept of the nephrotic system was developed we have to go further back.

One of the earliest observations of possibly nephrotic symptoms leads us back to Hippocrates: “when bubbles settle on the surface of the urine, it indicates a disease of the kidney and that the disease will be protracted.” (3) Although Hippocrates stated the connection of the disease to the kidney it seems his discoveries have been forgotten.

One of the main symptoms of the nephrotic syndrome is oedema, formerly often referred to as ‘dropsy’. In the 16th to the 18th century the general opinion was that dropsy was a disease itself and not a symptom. Physicians did not think that those swellings had a cause, they did not scrutinise the origin. (2)

Richard Bright (1789-1858) investigated the origin and was one of the first to clearly define that disease of the kidney is the origin of dropsy and proteinuria, this was a watershed in medicine. Together with the chemist John Bostock (1773-1846), they concluded that patients suffering from dropsy had a very great loss of albumin in their blood and concurrent they observed that it was eliminated from the system by of the kidneys. Although their almost thorough definition in 1827 of what we describe today as the ‘nephrotic syndrome’, it took more than hundred years until it was broadly acknowledged. (2)

1.2 Definition

The term ‘nephrotic syndrome’ assigns to a specific constellation of laboratory and clinical features of renal disease. It is exactly described by the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 hours), hypoalbuminemia (less than 3 g/dL), peripheral oedema and hyperlipidaemia. In severe cases thrombotic complications are possible. (4)

1.2.1 Aetiology

A vast array of primary and systemic diseases are linked to heavy proteinuria with or without the nephrotic syndrome. In children the prevailing cause is minimal change disease (MCD), compared to adults, in which about 30 percent the cause is a systemic disease like diabetes mellitus, amyloidosis or systemic lupus erythematosus. Renal disorders like MCD, focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) account for the remaining cases. (4)

1.2.2 Heavy proteinuria

Glomerular proteinuria is defined as an increased filtration of macromolecules across the glomerular capillary wall and is the main cause of protein loss in the nephrotic syndrome. The primary target of injury in diseases that induce idiopathic nephrotic syndrome in children and adults (like MCD, FSGS and MN) seems to be the podocyte.(5)
Podocyte foot process effacement, relative or absolute depletion of podocytes and slit diaphragm disruption are the frequent ultrastructural phenotypes observed in above mentioned diseases. (6–8)
In patients suffering from congenital nephrotic syndrome, hereditary podocyte injury is observed. Those injuries are caused by mutations of podocyte proteins like nephrin and podocin, which are crucial in the conservation of the slit diaphragm and other mutations in proteins like alpha-actinin-4 that disturb the podocyte cytoskeleton integrity. (8)
Circulating factors that influence the podocyte or autoantibodies against podocyte antigens may be the cause for diseases like FSGS and adult-onset primary membranous nephropathy.
Due to the activation of these podocyte proteins the podocyte cytoskeleton or the structure of the slit diaphragm are changed. Patients suffering from nephrotic syndrome, primarily

show a urinary loss of albumin. However other plasma proteins such as immunoglobulins, clotting inhibitors, transferrin and hormone carrying proteins like vitamin D-binding protein can also be lost. (4)

1.2.3 Hypoalbuminemia

The main reason for albumin loss in patients with nephrotic syndrome is urinary excretion, however, the exact mechanism how hypoalbuminemia develops in those patients is not fully understood.
It has been observed that patients with nephrotic syndrome, having the same level of albumin loss, show a lower plasma albumin concentration in comparison to patients who have been treated with continuous ambulatory peritoneal dialysis, showing a compelling loss of albumin the dialysate. A controversial idea states that the much greater loss of albumin than predicted from the excretion rate of albumin is a result of the uptake and catabolization in the proximal tubular cells of considerable amount of filtered albumin. (9,10)
The result of the albumin loss is a low oncotic pressure. This low oncotic pressure has two crucial effects: it partly stimulates the hepatic albumin gene expression and increases the hepatic lipoprotein synthesis (hyperlipidaemia). (4) It remains unclear why the liver in patients with nephrotic syndrome is not able to increase the albumin synthesis adequately and normalizing the concentration of albumin in the plasma. (11)

1.2.4 Oedema

Two theories have been introduced to describe the sodium retention, leading to the development of oedema in nephrotic patients.
One theory states that renal disease per se causes primary sodium retention, this theory is known as the ‘overfill’ theory. (12) The sodium retention is thought to be mediated by the epithelial sodium channel (ENaC) and the basolateral Na-K-ATPase in the collecting tubules. (4)
The other theory is described as the ‘underfill’ theory, in which low plasma oncotic pressure (a result of hypoalbuminemia) causes a shift of fluid from the vascular space toward the interstitial space, which activates the renin-angiotensin-aldosterone system and induces vascular underfilling, resulting in secondary sodium retention. (12)

Although in most patients, hypoalbuminemia does not lead to a decreased plasma oncotic pressure, a parallel fall int the protein concentration of the interstitial space and slight change in the transcapillary oncotic pressure gradient have been observed. (4)
However, those two theories are discussed, it is suggested that both of them are interacting in nephrotic patients. (12)

1.2.4.1 ENaC

As previously mentioned, the increased activity of ENaC is supposed to be a key in understanding sodium retention and oedema. In patients with nephrotic syndrome an increased concentration of serine proteases is found in the urine due to an abnormal glomerular filtration.
One serine protease that could be a probable origin of sodium retention is plasminogen. Plasminogen is activated by epithelial urokinase-type plasminogen activator (uPA) to plasmin and might activate ENaC via proteolytic cleavage of the gamma chain.(12)
Although, M. Xiao suggests in her work about plasminogen deficiency in mice with experimental nephrotic syndrome, that the uPA-plasminogen-plasmin axis is not crucial in the development of sodium retention and oedema. (13)
This indicates that other serine proteases may be the cause, which have not been identified yet.

1.2.5 Hyperlipidaemia

Hypercholesterolemia and hypertriglyceridemia are common abnormalities found in patients suffering from the nephrotic syndrome. Hypercholesterolemia is caused by stimulation of the hepatic lipoprotein synthesis induced by a low oncotic plasma pressure (4), it seems that it stimulates hepatic apolipoprotein B gene transcription, although, how a low oncotic plasma pressure affects lipoprotein production in hepatocytes, is still unknown.
It has been observed, that by using albumin or dextran, the plasma oncotic pressure raises and a reduction in lipid levels can be seen. Similar observations have been made in patients with spontaneous or drug-induced resolution of the nephrotic syndrome.
The increased hepatic synthesis can't be a compensatory mechanism, due to the fact that the lipoproteins are too large to affect the oncotic pressure in a considerable way so the effect on the oncotic pressure is insignificant.(14)

Another reason for hypercholesterolemia might be impaired clearance, as for nephrotic hypertriglyceridemia a diminished metabolism seems to be the cause. (4)
Primarily affected by impaired clearance, secondarily affected by increased synthesis, cholesterol and the main lipoproteins (such as intermediate density lipoprotein (IDL), very low density lipoprotein (VLDL) and low-density lipoprotein (LDL)) are found to be increased in the plasma of patients with nephrotic syndrome.
Decreased lipoprotein lipase (LPL) activity in peripheral tissues (muscle, adipose) and endothelium and decreased hepatic lipase activity are the origin of impaired clearance.
Moreover, patients suffering from nephrotic syndrome, show higher levels of proprotein convertase subtilisin/kexin type 9 (PCSK9). The PCSK9 has gained therapeutic importance in the last years for lipid lowering by degrading the LDL receptor.
Evidence also exists, that an accumulation of oxidized LDL, IDL and chylomicrons remnants found in nephrotic syndrome, stimulate macrophages and monocytes to release proinflammatory cytokines and chemokine, probably causing the progression of chronic kidney disease. (1)

2.0 Minimal change disease

2.1 Definition

The minimal change disease (MCD) accounts to the podocytopathies: pathogenic mechanisms that directly affect the podocyte. MCD is not characterized by immune deposits, but circulating factors may play a key role in the origin and development of the disease. In children the MCD is one of the major causes of nephrotic syndrome it accounts for around 90 percent, whereas in adults it only accounts for around 10 percent.(15)

2.2 Epidemiology

In children, the incidence varies between two and seven new cases per 100,000 children and the estimated prevalence is reported to be 10-50 cases per 100,000 children. (16) Around 90 percent of children under the age of 10 who suffer from idiopathic nephrotic syndrome are diagnosed with MCD, whereas children above the age of 10, only about 50 percent are diagnosed with MCD and an increased number of FSGS cases are found in this age group. In brief, evidence shows that the incidence of MCD varies based upon age. (15) In children the term glucocorticoid-sensitive nephrotic syndrome is often used to describe MCD.

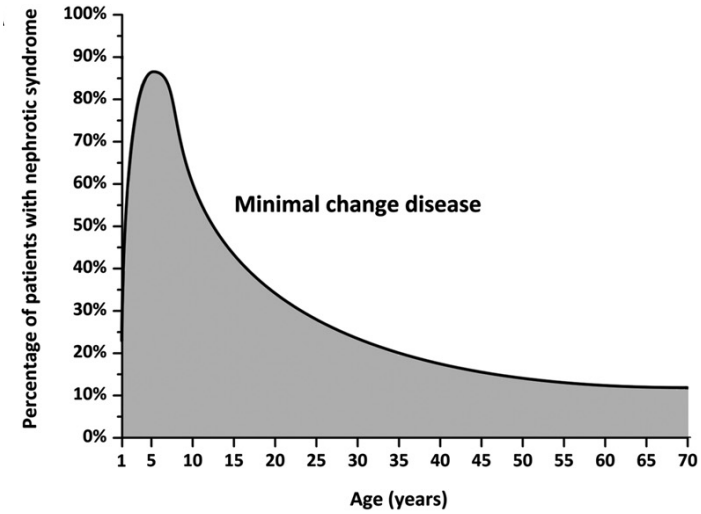

Figure 1. Distribution of nephrotic patients for minimal change disease (16)

As mentioned previously, MCD in adults is only a minor cause for nephrotic syndrome. It has been observed that during the last years the number of adults with MCD suffering from nephrotic syndrome has decreased, whereas the number of nephrotic adults with FSGS has

increased. Caucasian and Asian populations report the highest numbers of nephrotic patients with MCD, whereas in the African-American population FSGS is highest in patients with nephrotic syndrome. (15)

2.3 Aetiology

Most patients with MCD suffer from an idiopathic or primary form not correlating with any other disease or event. In contrast, the secondary form of MCD is associated with drugs, neoplasms, infections, allergy and other glomerular diseases. (15)

Allergy
Pollen
Dust
Fungi
Bee sting
Cat fur
Food allergies (cow's milk, egg)
Malignancies
Hodgkin disease
Non-Hodgkin lymphoma
Leukaemia
Multiple myelome
Thymoma
Bronchogenic cancer
Colon cancer
Eosinophilic lyphoid granuloma (Kimura disease)
Drugs
Nonsteroidal anti-inflammatory drugs
Salazopyrin
D-penicillamine
Mercury
Gold
Tiopronin
Lithium
Tyrosine-kinase inhibitors
Infections
Viral
Parasitic
Mycoplasma pneumoniae
Autoimmune disorders
SLE
Diabetes mellitus
Myasthenia gravis
Autoimmune pancreatitis
Celiac disease
Allogenic stem cell transplantation

Table 1. Secondary causes of minimal change disease adapted from Vivarelli et al. (16)

2.4 Pathology

Patients with MCD show normal glomeruli in light microscopy (LM) and on immunofluorescence microscopy no complement or immunoglobulin deposits are present. In LM, enlarged glomeruli can be found, but usually they appear to be normal. (15) Mild focal mesangial prominence with no more than three or four cells per segment have been observed by LM, if there are more than four mesangial cell present per mesangial region and it affects at least 80% of the glomeruli it is described as the hypercellularity variant of MCD. (16) Diffuse effacement (often also described as fusion) of the epithelial foot processes is the characteristic histological lesion found on electron microscopy (EM) in patients with MCD. Moreover retraction, shortening and widening of the podocyte foot processes is observed. (15)

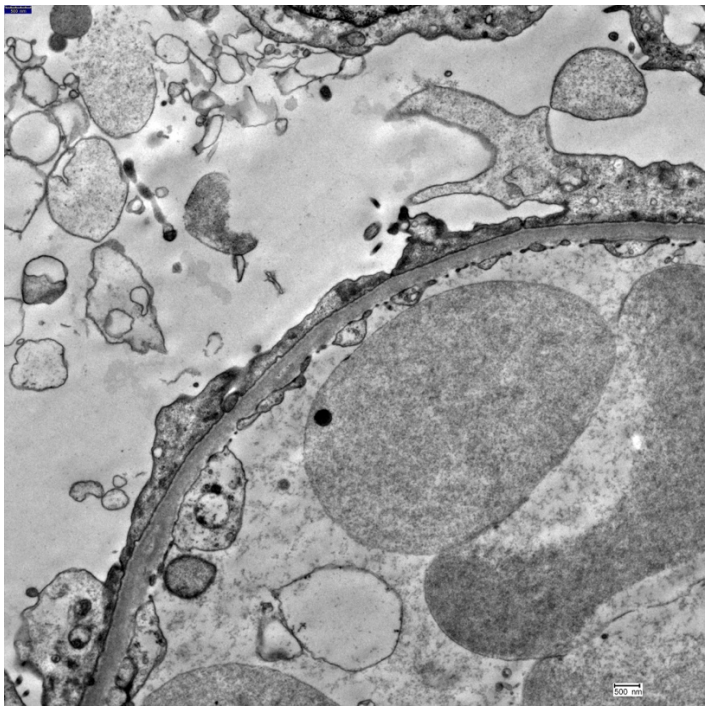

Figure 2. Podocyte effacement in minimal change disease (electrton microscopy), courtesy of Dr. Marion Pollheimer, Medical University of Graz, Department of Pathology

There has not been found any correlation between the extent of effacement and the extent of proteinuria yet. With the remission of proteinuria the podocyte foot processes regain normal structure. (15)

2.5 Diagnosis

The diagnosis of MCD is a diagnosis of exclusion, the only morphological feature is the

podocyte foot process effacement observed by EM, if any other pathological features are to be found they rule out that MCD is diagnosed. (16)

2.6 Pathogenesis

There have been made different observations and theories have been suggested, but it remains still unknown what causes MCD.
One of the main theories supported by evidence is that due a systemic T cell dysfunction a glomerular permeability factor is produced, which changes the glomerular capillary wall directly and ending in proteinuria and podocyte foot process effacement.(15)
This and other theories will be discussed in the following paragraphs:

2.6.1 T cell dysfunction

The theory of T cell dysfunction is supported by the following observations: it was discovered, that a measle infection may induce remission in patients with MCD, perhaps due to the fact that measle infections alter cell-mediated immunity. Furthermore, it has been observed, that decreased T regulatory cells have been associated with relapse in children with glucocorticoid-sensitive nephrotic syndrome. A correlation between Hodgkin lymphoma and MCD has been made, patients with Hodgkin lymphoma suffer more often of MCD than the general population. Patients suffering from allergies seem to have a greater risk in developing MCD. Drugs, that alter cell-mediated responses, such as glucocorticoids and cyclophosphamide show positive effects in the treatment of MCD. (15)

2.6.2 B cell dysfunction

Other publications suggest that B cell dysfunction plays a key role in the pathophysiology of MCD. The chimeric monoclonal antibody rituximab decreases CD20+ B cell population has a positive effect on patients with MCD. This observation leads to the conclusion that B cells or T cells may produce a glomerular permeability factor and that this mechanism is stimulated and regulated by B cells.

The success in treating MCD with rituximab, a recombinant anti CD20 antibody, that can be observed in some patients leads to the understanding that B cells in addition to T cells play an important role in causing MCD.
Rituximab treatment seems to be effective in glucocorticoid-responsive but not glucocorticoid-resistant MCD, this shows that sensitivity and resistance to glucocorticoids may be connected to contrasting pathogenic pathways.(15)

2.6.3 Glomerular permeability factor

As mentioned previously a circulating factor somehow produced by the immune system seems to change the permeability of the glomerulus in patients with MCD leading to proteinuria. (15)
The following evidence supports this hypothesis(15):

-It has been observed that by injecting a T cell hybridoma created from MCD patients a substance is produced leading to foot process fusion and proteinuria.

-A case is described in which unintentionally kidneys from an MCD patient were transplanted into two patients. Those patients before the transplantation did not show a considerable proteinuria, although both developed proteinuria at the time of grafting that promptly diminished and within six weeks was at a normal range.

Although the glomerular permeability factor in MCD has not been identified yet, interleukin (IL)-13 a T helper type 2 (Th2)- derived cytokine may be key to understanding the pathogenesis. A Systemic overexpression of IL-13 in rats leads to hypoalbuminemia and albuminuria. Biopsies of the rat kidneys by examination with EM present podocyte foot process effacement up to 80 percent and on LM no histological changes are shown. (15)
Findings that suggest IL-13 as a part of pathogenesis of MCD(15):

-In patients with nephrotic syndrome T cells impromptu **produce IL-13** and the IL-13 receptor is expressed by B cells

-The expression of IL-13 in T cells is increased in patients with relapsed MCD compared

to patients in remission

-In podocytes IL-13 induces CD80 expression leading to proteinuria and podocyte foot process effacement.

3.0 Focal segmental glomerulosclerosis

3.1 Definition

The concept of focal segmental glomerulosclerosis (FSGS) is referring to a histological lesion caused by a variety of aetiologies that all present themselves with podocyte depletion and injury leading to nephrotic syndrome in children and adults. (17,18)

3.2 Epidemiology

Major global differences in accessibility, indications and pathology support for kidney biopsies make it challenging to determine the exact incidence and prevalence of FSGS. FSGS is a leading cause in the development of end-stage renal disease (ESRD) and observations suggest that the prevalence of FSGS compared to other glomerular disease diagnoses is globally rising. A study shows that the annual incidence rates from around the world range from 0.2 to 1.8/100,000 population per year.(17)

The incidence rates of FSGS are 1.5 to 2-fold higher in men than in women, further a major preference regarding race and ethnicity (higher in black patients than in white and Asian) has been observed.(17,18)

The percentage of FSGS as a cause of nephrotic syndrome varies from country to country. In Spanish study of 2000 patients in only 12 percent the cause was FSGS and in a Chinese study in only under 5 percent of the biopsies FSGS seems to be the underlying cause (18), whereas in a study from the United States with 39 percent of the biopsies FSGS was the most common cause.(17)

3.3 Aetiology

3.3.1 Classifications

Primary or idiopathic, secondary and genetic forms are classifications for the lesions of FSGS. The primary or idiopathic form of FSGS is caused by generalized a dysfunction of podocytes, presumably due to the toxicity of a circulating factor and presents most frequent with nephrotic syndrome. The secondary form of FSGS most frequent presents itself with non-nephrotic proteinuria and renal insufficiency. This form usually describes an adaptive phenomenon to glomerular hyperfiltration or hypertrophy including disorders

linked to reduction of renal mass and/or renal vasodilatation. Viral infections (most frequent HIV) and drugs and toxins such as interferon, pamidronate and heroin are different causes for secondary FSGS. A number of genetic mutations coding for proteins expressed at the slit diaphragm and podocytes cause the genetic form of FSGS. Nephrotic syndrome and massive proteinuria during early childhood or less heavy proteinuria in adolescence or adulthood are typical for the genetic forms of FSGS.

It is very important for treatment and prognosis to distinguish between primary, secondary and genetic forms of FSGS. Immunosuppressive drugs are used in the treatment for primary FSGS. Treating the underlying disorder is key in therapies for genetic and secondary forms of FSGS. (18)

3.4 Pathology

Looking at the histology of primary and secondary FSGS some similarities can be found, but overall those forms present different. By examining kidney biopsies via EM the extent of podocyte foot process fusion is useful in distinguishing primary from secondary FSGS. (18)

3.4.1 Histologic variants

The Columbia classification is based upon LM examination has established five morphologic patterns used to classify FSGS, on LM all of them show an obliteration of the capillary lumens.(17,18)

●FSGS not otherwise specified (NOS):

The most common form of FSGS is the NOS, it is formerly known as classic FSGS. In regard to make the diagnosis of FSGS NOS all other variants have to be excluded. By LM examination some sclerotic glomeruli and mesangial collapse in segmental areas are present. In juxtamedullary glomeruli these sclerotic alterations appear first and are often missed due to superficial biopsies. Other characteristics of FSGS NOS are hyaline deposits partially occluding the capillary lumens and mild mesangial hypercellularity.(18)

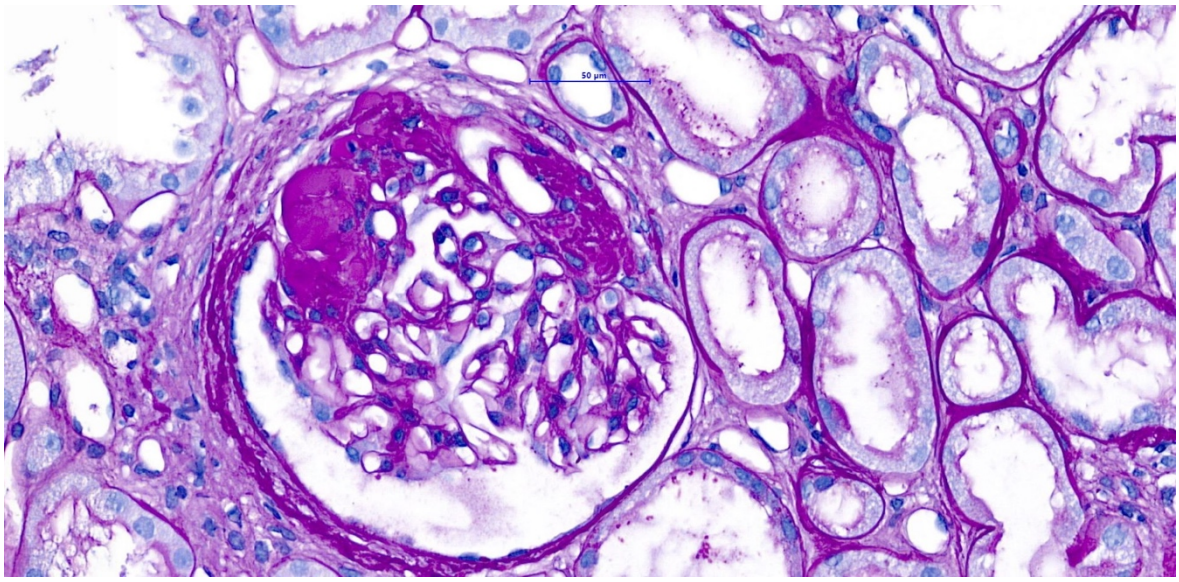

Figure 3. Focal segmental glomerulosclerosis: not otherwise specified (NOS) (lightmicroscopy picture), courtesy of Dr. Marion Pollheimer, Medical University of Graz, Department of Pathology

●Collapsing variant:

The histological characteristics are sclerosis and collapse of the whole glomerular tuft not segmental injury. The aetiology of Collapsing FSGS could be idiopathic, although it can be related to HIV infection, parvovirus B19 infection, lupus and drugs. There exist opinions that due to the unique pathology of this variant it should not be considered a variant of FSGS but should be named collapsing glomerulopathy. (18)

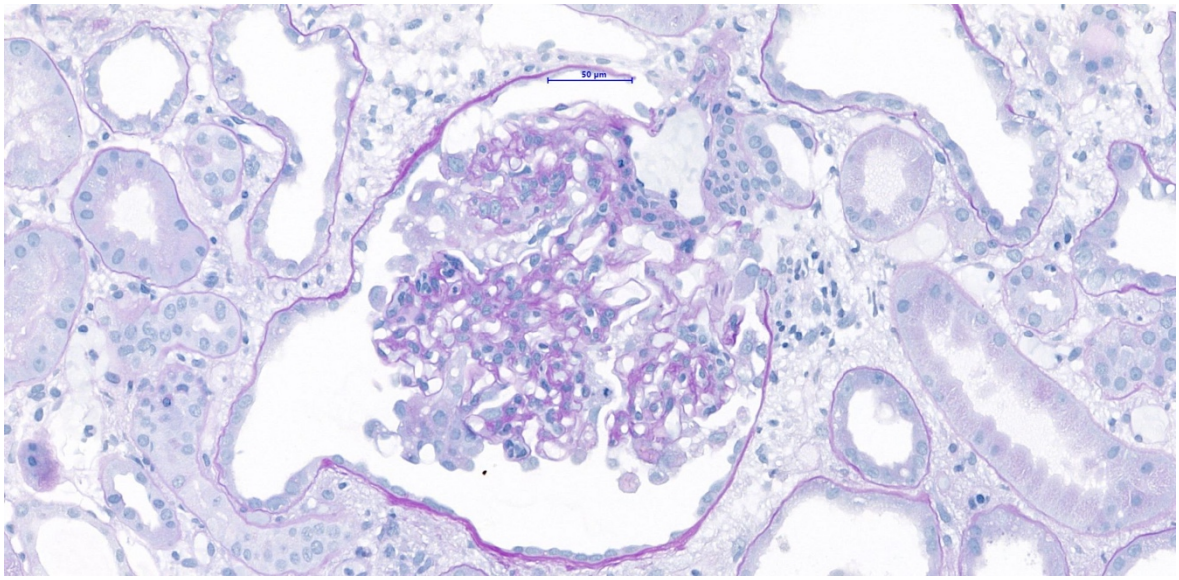

Figure 4. Focal segmental glomerulosclerosis: Collapsing variant (lightmicroscopy), courtesy of Dr. Marion Pollheimer, Medical University of Graz, Department of Pathology

●Tip variant:

The tip variant show lesions of the glomerular tuft next to the tubular pole. Hypercellularity, adhesion to Bowman's capsule at the tip, foam cells and/or sclerosis are histological findings present in the tip variant of FSGS. (17)

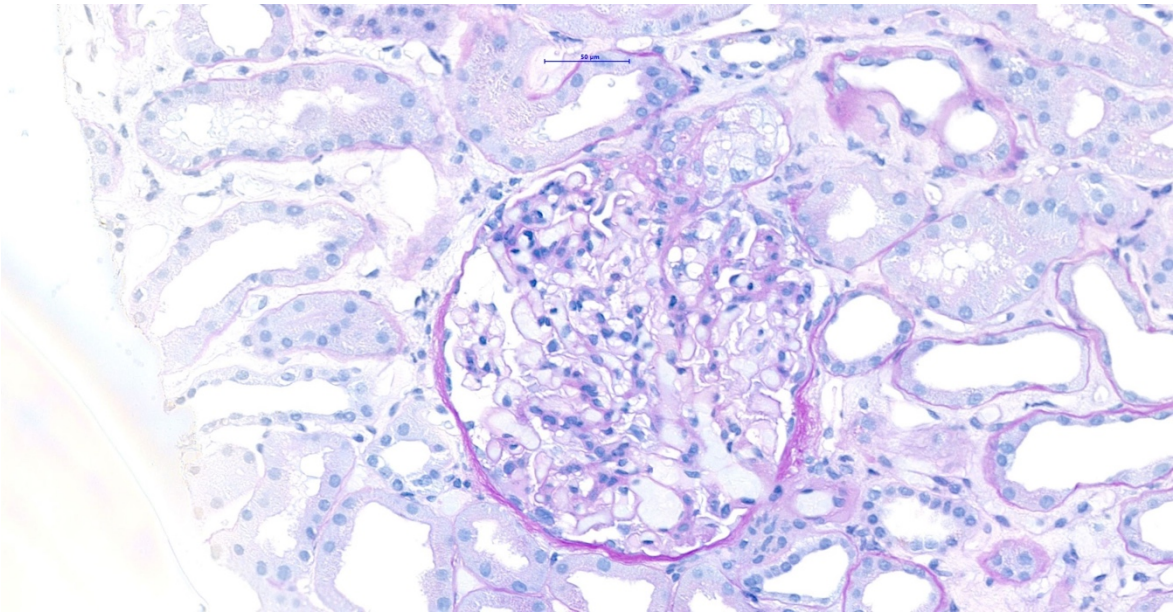

Figure 5. Focal segmental glomerulosclerosis: Tip variant (lightmicroscopy picture), courtesy of Dr. Marion Pollheimer, Medical University of Graz, Department of Pathology

●Perihilar variant:

Perihilar hyalinosis and sclerosis are present in more than 50 percent of the segmentally sclerotic glomeruli. FSGS NOS and the perihilar variant show similar abnormalities in EM and IF. (18)

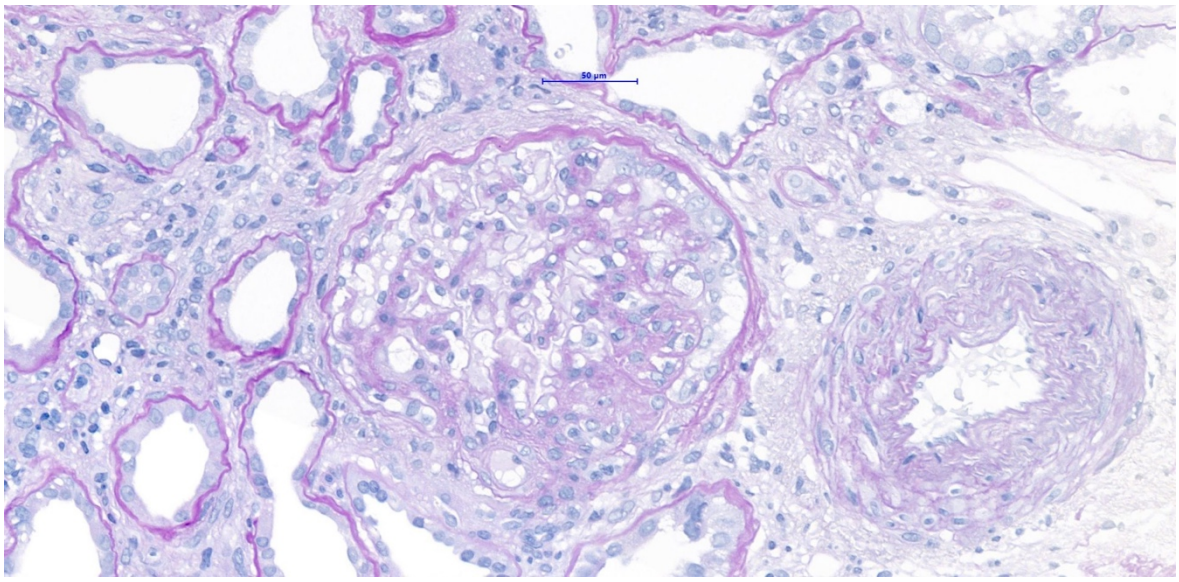

Figure 6. Focal segmental glomerulosclerosis: Perihilar variant (lightmicroscopy picture), courtesy of Dr. Marion Pollheimer, Medical University of Graz, Department of Pathology

●Cellular variant:

By LM examination obliteration of the capillary lumen due to segmental endocapillary hypercellularity is observed, karyorrhexis and foam cells are to be found. (17)

4.5 Pathogenesis

Podocyte injury is the underlying cause of FSGS. The origin of podocyte injury varies and not all causes are known, even though an identical effect on podocytes is observed.
Some research evidence suggests that injured podocytes are progressively lost into the urinary space. Due to the loss of podocytes the remaining one's hypertrophy to be able to cover more of the glomerular capillary surface. (17)

In the following paragraph we will focus on the primary FSGS and only superficially deal with the secondary forms.
As mentioned previously primary FSGS is likely caused by a circulating factor. The toxicity of the circulating factor results in podocyte foot process effacement. Further it has been observed that rats suffer from proteinuria after administrated with serum from patients with FSGS. Other findings describe neonatal proteinuria on the ground of permeability factors, which are transmitted over the placenta. In addition, it has been reported that by transplanting a kidney from an FSGS patient and implant it into a patient

with end-stage kidney disease (not caused by FSGS), histologic alternations and proteinuria are no longer observed. The exact origin of primary FSGS remains still unidentified. Presumably not only one but more circulating factors are involved in the pathogenesis, however no individual factor has been found that is the probable cause for all forms of primary FSGS. (19)

The possible circulating factors that are being investigated are: anti-CD40 antibody, apoA1b (isoform of ApoA1), cardiothrophin-like cytokine factor 1 and serum urine-type plasminogen activator receptor (suPAR). (17)
The suPAR intervenes in the controlled adhesion to the glomerular basement membrane and the dynamic regulation of mature foot processes by activating alpha v beta integrin in podocytes. As a consequence of overproduction by immature myeloid cells of the bone marrow high levels of suPAR in kidney disease are explained. In mice all forms of suPAR can lead to sclerotic lesions, the substructure determines the extent and the timing of the injury. (19)

Although evidence supports suPAR as a leading cause of primary FSGS there is evidence against it, its role remains controversial and further investigations have to be made. (17)

3.5.1 Secondary forms of FSGS

Glomerular hypertrophy and hyperfiltration are involved in the adaptive form of secondary FSGS. Other secondary forms involve drugs/toxins or viruses directly injuring the podocytes.
As mentioned previously it is crucial to distinguish primary from secondary clinically. Treating secondary FSGS involves conservative therapy with the goal blood pressure control (by inhibiting the renin-angiotensin system) and low-salt/low-protein diet, in contrast to primary FSGS treatment where glucocorticoids or immunosuppressive drugs are important.
(19)

4.0 Membranous nephropathy

4.1 Definition

One of the most prevalent causes of nephrotic syndrome in nondiabetic adults is the membranous nephropathy (MN). The histological alternations seen under LM, in particular are: few or no infiltration or proliferation of cells with a thickening of the glomerular basement membrane (GMB). Most reported cases present a primary form of MN, secondary forms have been linked to malignancies, autoimmune diseases, hepatitis B and drugs like gold, penicillamine, nonsteroidal anti-inflammatory drugs and captopril. (20) The primary form of MN is an autoimmune disease affecting the glomerulus resulting in proteinuria and distinct glomerular lesions. (21)

4.2 Epidemiology

The worldwide annual incidence ranges from 0.2/100.000/year to 1.4/100.000/year and it is presumed to be 1.2/100.000/year. A male predominance has been observed in MN and it is uncommon in children. (21,22)

4.3 Aetiology

Primary MN accounts for most of the cases of MN in adults (around 75 percent). As already mentioned, secondary MN underlies a variety of causes, by treating the cause or removing a certain drug or toxin symptoms of nephrotic syndrome disappear. (20) Around 20 percent of the MN cases are due to its secondary form. (21)

Causes	Examples
Infections	HBV, HCV, HIV, parasites (filariasis, schistosomiasis, malaria), leprosy, syphilis, hydatid disease, sarcoid
Malignancy	Solid tumours (lung 26%, prostate 15%, hematologic [plasma cell dyscrasias, non-Hodgkin lymphoma, CLL] 14%, colon 11%),mesothelioma, melanoma, pheochromocytoma; some benign tumours
Autoimmune diseases	SLE (class V), thyroiditis, diabetes, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, mixed connective tissue disease, ankylosing spondylitis, retroperitoneal fibrosis, renal allografts, Anti-GBM disease, IgAN, ANCA-associated vasculitis, IgG4 disease, Membranous-like glomerulopathy with masked IgG k deposits
Alloimmune diseases	Graft versus host disease, autologous stem cell transplants, de novo MN in transplants/transplant glomerulopathy
Drugs/toxins	NSAIDs and cyclooxygenase-2 inhibitors, gold, d-penicillamine, bucillamine, captopril, probenecid, sulindac, anti-TNFα, thiola, trimetadione, tiopronin, mercury, lithium, hydrocarbons, formaldehyde, environmental air pollution (China) Cationic BSA (infants)

Table 2. Secondary causes of membarnous nephropathy adapted from Couser et al. (21)

HBV hepatitis B, HCV hepatitis C, HIV Human Immunodeficiency Virus. CLL chronic lymphocytic leukaemia, MN, membranous nephropathy, NSAIDs non-steroidal anti-inflammatory drugs

The majority of primary MN cases is mediated by circulating IgG4 antibodies to antigens such as the podocyte membrane antigen M-type phospholipase A2 receptor (PLA2R), accounting for around 85 percent, thrombospondin type 1 domain containing 7A (THSD7A) (3-5 percent). The remaining percentage is mediated by antibodies that have still to be identified. (21)

4.4 Pathology

A diffuse thickening of the GBM in all glomeruli without showing a considerable hypercellularity is a classical histology pattern on LM. By LM in early stages of MN glomeruli may seem normal. The pathognomonic ‘spikes’ of GMB growing in between the

immune deposits can be seen in progressed stages with appropriate staining. In later stages of the disease chronic glomerular and tubulointerstitial sclerotic alternations develop. By EM the characteristic lesions are podocyte foot process effacement, proliferation of the GBM by deposition of new extracellular matrix in between the deposits (spikes) and on the outer aspect of GBM subepithelial electron-dense deposits are present.(23) Anti-PLA2R/THSD7A positive patients present uniform, diffuse and finely granular deposits of IgG4 along the outer surface of the capillary walls, when examined by immunofluorescences. (21) The enlargement of the GMB is a process that proceeds over time. From the basal surface of the podocytes the immune deposits are detached and are absorbed into the thickened GBM as the injured podocytes deposit new extracellular matrix. In relation to the extent of subepithelial immune deposits are encircled by the GMB MN can be staged, although there seems to be no connection between the stage and the gravity of proteinuria or treatment response. (23)

4.5 Pathogenesis

In the following paragraph we will examine the pathogenesis of primary MN and will not further explain secondary causes.

The rat model of Heymann nephritis mirrors the human disease regarding the histologic and clinical observations. The endocytic receptor megalin (gp330) found on the foot processes of podocytes is the target of circulating antibodies in Heymann nephritis.

Due to complement activation by the forming subepithelial immune deposits the membrane attack complex (C5b-9) is constructed and inserted into the plasma membrane of the podocyte.

The complement induces podocyte injury and results in proteinuria, caused by redistribution of actin and a loss of the integrity of the slit diaphragm on the ground of signalling pathways activated in the podocyte. Further changes are GMB thickening due to type laminin and VI collagen overproduction (by podocytes suffering injuries).(20)

In rodents and other experimental animals, podocytes do not express PLA2R, therefore a direct prove of the pathogenicity of human anti-PLA2R antibodies in animal models was not feasible. Anti-THSD7A serum from MN patients, if transferred passively into mice presents characteristics of MN such as Subepithelial electron-dense deposits, proteinuria and granular immune complexes of human IgG. (20)

The following observations describe correlations between PLA2R and THSD7A antibodies with primary MN(22):

-remission is achieved faster if PLA2R-Ab levels are low in comparison to higher titers

-higher serum creatinine/lower eGFR, urinary IgG excretion and severe proteinuria are linked to higher PLA2R-Ab titres exceeding 250-300 IU/L

-a connection between higher baseline PLA2R-Ab titres with immunosuppressive therapy resistance and worse renal outcome has been observed.

-declining antibody levels seem to precede alterations in proteinuria by months

-The reappearance of PLA2R-Ab are valuable factors in predicting the relapse of the disease

-there may be a connection between malignancy and THSDA7A-positvity

5.0 Goal of this thesis

The goal of the thesis is to display the epidemiology of kidney diseases causing nephrotic syndromes, comparing patient characteristics with the current literature by using descriptive statistics collected over the period of 10 years at the department of nephrology at the medical university of Graz.

6.0 Methods

In this study we collected and reviewed data of glomerular diseases that were proven via biopsy at the Medical University of Graz, the data was collected over the period from January 1° of 2007 to December 31st of 2017. The Division of Nephrology has been collecting patient identification that underwent renal biopsy since 2007.
At the start of this thesis the hospital information system "MEDOCS" was used to identify the patients, then the histological diagnosis was linked to the patients using an excel chart. To eliminate the possibility that specific renal diseases are overrepresented just the first representative biopsy was chosen. Thus, follow-up biopsies in individual patients were not accounted for. Renal allograft and nephritic patients were excluded from this study, due to the fact that the renal allograft data will be part of a different study.
Glomerular diseases were classified as nephrotic and other, including the following: minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, hypertensive nephropathy, diabetic nephropathy, amyloidosis, acute kidney injury, malignant disease, thrombotic microangiopathy, fibrillary glomerulonephritis, IgM nephropathy, acute tubulointerstitial nephritis, normal kidney parenchyma, Alport-syndrome.
In this retrospective study we defined the nephrotic syndrome as a combination of proteinuria over 3,5 mg/d and hypalbuminaemia lower than 2,5 g/dl. We excluded the criteria oedema and hyperlipidaemia due limitations in collecting data in a retrospective study, data not collected or poorly collected.
At the Medical University of Graz data from the electronic record system was gathered such as renal biopsy diagnosis pattern of injury, as well as demographic data: date of date of biopsy, age at biopsy, sex, weight, height, BMI, Diabetes mellitus, active hepatitis B, hepatitis C, and/or Human Immunodeficiency Virus (HIV) infection. Additionally, the number and type of antihypertensive drugs at the time of biopsy was collected.
Different laboratory values including a complete blood count (haemoglobin in g/dL, leukocytes in 10^9/L and platelets 10^9/L), C-reactive protein in mg/L, parathormone level in pg/mL, creatinine in mg/dL, albumin in g/dL, Hb1c mmol/L and % where gathered, further proteinuria in urine mg/g creatinine or mg/day, albuminuria in mg/g creatinine or mg/day and haematuria with cut-off defined as >10/µL as a part of quantitative measurements of urine analysis. Nephritic sediment was defined via urine-cytology, which was reviewed by experienced technicians and physicians and furthermore evaluated, using

urine microscopy by the presence of dysmorphic red blood cells and red blood cell casts. Renal haematuria was defined as the presence of dysmorphic erythrocytes such as acanthocytes or ring forms.

With the creatinine values we calculated the estimated glomerular filtration rate (eGFR) using the chronic kidney disease epidemiology collaboration equation (CKD-EPI formula) for every patient.(24)

Histological characteristics were gathered such as tubular atrophy and interstitial fibrosis, stages of membranous nephropathy and the histological groups of FSGS.

The cut off for the creatinine maximum was defined as ~ 2 week cut off before and after biopsy. From the electronic health record system MEDOCs the data for the creatine levels after 1 month, 1 year, 2 years, 5 years after biopsy was collected.

With a cut off of 3 months before and after biopsy additional serological studies were collected: evidence of autoimmune mediated disease by assessing levels of antinuclear antibodies (ANAs), extractable nuclear antigen (ENA), antineutrophil cytoplasmic antibodies (ANCAs) in U/mL anti double stranded deoxyribonucleic acid (dsDNA) antibody in U/mL anti-glomerular basement membrane (GBM) antibodies in U/mL, evidence of elevated immunoglobulin A (IgA) levels, complement pathway activation by measuring for serum C3 and C4, the evidence of monoclonal bands, evidence of lambda and kappa free light chains in mg/L and the evidence of positive antibodies for phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain containing 7A (THSD7A).

Further we evaluated patients requiring kidney replacement therapy (KRT), duration of kidney replacement therapy and time between biopsy and start of kidney replacement therapy. In addition, plasmapheresis and numbers of cycles were evaluated.

We collected data from patients that had AKI (acute kidney injury) stage 3 using the definition regarding the KDIGO definition of acute kidney injury. Information about complications related with kidney biopsies were gathered including hematoma, post puncture hematoma, bleeding requiring radiological intervention or surgery and bleeding leading to death.

Data quality was defined as the percentage of the data availability in comparison to the whole data set. All statistical calculations and several figures were made using the IBM SPSS Statistics 28.0.1 program. This study was approved by the ethics committee of the Medical University of Graz EK-number 30-344 ex 17/18.

7.0 Results

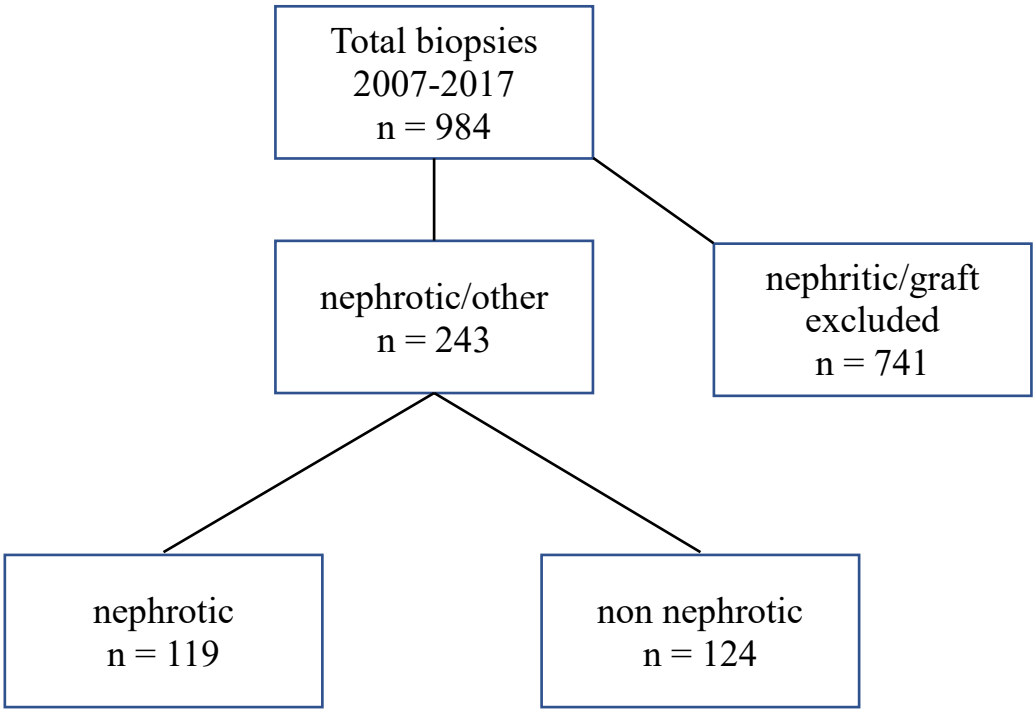

Figure 7. Numbers of total biopsies and biopsies included in thesis

During the period from the year 2007 to 2017 at the division of nephrology at the Medical University of Graz a total of 984 kidney biopsies were performed. In this thesis the focus lays on 243 of them, nephritic patients and graft biopsies were excluded. This patient group was then sorted firstly as nephrotic or other and then divided into two patient groups: non nephrotic patients and patients showing signs of nephrotic syndrome as defined in the methods part. A total of 119 patients were characterized as nephrotic. Further to that we divided our total patient group into 14 groups regarding the disease type as seen in table 3.

Disease type	Patients [n, %]	Median age at biopsy in years	*IQR*	Male [n, %]	Median BMI [kg/m^2]	*IQR*	DM [n, %]
Total	243 (*100%)*	52	*[37,0-63,0]*	158 (65%)	26,6	*[23,1-30,6]*	38 (*15,7%)*
Minimal change disease (MCD)	34 *(14%)*	52,5	*[35,8-64,3]*	20 (58,8%	26,8	*[22,7-31,9]*	1 (2,9%)
Focal segmental glomerulosclerosis (FSGS)	24 *(9,9%)*	49,0	*[30,5-57,0]*	14 (58,3%	27,2	*[23,2-30,0]*	2 (8,3%)
Membranous nephropathy (MN)	53 *(21,8 %)*	55	*[42,0-64,0]*	37 (69,8%)	27,2	*[23,3-31,3]*	7(13,2%)
Hypertensive nephropathy (HN)	46 *(18,9%)*	54,5	*[42,8-63,5]*	38 (82,6%)	27,3	*[25,2-31,2]*	8 (17,4%)
Diabetic kidney disease (DKD)	19 *(7,8%)*	56,0	*[45,0-61,0]*	14(73,7%)	28,1	*[24,2-32,5]*	19 (100%)
Amyloidosis (AL)	14 *(5,8%)*	64,5	*[53,5-67,0]*	8(57,1%)	22,3	*[20,7-27,8]*	1(7,1%)
Acute kidney injury (AKI)	22 *(9,1%)*	34,5	*[22,8-54,3]*	13(59,1%)	24,6	*[22,3-27,3]*	0
Malignant disease (MD)	6 *(2,5%)*	67,5	*[47,3-80,0]*	4(66.7%)	24,9	*[22,4-27,6]*	0
Thrombotic microangiopathy (TMA)	5 *(2,1%)*	40,0	*[20,8-48,0]*	2(40%)	25,1		0
Fibrillary glomerulonephritis (FGN)	3 *(1,2%)*	60,0		2(66.7%)	31,5		0
IgM nephropathy (IgMN)	3 *(1,2%)*	43,0		1 (33,3%)	26,3		0
acute tubulointerstitial nephritis (ATIN)	1 *(0*,4%)	21,0		0	17,1		0
Normal kidney parenchyma (NKP)	12 *(4,9%)*	34,5	*[24,3-46,5]*	5(41,7%)	24,6	*[21,5-31,5]*	0
Alport-syndrome (AS)	1 *(0,4%)*	23,0		0	22,3		0

Table 3. Patient characteristics

BMI = body mass index, DM = diabetes mellitus, IQR = interquartile ratio

Table 3 displays the patient characteristics. Looking at the median age, it can be seen, that the oldest disease groups within our study lay in the amyloidosis and malignant group, whereas the younger groups are represented by the AKI (acute kidney injury), NKP

(normal kidney parenchyma), ATIN (acute tubulointerstitial nephritis) and AS (Alport syndrome). Outside our disease type group DKD (diabetic kidney disease), we find the most DM patients in the MN and HN (hypertensive nephropathy) group. Additionally, we see that most of the DKD group are male patients and have the highest median BMI (body mass index). The lowest BMI is represented by the ATIN disease type. From here on we will sum up the disease type groups MD (malignant disease), TMA (thrombotic microangiopathy) FGN (Fibrillary glomerulonephritis), IgMN (IgM nephropathy), ATIN and AS into one group and will refer to them as “other”.

Disease type	Total	MCD	FSGS	MN	HN	DKD	AL	AKI	NKP
Patients (n)	243	34	24	53	46	19	14	22	12
Median Crea at biopsy [mg/dL]	1,40	1,12	1,34	0,97	1,96	2,09	1,16	3,62	0,97
IQR	*[0,97-2,60]*	*[0,88-1,69]*	*[0,83-1,93]*	*[0,78-1,28]*	*[1,17-4,07]*	*[1,84-2,41]*	*[1,02-1,66]*	*[2,21-7,59]*	*[0,73-1,33]*
Median eGFR at biopsy [mL/min]	54,1	65,0	56,0	84,4	36,5	31,4	59,0	18,1	86,8
IQR	*[23,4-84,4]*	*[44,1-91,5]*	*[35,3-96,1]*	*[63,7-96,7]*	*[16,0-61,6]*	*[24,6-39,1]*	*[40,8-74,6]*	*[8,5-34,8]*	*[63,6-107,8]*
DQ eGFR/crea	*93,0%*	*88,2%*	*91,7%*	*92,5%*	*95,7%*	*94,7%*	*92,9%*	*90,9%*	*91,7%*
Median PCR [mg/g]	4874	8317	5623	6110	2047	6289	8106	711	1388
IQR	*[2127-8475]*	*[5377-11810]*	*[2527-9307]*	*[4300-8978]*	*[749-3812]*	*[4436-10908]*	*[5063-13398]*	*[262-4143]*	*[276-2505]*
DQ	*90,1%*	*94,1%*	*79,2%*	*96,2%*	*87,0%*	*94,7%*	*92,9%*	*81,8%*	*91,7%*
Mean PCR [mg/day]	5526(±5132)	4148(±5330)	9774(±4629)	8646(±4901)		5343		61(±6)	575
DQ	*5,3%*	*5,9%*	*16,7%*	*3,8%*	*0,0%*	*5,3%*	*0,0%*	*9,1%*	*8,3%*
Median ACR [mg/g]	3981	7415	5364	5659	1598	5268	6570	471	990
IQR	*[1595-7130]*	*[5051-10143]*	*[2198-8651]*	*[3439-7487]*	*[663-3092]*	*[3643-7955]*	*[3512-8771]*	*[131-2760]*	*[85-1492]*
DQ	*88,5%*	*94,1%*	*75,0%*	*96,2%*	*87,0%*	*94,7%*	*92,9%*	*77,3%*	*83,3%*
Mean ACR [mg/day]	5069 (±4179)	7361	7409 (± 3535)	7775 (±4080)		2893		37 (±5)	244
DQ	*4,5%*	*2,9%*	*16,7%*	*3,8%*	*0,0%*	*5,3%*	*0,0%*	*9,1%*	*8,3%*
Median Serum Albumin [g/dL]	3,2	2,4	2,9	2,8	4,1	3,4	2,3	3,5	4,1
IQR	*[2,3-3,8]*	*[1,9-2,9]*	*[1,9-4,0]*	*[2,4-3,2]*	*[3,4-4,4]*	*[2,3-3,7]*	*[1,8-2,9]*	*[3,0-4,0]*	*[3,4-4,7]*
DQ	*94,7%*	*100%*	*87,5%*	*96,2%*	*93,5%*	*94,7%*	*100%*	*90,9%*	*83,3%*
NS	119 (49%)	29 (85,2%)	11 (45,8%)	37 (69,8%)	8 (17,4%)	10 (52,6%)	11 (78,6%)	4 (18,2%)	0 (0%)

Table 4. Renal and nephrotic parameters

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, Crea = creatinine, eGFR = estimated glomerular filtration rate, PCR = protein-creatinine ratio, ACR = albumin-creatinine ratio, NS = nephrotic syndrome, IQR = interquartile ratio, DQ = data quality

Table 4 is focussing on renal and nephrotic parameters and displays that MCD is the disease type group with the highest range of proteinuria, whereas the HN disease type group shows the least nephrotic patients. The disease type group AKI represents the lowest serum albumin values and eGFR values in comparison to the other groups. The highest PCR (protein-creatine ratio) value we found in the MCD disease type group, whereas the lowest one is found in the AKI group.

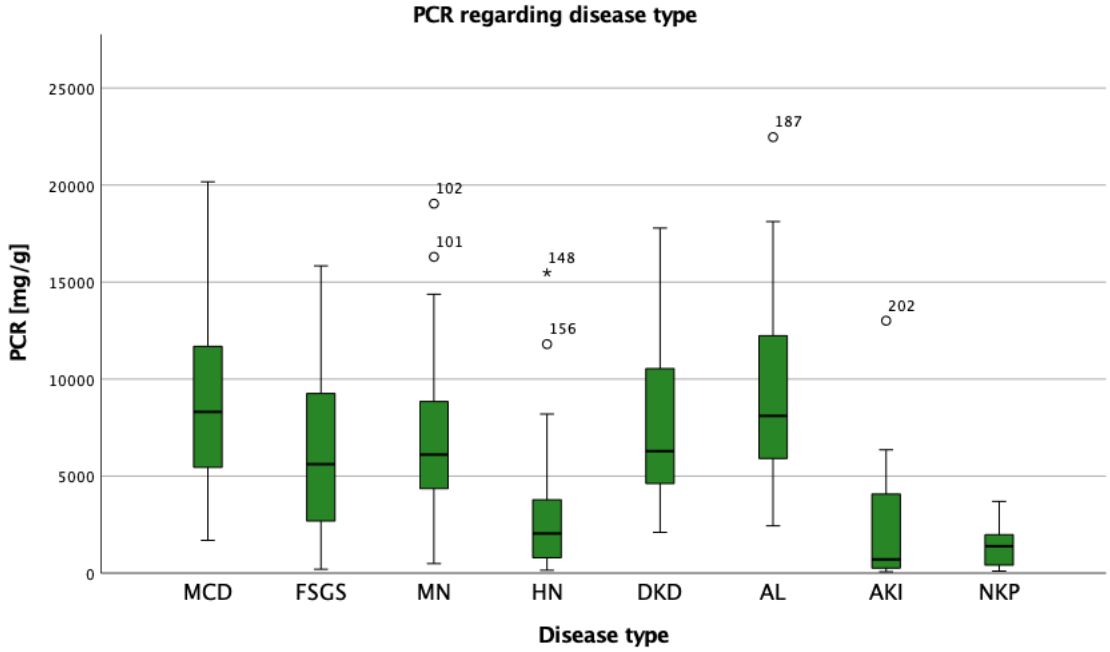

Figure 8. Median proteinuria according to different disease types

An outliner from the disease type membranous nephropathy was excluded (Outliner 67873mg/g) PCR = protein-creatinine ratio, MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

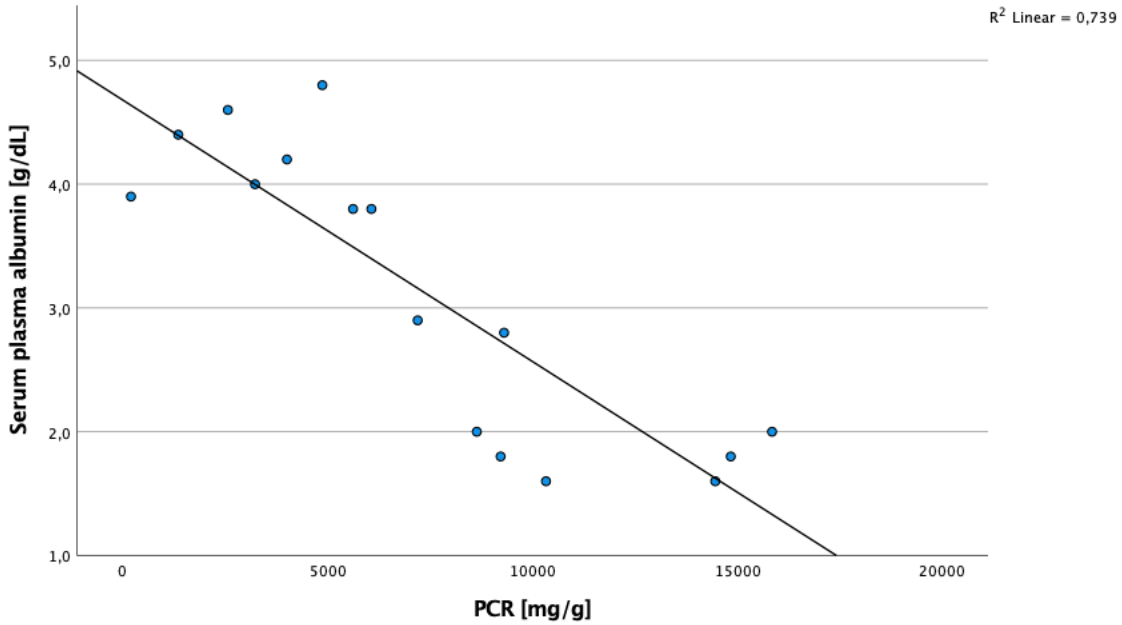

Figure 9. Scatter diagram; corelation between proteinuria and serum plasma albumin for FSGS

PCR = protein-creatinine ratio

Corelation PCR [mg/g] to Serum Albumin [g/dL]	p value	correlation coefficient
Total	0,000	-,683
MCD	0,025	-,396
FSGS	0,000	-,855
MN	0,001	-,476
HN	0,012	-,409
DKD	0,085	-,431

Table 5. Spearman rho test correlation results

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, PCR = protein-creatinine ratio

In table 5, except for DKD, we found significant negative correlations between PCR (mg/g) to Serum albumin (g/dL), with the strongest value for FSGS (figure 42), expressing a strong negative correlation . The corelation between PCR (mg/d) and Serum plasma albumin has a cc of -,902 and a p = 0,000 but is not mentioned in the table because the total data quality lies

by 5,5%.

Disease type	Patients (n, %)	Nephrotic syndrome	Renal haematuria	Nephritic sediment	*DQ (%) RH and NS*
Total	243 (*100%)*	119 (49%)	171 (70,4%)	116 (47,7%)	*90,5%*
MCD	34 (14%)	29 (85,2%)	22 (64,7%)	17 (50%)	*88,2%*
FSGS	24 (9,9%)	11(45,8%)	19 (79,2%)	11 (45,8%)	*100%*
MN	53 (21,8 %)	37 (69,8%)	43 (81,1%)	35 (66%)	*92,5%*
HN	46 (18,9%)	8 (17,4%)	29 (63,0%)	17 (37%)	*89,1%*
DKD	19 (7,8%)	10 (52,6%)	17(89,5%)	14(73,7%)	*94,7%*
AL	14 (5,8%)	11 (78,6%)	10 (71,4%)	5 (35,7%)	*85,7%*
AKI	22 (9,1%)	4 (18,2%)	13 (59,1%)	8 (36,4%)	*86,4%*
NKP	12 (4,9%)	0 (0%)	5 (41,7%)	0 (0%)	*83,3%*

Table 6. Renal haematuria and nephritic sediment regarding to nephrotic syndrome

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, DQ = data quality,

Renal haematuria was present in in 70,4% of the total biopsies and most present in the DKD disease type group. As seen in this table, there was a high percentage both in renal haematuria and nephritic sediment in MCD patients. Performing a chi-quadrat test for the group nephrotic and haematuria we got a significant difference between the expected and the observed numbers with a p value of 0,012. A significant difference between the expected and the observed numbers is shown at the amyloidosis group with a p value of 0,007. In the other disease groups the difference was not significant. Additionally, we performed a chi-quadrat test for nephrotic syndrome and nephritic sediment showing a significance with a p value of 0,001. FSGS showed a significance between the expected and the observed numbers with a p value of 0,001. MN showed a significance between the expected and the observed numbers with a p value 0,036. All the other tested parameters showed no significance.

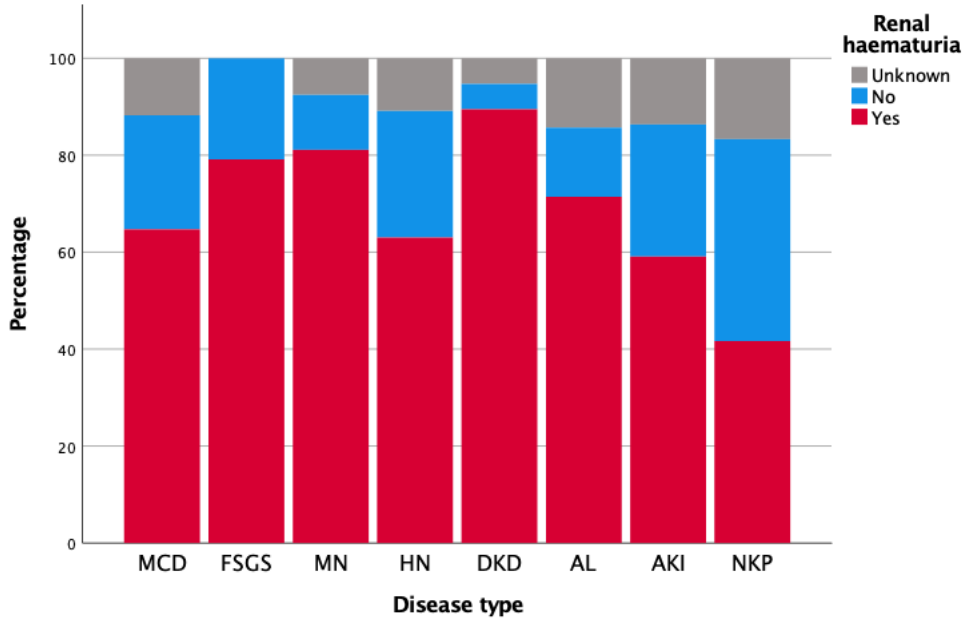

Figure 10. Total percentage of renal haematuria regarding the disease type

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

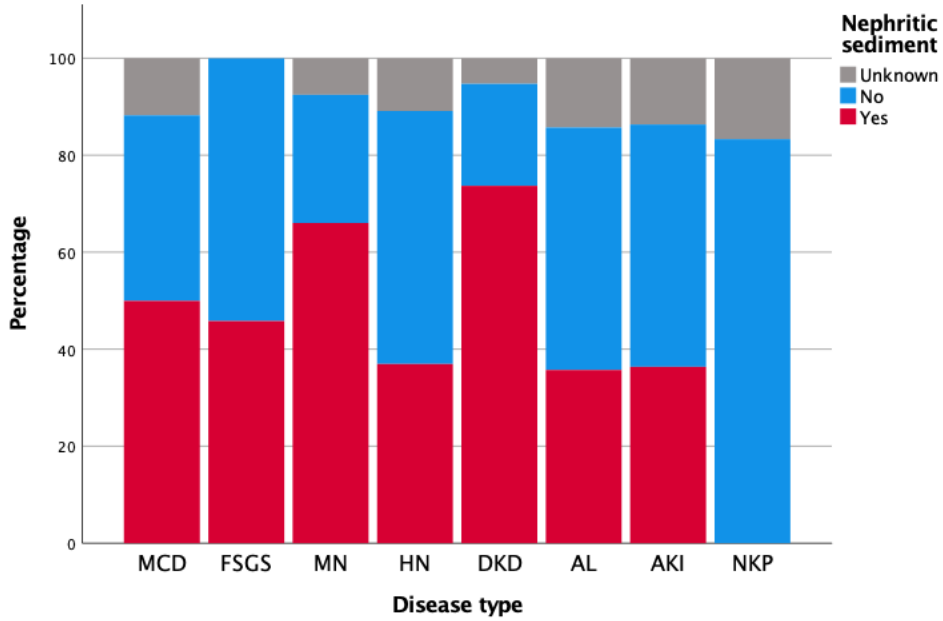

Figure 11. Percentage of nephritic sediment regarding the disease type

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

Disease type	Total	MCD	FSGS	MN	HN	DKD	AL	AKI	NKP
Patients (n, %)	243 (*100%)*	34 (14%)	24 (9,9%)	53 (21,8 %)	46 (18,9%)	19 (7,8%)	14 (5,8%)	22 (9,1%)	12 (4,9%)
ANA positivity	11 (4,5%)	1 (2,9%)	0 (0%)	2 (3,8%)	3 (6,5%)	1 (5,3%)	0 (0%)	1 (4,5%)	2 (16,7%)
DQ	*62,1%*	*73,5%*	*41,7%*	*64,2%*	*60,9%*	*63,2%*	*50,0%*	*68,2%*	*66,7%*
Complement deficiency C3	17 (7,0%)	2 (5,9%)	0 (0%)	4 (7,5%)	2 (4,3%)	1 (5,3%)	2 (14,3%)	3 (13,6%)	0 (0%)
DQ	*57,6%*	*64,7%*	*50,0%*	*66,0%*	*47,8%*	*52,6%*	*50,0%*	*72,7%*	*50,0%*
Complement deficiency C4	3 (1,2%)	1 (2,9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7,1%)	0 (0%)	0 (0%)
DQ	*56,8%*	*61,8%*	*50,0%*	*66,0%*	*45,7%*	*52,6%*	*50,0%*	*72,7%*	*50,0%*
Cytoplasmatic antibodies	1 (0,4%)	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DQ	*9,5%*	*2,9%*	*4,2%*	*11,3%*	*4,4%*	*10,5%*	*14,3%*	*13,6%*	*8,3%*
ENA positivity	8 (3,3%)	0 (0%)	0 (0%)	0 (0%)	2 (4,3%)	1 (5,3%)	0 (0%)	1 (4,5%)	2 (16,7%)
DQ	*61,3%*	*70,6%*	*41,7%*	*64,2%*	*60,9%*	*57,9%*	*50,0%*	*68,2%*	*66,7%*
dsDNA antibodies	5 (2,1%)	0 (0%)	0 (0%)	1 (1,9%)	1 (2,2%)	0 (%)	0 (0%)	0 (0%)	2 (16,7%)
DQ	*57,2%*	*70,6%*	*33,3%*	*54,7%*	*60,9%*	*63,2%*	*50,0%*	*59,1%*	*58,3%*
ANCA ELISA PR3	3 (1,2%)	0 (0%)	1 (4,2%) PR3	0 (0%)	2 (4,4%)	2(10,3%)	0 (0%)	0 (0%)	0 (0%)
ANCA ELISA MPO	4 (1,6%)	1 (2,9%)	0 (0%)	0 (0%)	2 (4,4%)	2 (4,4%)	0 (0%)	1 (4,5%)	0 (0%)
DQ ANCA ELISA	*60,1%*	*70,6%*	*37,5%*	*62,3%*	*60,9%*	*63,2%*	*50,0%*	*68,2%*	*58,3%*
ANCA IF c-ANCA	1 (0,4%)	0 (0%)	1 (4,2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ANCA IF p-ANCA	4 (1,6%)	0 (0%)	0 (0%)	0 (0%)	2 (4,3%)	1 (5,3)	0 (0%)	1 (4,5%)	0 (0%)
DQ ANCA IF	*59,7%*	*73,5%*	*33,3%*	*62,3%*	*60,9%*	*63,2%*	*50,0%*	*68,2%*	*50,0%*
Anti GBM elevated	3(1,2%)	1 (2,9%)	0 (0%)	1 (1,9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8,3%)
DQ	*55,1%*	*61,8%*	*29,2%*	*62,3%*	*56,5%*	*63,2%*	*57,1%*	*63,6%*	*33,3%*
Elevated IgA	20 (8,2%)	2 (5,9%)	1 (4,2%)	4 (7,5%)	5 (10,9%)	1 (5,3%)	3 (21,4%)	2 (9,1%)	2 (16,7%)
DQ	*56,4%*	*55,9%*	*54,2%*	*71,7%*	*50,0%*	*63,2%*	*78,6%*	*45,5%*	*33,3%*
HBV positivity	9 (3,7%)	3 (8,8%)	0 (0%)	4 (7,5%)	1 (2,2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DQ	*80,7%*	*85,3%*	*75,0%*	*94,3%*	*80,4%*	*89,5%*	*64,3%*	*59,1%*	*50%*
HCV positivity	2 (0,8%)	0 (0%)	0 (0%)	2 (3,8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DQ	*81,5%*	*82,4%*	*75,0%*	*94,3%*	*82,6%*	*94,7%*	*71,4%*	*59,1%*	*50%*

HIV positivity	3 (1,2%)	0 (0%)	0 (0%)	1 (1,9%)	1 (2,2%)	0 (0%)	0 (0%)	1 (4,5%)	0 (0%)
DQ	*43,2%*	*32,4%*	*25,0%*	*49,1%*	*54,3%*	*47,4%*	*35,7%*	*31,8%*	*41,7%*
Anti PLA2R positivity (%)	22 (9,0%)	0 (0%)	0 (0%)	22 (41,5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DQ	*19,3%*	*5,9%*	*4,2%*	*58,5%*	*4,3%*	*5,3%*	*21,4%*	*4,5%*	*0%*
Median CRP [mg/L]	3,6	2,2	1,6	2,2	4,0	6,4	2,9	24,8	4,7
IQR	*[1,3-10,8]*	*[1,0-5,4]*	*[1,0-7,3]*	*[0,7-8,3]*	*[2,0-10,3]*	*[1,9-10,4]*	*[1,8-15,9]*	*[15,9-47,0]*	*[2,2-7,7]*
Leucozytes [10^9/L]	7,72	6,88	7,6	7,42	8,04	7,75	8,63	8,28	6,55
IQR	*[6,22-9,89]*	*[5,55-8,69]*	*[6,01-9,75]*	*[5,79-9,27]*	*[6,97-10,27]*	*[6,82-9,89]*	*[6,79-13,57]*	*[6,34-11,78]*	*[5,64-8,77]*

Table 7. Immunological parameters regarding to the disease type at baseline

* THSD7A was tested 0,5% of the MN patients and never tested positive

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, ANA = antinuclear antibodies, ENA = extractable nuclear antigen, dsDNA = double stranded deoxyribonucleic acid, ANCA = antineutrophil cytoplasmic antibodies, ELISA = Enzyme-linked Immunosorbent Assay, PR3 = proteinase 3, MPO = myeloperoxidase, IF = immunofluorescence, c-ANCA = cytoplasmatic antineutrophil cytoplasmic antibodies, p-ANCA = perinuclear antineutrophil cytoplasmic antibodies, GBM = glomerular basement membrane, IgA = immunoglobulin A, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PLA2R = phospholipase A2 receptor, THSD7A = thrombospondin type 1 domain containing 7A, CRP = c-reactive protein, DQ = data quality

Table 7 lists the immunological parameters that we collected. The most HBV positive tests were found in the MN disease group, most elevated ANCA in the HN disease type group as well as the most patients found with elevated IgA levels. Correlations between C3, C4 deficiency and nephrotic syndrome were not significant for all disease type groups, as where the correlations between elevated IgA, HBV and PLA2R positivity. A positive correlation performing a Spearman test was found between CRP and nephrotic syndrome for the MN (p= 0,002) and DM (p= 0,029) disease type group. Furthermore, a Spearman tests shows a negative correlation between ANA and NS for MCD (p = 0,006).

Disease type	Patients (n, %)	Median Number of ATH drugs	*IQR*	*DQ*	Percentage of at least one RAASI	Percentage of diuretic therapy
Total	243 (*100%)*	2,0	*[1,0-3,0]*	*98,8%*	53,5%	49,4%
MCD	34 (14%)	2,0	*[2,0-4,0]*	*97,1%*	55,9%	82,4%
FSGS	24 (9,9%)	2,0	*[1,0-4,0]*	*100%*	62,5%	37,5%
MN	53 (21,8 %)	2,0	*[1,0-3,0]*	*100%*	60,4%	43,4%
HN	46 (18,9%)	3,0	*[1,0-4,0]*	*100%*	65,2%	50,0%
DKD	19 (7,8%)	4,0	*[3,0-5,0]*	*100%*	68,4%	78,9%
AL	14 (5,8%)	2,0	*[0,8-3,0]*	*100%*	42,9%	50,0%
AKI	22 (9,1%)	0,0	*[0,0-1,0]*	*95,5%*	4,5%	13,6%
NKP	12 (4,9%)	0,5	*[0,0-1,0]*	*100%*	33,3%	8,3%

Table 8. Antihypertensive drug therapy regarding the disease type

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, ATH = antihypertensive, RAASI = renin-angiotensin-aldosterone-system inhibition, IQR = interquartile ratio, DQ = data quality

Table 8 deflects the primarily antihypertensive drug management in our disease type groups. The highest number of ATH drugs taken were in the DKD disease type group followed by the HN disease type group. The least amount of ATH drugs taken we found in the AKI group.

Disease type	No RAASI	1 RAASI	2 RAASI	3 RAASI
total	79	83	29	2
MCD	8	19	5	1
FSGS	4	15	4	1
MN	13	32	8	0
HN	11	30	5	0
DKD	2	13	4	0
AL	6	6	2	0
AKI	19	1	1	0
NKP	8	4	0	0

Table 9. Number of RAASI per disease type group

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DN = diabetic nephropathy, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, renin-angiotensin-aldosterone-system inhibition

Table 9 gives us an overview of how many RAASI were taken by the different disease type groups. RAAS inhibition was most commonly used in patients with MN.

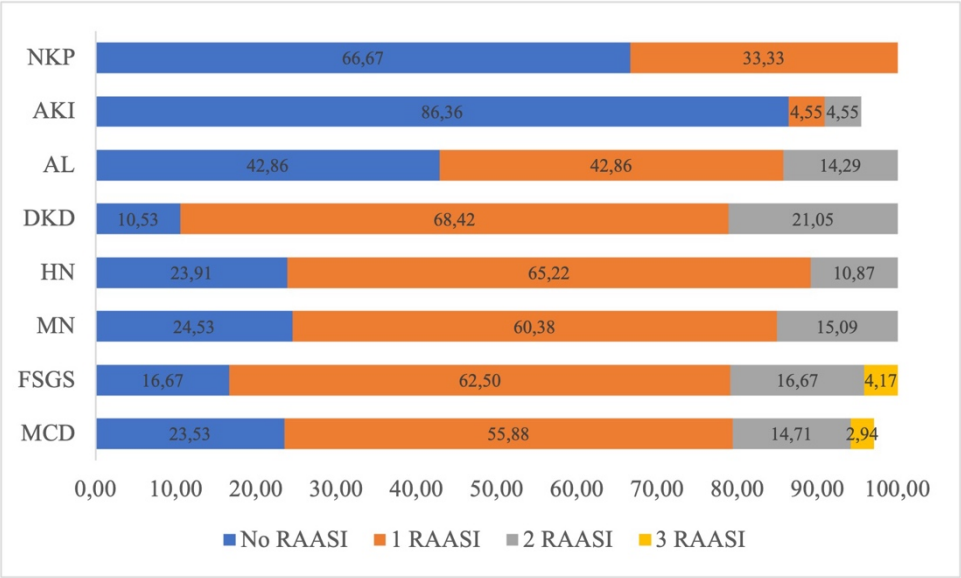

Figure 12. Number of renin-angiotensin-aldosterone system inhibitor (RAASI) regarding disease type group in percent

For the disease type group MCD and AKI the sum is not 100% due to a lower data quality.
MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

7.1 Complications of biopsy

A total of 21 patients suffered complications of biopsy. Complications included haematoma, haematuria, bleeding requiring radiological intervention and pain and nausea. The complication from whom most patients suffered was haematoma with a total of 15 (6.2%) patients. The most haematoma complications were reported in the MN disease type group with a total of 5 (9,4%) Patients.

7.2 Centre specific variation over time

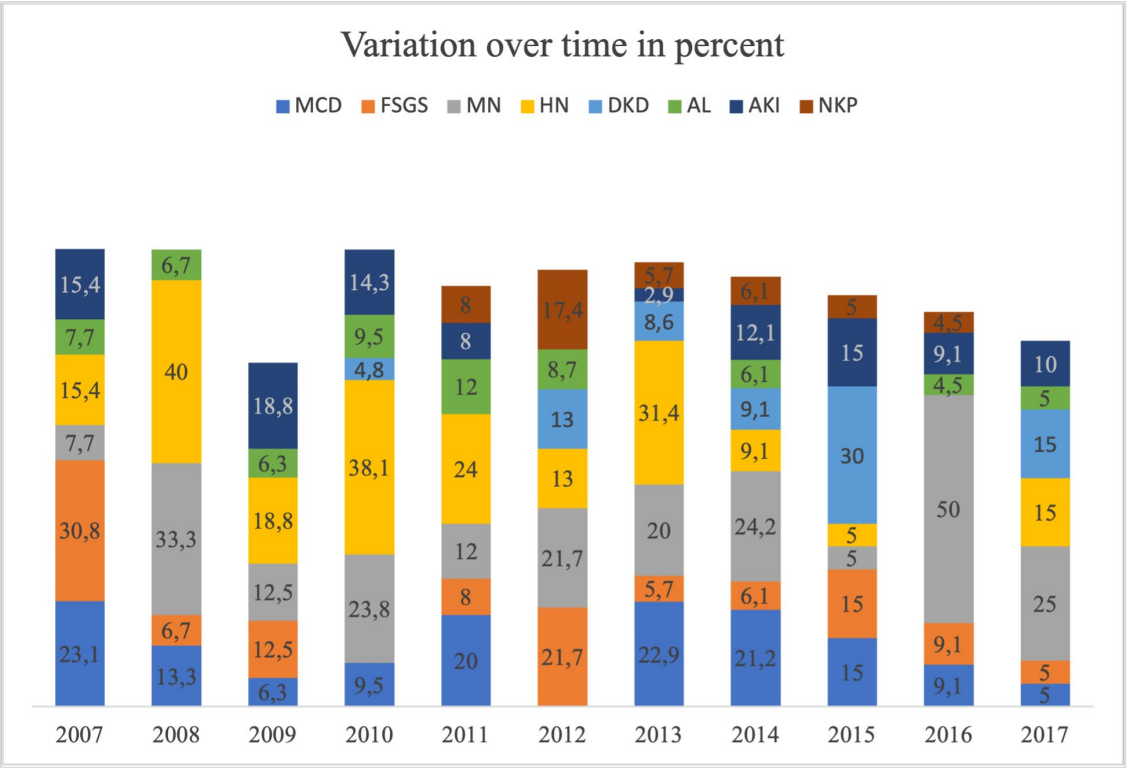

Figure 13. Centre specific variation over time

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

8.0 Outcome

Disease type	Patients (n, %)	Median Crea max [mg/dL]	Crea at biopsy [mg/dL]	Crea after 1 month [mg/dL]	Crea after 1 year [mg/dL]	Crea after 2 years [mg/dL]	Crea after 5 years [mg/dL]	Crea last seen [mg/dL]	Delta Crea (after 1m – at biopsy)	Median Duration last seen [d]
Total	243 (*100 %)*	1,41	1,4	1,18	1,25	1,21	1,39	1,2	-0,01	1980
IQR		*[0,98-2,60]*	*[0,97-2,60]*	*[0,91-2,02]*	*[0,96-2,12]*	*[0,93-2,18]*	*[1,00-2,27]*	*[0,91-2,07]*	*[-0,28-0,16]*	*[961-3033]*
DQ		*95,9%*	*93,0%*	*68,7%*	*64,6%*	*64,2%*	*60,1%*	*97,5%*	*63,8%*	*97,1%*
MCD	34 (14%)	1,15	1,12	1,10	0,99	0,94	1,09	0,92	-0,12	2297
IQR		*[0,85-1,70]*	*[0,88-1,69]*	*[0,85-1,23]*	*[0,80-1,19]*	*[0,83-1,11]*	*[0,86-1,65]*	*[0,79-1,23]*	*[-0,53-0,06]*	*[832-3347]*
DQ		*97,1%*	*88,2%*	*85,3%*	*58,8%*	*58,8%*	*38,2%*	*100%*	*73,5%*	*97,1%*
FSGS	24 (9,9%)	1,27	1,34	1,27	1,21	1,11	1,45	1,43	0,09	2049
IQR		*[0,89-1,89]*	*[0,83-7,93]*	*[0,95-1,91]*	*[0,90-1,64]*	*[0,91-1,91]*	*[1,01-3,47]*	*[0,99-3,36]*	*[-0,21-0,22]*	*[1405-3085]*
DQ		*100%*	*91,7%*	*66,7%*	*70,8%*	*75,0%*	*41,7%*	*100%*	*62,5%*	*100%*
MN	53 (21,8 %)	0,98	0,97	0,95	1,09	1,13	1,10	1,13	0,3	2107
IQR		*[0,83-1,28]*	*[0,78-1,28]*	*[0,82-1,24]*	*[0,89-1,43]*	*[0,93-1,37]*	*[0,99-1,94]*	*[0,68-1,33]*	*[-0,07-0,17]*	*[1060-3490]*
DQ		*88,7%*	*92,5%*	*81,1%*	*88,7%*	*77,4%*	*49,1%*	*100%*	*73,6%*	*100%*
HN	46 (18,9%)	1,98	1,96	1,60	2,13	2,32	2,03	1,67	-0,04	2442
IQR		*[1,17-4,08]*	*[1,17-4,07]*	*[1,21-2,19]*	*[1,29-4,79]*	*[1,39-5,39]*	*[1,39-3,61]*	*[1,23-2,59]*	*[-0,19-0,23]*	*[865-3155]*
DQ		*97,8%*	*95,7%*	*43,5%*	*48,8%*	*56,5%*	*39,1%*	*95,7%*	*41,3%*	*95,7%*
DKD	19 (7,8%)	2,11	2,09	2,13	2,76	2,88	2,50	2,86	0,24	2059
IQR		*[1,84-2,34]*	*[1,84-2,41]*	*[2,00-3,18]*	*[2,32-3,78]*	*[1,38-3,97]*	*[1,39-4,42]*	*[1,76-4,15]*	*[0,16-0,50]*	*[1326-2701]*
DQ		*100%*	*100%*	*42,1%*	*68,4%*	*78,9%*	*57,9%*	*94,7%*	*42,1%*	*94,7%*
AL	14 (5,8%)	1,12	1,16	1,19	1,42	1,46	2,02	1,64	0,03	1226
IQR		*[0,94-1,94]*	*[1,02-1,66]*	*[0,94-2,01]*	*[1,11-3,76]*	*[1,19-2,02]*	*[1,66-2,15]*	*[0,96-2,14]*	*[-0,05-0,28]*	*[716-2736]*
DQ		*100%*	*92,9%*	*100%*	*78,6%*	*78,6%*	*64,3%*	*92,9%*	*92,9%*	*92,9%*
AKI	22 (9,1%)	4,18	3,62	1,38	1,28	1,07	0,97	1,09	-1,70	1930
IQR		*[2,29-7,51]*	*[2,12-7,59]*	*[0,95-3,20]*	*[0,82-1,40]*	*[0,80-1,48]*	*[0,79-1,12]*	*[0,77-1,42]*	*[-9,19--0,66]*	*[588-2911]*
DQ		*95,5%*	*90,9%*	*50,0%*	*31,8%*	*72,7%*	*72,7%*	*95,5%*	*45,5%*	*95,5%*
NKP	12 (4,9%)	0,97	0,97	1,00	0,96	1,05	0,96	0,93	-0,01	2577
IQR		*[0,77-1,45]*	*[0,73-1,33]*	*[0,81-1,28]*	*[0,75-1,25]*	*[0,88-1,37]*	*[0,60-1,27]*	*[0,74-1,08]*	*[-0,12-0,02]*	*[1427-3142]*
DQ		*91,7%*	*91,7%*	*66,7%*	*41,7%*	*50,0%*	*33,3%*	*91,7%*	*66,7%*	*91,1%*

Table 10. Creatinine in comparison to the different disease types

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, Crea = creatinine, IQR = interquartile ratio, DQ = data quality, m = month, d = day

Table 10 displays the different disease type groups and compares the different creatinine values at different times. It demonstrates that the highest creatinine values at the time of biopsy are represented by the AKI. Looking at the delta creatinine we see that the DKD is the one that recovers the least from all the patient groups and has the highest after 5 years value.

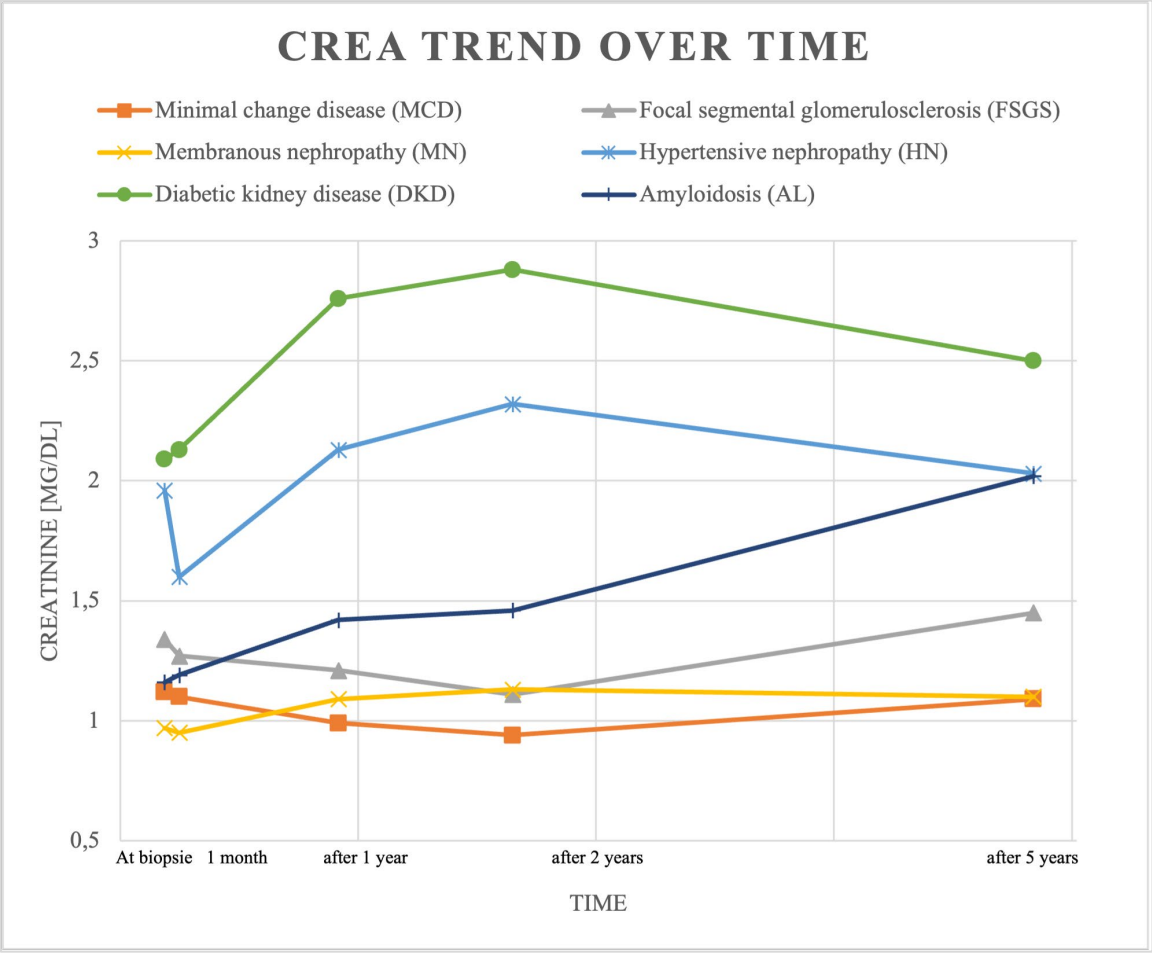

Figure 14. Creatinine trend over time: at biopsy, after 1 month, after 1 year, after 2 years and after 5 years

Figure 9. Creatinine trend over time: at biopsy, after 1 month, after 1 year, after 2 years and after 5 years. The drop at the 1month mark for the disease type group DKD could be explained by a sampling error and a low data quality.

Disease type	Patients (n, %)	Tubular atrophy<25%	Tubular atrophy 26%-50%	Tubular atrophy >50%	*DQ*	Median PTH [ng/L]	*IQR*	*DQ*	Mean Hb
Total	243 (*100%)*	194 (79,8%)	32 (13,2%)	15 (6,2%)	*99,2%*	54,4	*[33,5-90,73]*	*51,9%*	12,9(±2,3)
MCD	34 (14%)	33 (97,1%)	1 (2,9%)	0 (0%)	*100%*	46,5	*[34,9-102,8]*	*55,9%)*	13,2(±2,3)
FSGS	24 (9,9%)	22 (91,7%	2 (8,3%)	0 (0%)	*100%*	35,0	*[29,5-60,9]*	*37,5%*	13,4(±1,9)
MN	53 (21,8 %)	47 (88,7%)	5 (9,4%)	1 (1,9%)	*100%*	38,9	*[27,9-59,6]*	*58,5%*	13,6(±1,9)
HN	46 (18,9%)	25 (54,3%)	11 (23,9%)	9 (19,6%)	*97,8%*	80,7	*[59,4-152,5]*	*45,7%*	13,0(±2,9)
DKD	19 (7,8%)	8 (42,1%)	8 (42,1%)	3 (15,8%)	*100%*	67,4	*[47,1-161,0]*	*78,9%*	12,2(±2,4)
AL	14 (5,8%)	14 (100%)	0 (0%)	0 (0%)	*100%*	42,7	*[41,3-62,7]*	*50,0%*	12,7(±1,7)
AKI	22 (9,1%)	19 (86,4%)	1 (4,5%)	1 (4,5%)	*95,5%*	53,4	*[40-97,7]*	*31,8%*	11,6(±2,1)
NKP	12 (4,9%)	12 (100%)	0 (0%)	0 (0%)	*100%*	32,8	*[29,8-34,6]*	*33,3%*	13,4(±2,1)

Table 11. Markers for chronicity

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, PTH = parathormone, Hb = haemoglobin, IQR = interquartile ratio, DQ = data quality

Table 11 presents the markers of chronicity measured by tubular atrophy, parathormone (PTH) and haemoglobin (Hb) levels. HN and DKD show the most and highest percentage of tubular atrophy. The highest PTH values were found in the group of patients of HT, exceeding the standard value of 12-72 ng/L.

Performing a Spearman-rho test for our total patient group following correlations have been found: a significant positive correlation between tubular atrophy and PTH blood levels has been found (p = 0,001), a negative correlation between tubular atrophy and eGFR (p = 0,001), a negative correlation between tubular atrophy and haemoglobin levels (p = 0,001), a negative correlation between PTH blood levels and eGFR (p = 0,001), a negative correlation between PTH blood levels and haemoglobin levels (p = 0,001) and a positive correlation between eGFR and haemoglobin levels (p = 0,001).
For the disease type MCD a negative correlation between PTH blood levels and eGFR (p = 0,003) has been found. For the disease type FSGS a negative correlation between PTH blood levels and eGFR (p = 0,001), a negative correlation between PTH blood levels and haemoglobin levels (p = 0,016) and a positive correlation between eGFR and haemoglobin levels (p = 0,007) has been found. For the disease type MN a positive correlation between tubular atrophy and PTH blood levels has been found (p = 0,022), a negative correlation between tubular atrophy and eGFR (p = 0,002), a negative correlation between tubular atrophy and haemoglobin levels (p = 0,001), a negative correlation between PTH blood levels and eGFR (p = 0,001) and a positive correlation between eGFR and haemoglobin levels (p = 0,008) have been found. For the HN disease group a negative correlation between PTH blood levels and eGFR (p = 0,001) and a positive correlation between eGFR and haemoglobin levels (p = 0,001) have been found. For the DKD disease group a negative correlation between PTH blood levels and eGFR (p = 0,001) and a positive correlation between eGFR and haemoglobin levels (p = 0,022) have been found. For the AKI disease group a positive correlation between eGFR and haemoglobin levels (p = 0,021) has been found.

Disease type	Patients (n, %)	AKI 3	KRT (n, %)	Median duration to start of KRT (d)	*IQR*	*DQ*	End of KRT (n, %)	No end of KRT	*DQ End KRT*	HD	PD	KTx
Total	243 (*100 %)*	36 (14,8 %)	59 (24,3%)	248	*[59-1039]*	*16,5 %*	10 (4,1%)	43	*21,8 %*	57 (23,5 %)	13 (5,3 %)	15 (6,2%)
MCD	34 (14%)	1 (2,9 %)	4 (11,8%)	1		*5,9%*	2 (5,9%)	0	*5,9%*	4 11,8 %)	2 (4,9 %)	2 (5,9%)
FSGS	24 (9,9%)	1 (4,2 %)	4 (10,7%)	1390	*[244-2469]*	*16,7 %*	0(0%)	4	*16,7 %*	4 (16,7 %)	2 (8,3 %)	0(0%)
MN	53 (21,8 %)	3 (5,7 %)	5 (9,4%)	10		*5,7%*	1 (1,9%)	3	*7,5%*	5 (9,4 %)	0(0%)	2 (3,8%)
HN	46 (18,9%)	12 (26,1 %)	19 (41,3%)	271	*[206-1153]*	*30,4 %*	1 (2,2%)	17	*39,1 %*	18 (39,1 %)	4 (8,4 %)	6 (13,0%)
DKD	19 (7,8%)	0(0%)	9 (47,4%)	570	*[209-1720]*	*42,1 %*	0(0%)	8	*42,1 %*	9 (47,4 %)	2 (10,5 %)	5*(21, 1%)
AL	14 (5,8%)	1 (7,1 %)	5 (35,7%)	228		*21,4 %*	0(0%)	4	*28,6 %*	4 (28,6 %)	1 (7,1 %)	0(0%)
AKI	22 (9,1%)	10 (45,5 %)	6 (27,3%)	9		*4,5%*	4 (18,2%)	2	*27,3 %*	6 (27,3 %)	1 (4,5 %)	0(0%)
NKP	12 (4,9%)	0(0%)	0(0%)			*0(0%)*	0(0%)	0	*0%*	0(0%)	0(0%)	0(0%)

Table 12. AKI 3 and kidney replacement therapy *PKTx

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma, KRT = kidney replacement therapy, HD = haemodialysis, PD = peritoneal dialysis, KTx = kidney transplant, PKTx = pancreas-kidney transplant, IQR = interquartile ratio, DQ = data quality, d = days

Table 12 describes the data regarding kidney replacement therapy and AKI. HN showed the most patients with KRT (HD, PD and NTX) followed by DKD. Furthermore, HN displayed the highest AKI 3 number.

*The sum of KRT exceeds the sum of patients with KRT due to multiple types of KRT per patient.

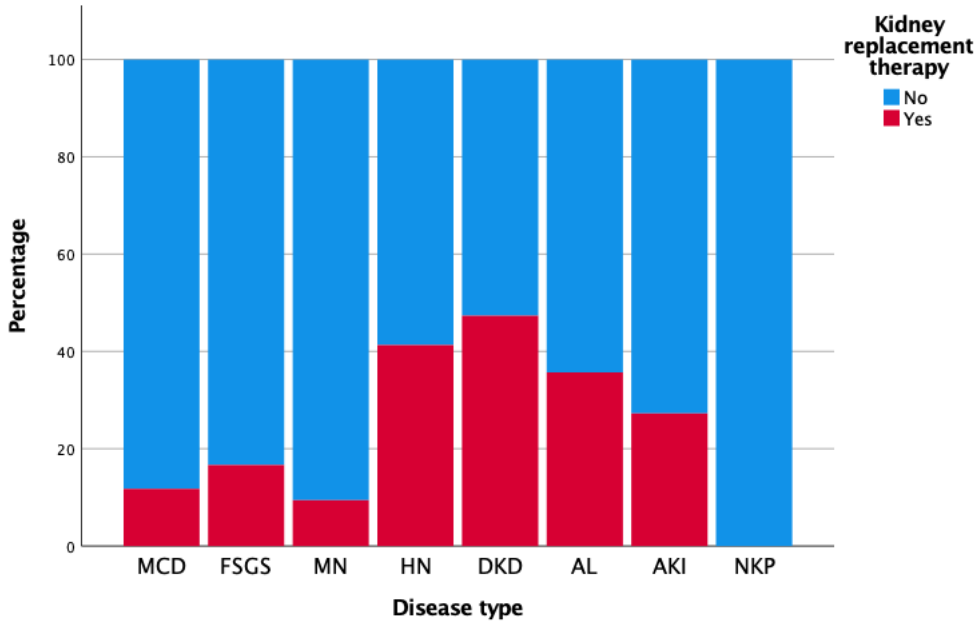

Figure 15. Percentage of kidney replacement therapy regarding to the different disease types

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

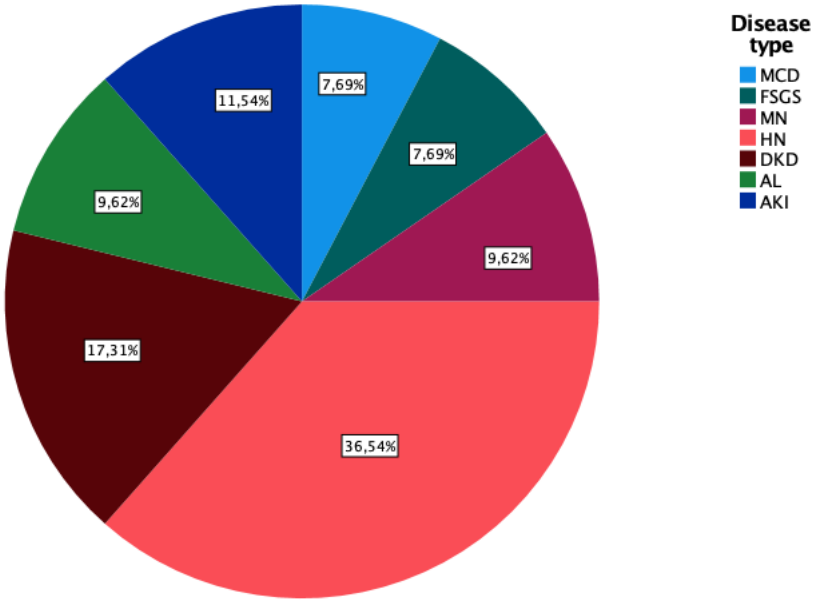

Figure 16. Percentage of disease types for kidney replacement therapy

MCD = minimal change disease, FSGS = focal segmental glomerular sclerosis, MN = membranous nephropathy, HN = hypertensive nephropathy, DKD = diabetic kidney disease, AL = amyloidosis, AKI = acute kidney injury, NKP = normal kidney parenchyma

8.1 Minimal change disease

Focussing on the data gathered about minimal change disease type group additional results were inquired such as the distribution of age was analysed and displayed in figure 12 and statistical test were performed.

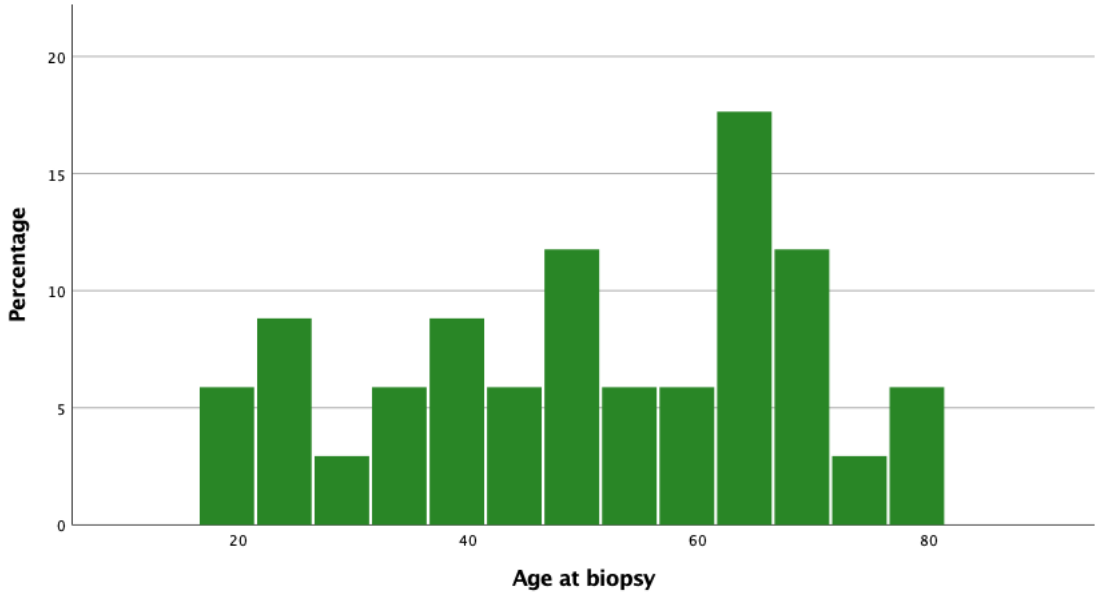

Figure 17. Displays the age distribution if the minimal change disease

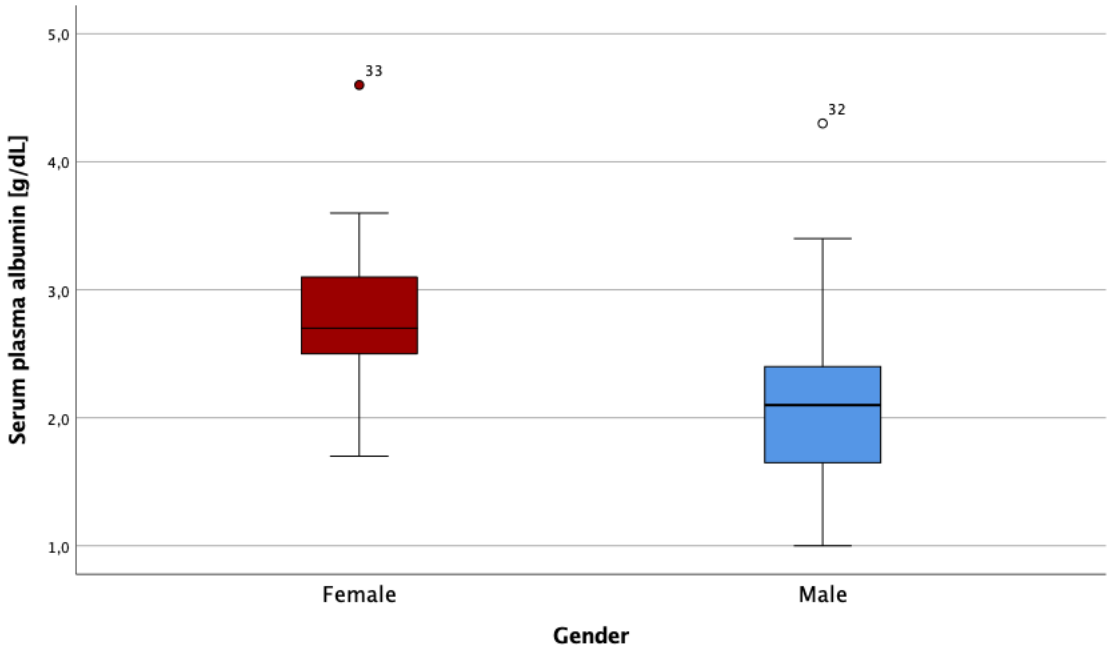

Figure 18. Differences in men and women between serum albumin at time of biopsy +/- 4 weeks for minimal change disease

Performing a Mann-Whitney-U test a significant difference between the gender and serum albumin in plasma with a p = 0,006 and a medium effect size of 0,4747 for the MCD disease type group. For age – gender and PCR – gender the Mann-Whitney-U test it showed no significant difference for this disease type. Performing a spearman test for the correlation between PCR and serum albumin in plasma showed no significant correlation.

8.2 Focal segmental glomerulosclerosis

A closer look was taken at the FSGS disease type group focussing on clinical and histological characteristics.

		CLINICAL			HISTOLOGICAL					
	FSGS total (24)	**Primary FSGS (1)**	**Secondary FSGS (6)**	**Unknown (16)**	**NOS (11)**	**Collapsing variant (1)**	**Tip variant (3)**	**Perihilar variant (1)**	**Cellular variant (0)**	**Unknown (7)**
Median Age at biopsy	49	30	44,5	50	51	26	50	67		32
IQR	*[30,5-57,0]*		*[32,0-61,8]*	*[29,8-56,0]*	*[41,0-57,0]*					*[27,0-48,0]*
male	14	0	6	7	7	1	1	0		4
Median PCR mg/g	5623	5623	3291	8642	8642		6636			2813
IQR	*[2527-9307]*		*[1202-7136]*	*[3232-14460]*	*[4443-12584]*					*[1360-9224]*
DQ	*79,20%*	*100%*	*100%*	*68,80%*	*81,80%*		*66,70%*			*100%*
Mean PCR mg/d	9774 (±4629)			9774 (±4629)	8680 (±5384)	14773	6963			
DQ	*16,70%*			*25%*	*18,20%*	*100%*	*33,30%*			
Median Albumin	2,9	3,8	4,2	2,1	2,4	1,6	2,9	4		4
IQR	*[1,9-4,0]*		*[2,7-4,5]*	*[1,8-3,7]*	*[1,9-3,9]*					*[1,7-4,5]*
DQ	*87,50%*	*100%*	*83,30%*	*87,50%*	*90,90%*		*100%*	*100%*		*71,40%*
Median Crea at biopsy [mg/dL]	1,34		1,54	1,22	1,68	6,83	0,9	1,15		0,8
IQR	*[0,83-7,93]*		*[1,05-1,84]*	*[0,82-2,42]*	*[1,31-2,87]*					*[0,70-1,38]*
DQ	*91,70%*		*83,30%*	*100%*	*81,80%*	*100%*	*100%*	*100%*		*100%*
Median BMI	27,2	20,2	29	26,7	26,6	30	27,8	20,1		29,1
IQR	*[23,2-30,0]*		*[26,5-31,8]*	*[22,5-29,4]*	*[20,5-29,0]*					*[27,1-30,4]*
DQ	*87,50%*	*100%*	*100%*	*93,80%*	*90,90%*	*100%*	*100%*	*100%*		*100%*
Median Number of AHTD	2	1	1,5	2	1	2	0	0		1
IQR	*[1,0-4,0]*		*[0,75-4,25]*	*[1,0-4]*	*[0,0-1,0]*					*[1,0-3,0]*
DQ	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*		*100%*

Table 13. FSGS clinical and histological characteristics

FSGS = focal segmental glomerular sclerosis, NOS = not otherwise specified, PCR = protein-creatinine ratio, Crea = creatinine, BMI = body mass index, AHTD = antihypertensive drugs, IQR = interquartile ratio, DQ = data quality

Table 13 describes the clinical and histological characteristics of the disease type group FSGS. Looking at the clinical classification the most patients we found in the unknown

subgroup with the highest PCR [mg/g] and the lowest serum albumin. The secondary FSGS subgroup presented itself with the highest creatinine values at biopsy and further the highest BMI compared to the other clinical subgroups. Focussing on the histological classification most patients were found in the NOS subgroup, highest creatinine at biopsy and BMI were seen in the collapsing variant subgroup.

Performing a Mann-Whitney-U test for BMI and NS, no significant difference was shown for the FSGS disease type group.

For the histological subgroup NOS a significant difference between NS and PCR is shown $p = 0,016$ with an effect size of 0,816, for the other subgroups no significant difference was found.

8.3 Membranous nephropathy

		HISTOLOGICAL STAGES						
	MN TOTAL (53)	MN Stage I (12)	MN Stage I-II (13)	MN Stage II (13)	MN Stage II-III (6)	MN Stage III (5)	MN Stage III-IV (2)	MN Stage IV (2)
Median age at biopsy	55	61	49	51	63	63	46	53
IQR	*[42,0-64,0]*	*[45,8-66,8]*	*[38,0-59,5]*	*[37,5-63,5]*	*[50,3-73,3]*	*[38,0-68,0]*		
male	37	6	10	9	5	3	2	2
Median PCR [mg/g]	6110	6110	7291	5681	6524	6678	6798	3221
IQR	*[4300-8978]*	*[3638-7728]*	*[3873-12313]*	*[3308-8494]*	*[4183-12232]*	*[5198-10125]*		
DQ	*96,20%*	*91,70%*	*100%*	*92,30%*	*100%*	*100%*	*100%*	*100%*
Mean PCR [mg/d]	8646 (±4901)	12111		5180				
DQ	*3,80%*	*8,30%*		*7,70%*				
Median serum albumin [mg/dL]	2,8	2,7	2,7	2,6	3,1	3,4	2,7	3
IQR	*[2,4-3,2]*	*[1,7-3,2]*	*[2,05-3,25]*	*[24-3,1]*	*[2,1-3,3]*	*[2,6-4,0]*		
DQ	*96,20%*	*91,70%*	*100%*	*100%*	*100%*	*100%*	*100%*	*50%*
Median Crea at biopsy [mg/dL]	0,97	0,86	0,93	0,9	1,06	2,02	4,45	1,28
IQR	*[0,78-1,28]*	*[0,75-1.11]*	*[0,68-1,01]*	*[0,8-1,39]*	*[0,94-1,56]*	*[1,1-2,99]*		
DQ	*92,50%*	*100%*	*92,30%*	*92,30%*	*83,30%*	*80%*		
Anti-PLA2R pos.	22	4	7	6	3	1	1	
DQ	*58,40%*	*75%*	*69,20%*	*46,20%*	*83,30%*	*20%*	*50%*	*0%*
HBV pos.	4	2	1	0	1	0	0	0
DQ	*94,30%*	*100%*	*100%*	*92,30%*	*100%*	*100%*	*50%*	*50%*
NS	37 (69,80%)	9 (75%)	8(61,5%)	8(61,5%)	6	3	2	1

Table 14. MN histological characteristics

MN = membranous nephropathy, PCR = protein-creatinine ratio, Crea = creatinine, PLA2R = Phospholipase-A2-receptor, HBV = hepatitis b virus, NS = nephrotic syndrome, IQR = interquartile ratio, DQ = data quality

Table 14 compares the histological stages of MN. The highest median PCR is found in the stage I-II. No significant difference was seen performing a Mann-Whitney-U for Age-Gender, PCR-Gender, SerumAlb-Gender in the MN disease type group.

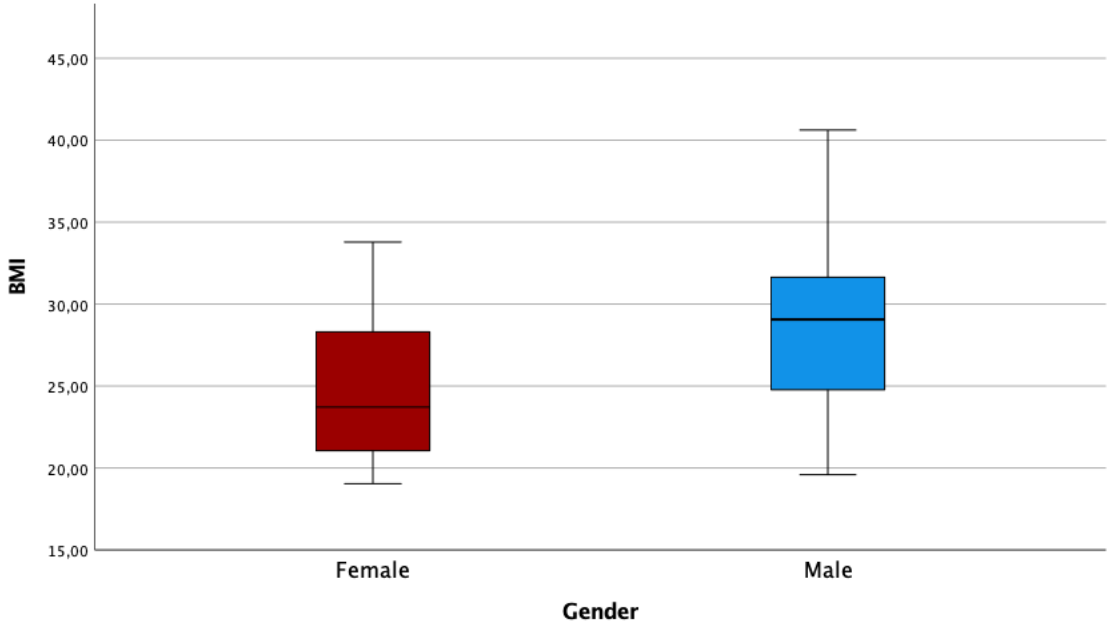

Figure 19. Boxplot displaying body mass index (BMI) and gender for the disease type membranous nephropathy

Performing a Mann-Whitney-U test for BMI and gender we found a significant difference with a p = value of 0,013 and an effect size of 0,346849.

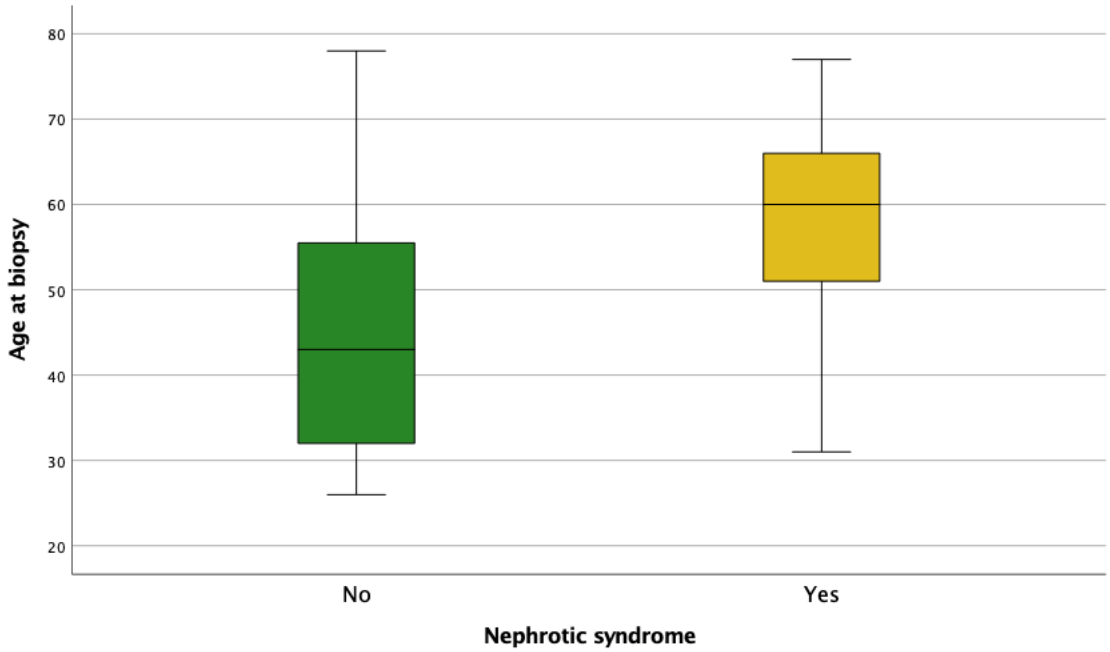

Figure 20. Boxplot displaying age at biopsy and nephrotic syndrome for the disease type membranous nephropathy

Performing a Mann-Whitney-U test for age and NS we found a significant difference with a p = value of 0,001 and an effect size of 0,44216.

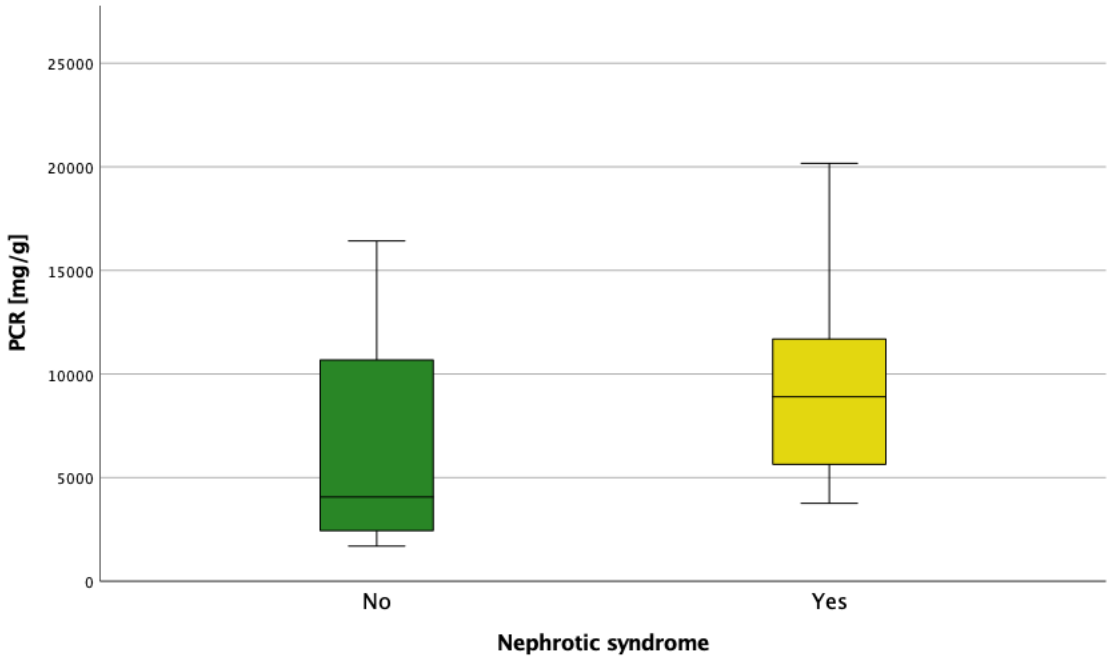

Figure 21. Boxplot displaying PCR (protein-creatinine ratio) and nephrotic syndrome for the disease type membranous nephropathy

Performing a Mann-Whitney-U test for PCR and NS we found a significant difference with a p = value of < 0,001 and an effect size of 0,67485.

8.4 Hypertensive nephropathy

Additionally statistical test were performed on the data collected for the HN.
No significant difference was seen performing a Mann-Whitney-U for eGFR-Gender in the HT disease type group. Performing a Mann-Whitney-U test for PCR and nephrotic syndrome a significant difference is seen a $p < 0{,}001$ and an effect size of 0,588.

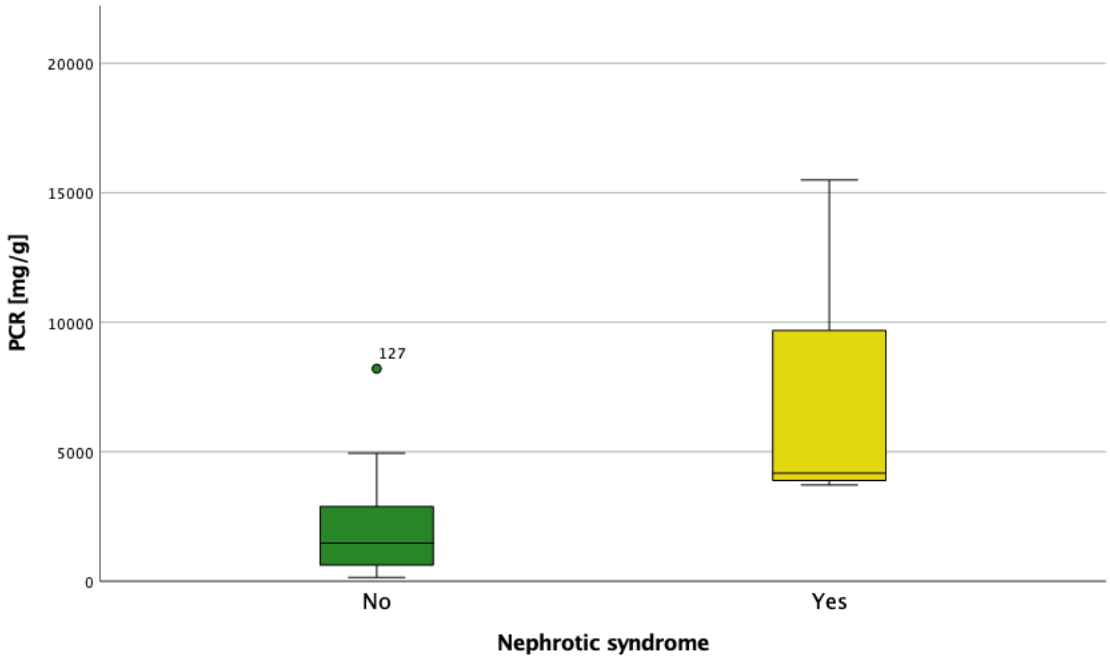

Figure 22. Boxplot displaying PCR (protein-creatinine ratio) and nephrotic syndrome for the disease type hypertensive nephropathy

8.5 Diabetic kideny disease

	DKD total (19)	DMT1 (5)	DMT2 (14)
Median Age at biopsy in years	56	43	59
IQR	*[45.0-61.0]*	*[38,5-46.5]*	*[53,0-63,0]*
Mean Duration of disease in years until biopsy	12,32 (±11,3)	23 (±7,65)	8,5 (±9,98)
male	14	2	12
Median PCR [mg/g]	6289	6097	6455
IQR	*[4436-10908]*	*[3449-10745]*	*[4871-11271]*
DQ	*94,70%*	*100%*	*93%*
Mean PCR mg/d	5343		5343
DQ	*0,70%*		*0,70%*
Median serum albumin [mg/dL]	3,4	3,2	3,5
IQR	*[2,3-3,7]*	*[2,6-3,4]*	*[2,2-3,8]*
DQ	*94,70%*	*100%*	*93%*
NS	10	4	6
Median Crea at biopsy [mg/dL]	2,09	1,85	2,23
IQR	*[1,84-2,41]*	*[1,35-2,0]*	*[1,90-2,81]*
DQ	*94,70%*	*100%*	*97%*
Hb1c [mmol]	54	86	53
IQR	*[49-75]*	*[70,5-100]*	*[48-58,5]*
DQ	*89,50%*	*100%*	*85,70%*
Median number of AHTD	4	4	4
IQR	*[3,0-5,0]*	*[2,0-5,5]*	*[3,75-5,0]*
Median CRP [mg/L]	6,4	6,4	4,7
IQR	*[1,9-10,4]*	*[1,25-7,85]*	*[3,3-23,8]*

Table 15. Diabetic kidney disease regarding DMT1 and DMT2

DKD = diabetic kidney disease, DMT1 = diabetes mellitus type 1, DMT2 = diabetes mellitus type 2, PCR = protein-creatinine ratio, Crea = creatinine, Hb1c = haemoglobin 1c, AHTD = antihypertensive drugs, CRP = C-reactive protein, IQR = interquartile ratio, DQ = data quality

Table 15 describes the DKD disease type group. The most DKD patients have DM type 2. It showed that the duration of disease until biopsy in years is highest in DM type 2. NS presented itself most in DM type 2 group. DM type 1 showed the highest Hb1c levels compared to DM type 2.

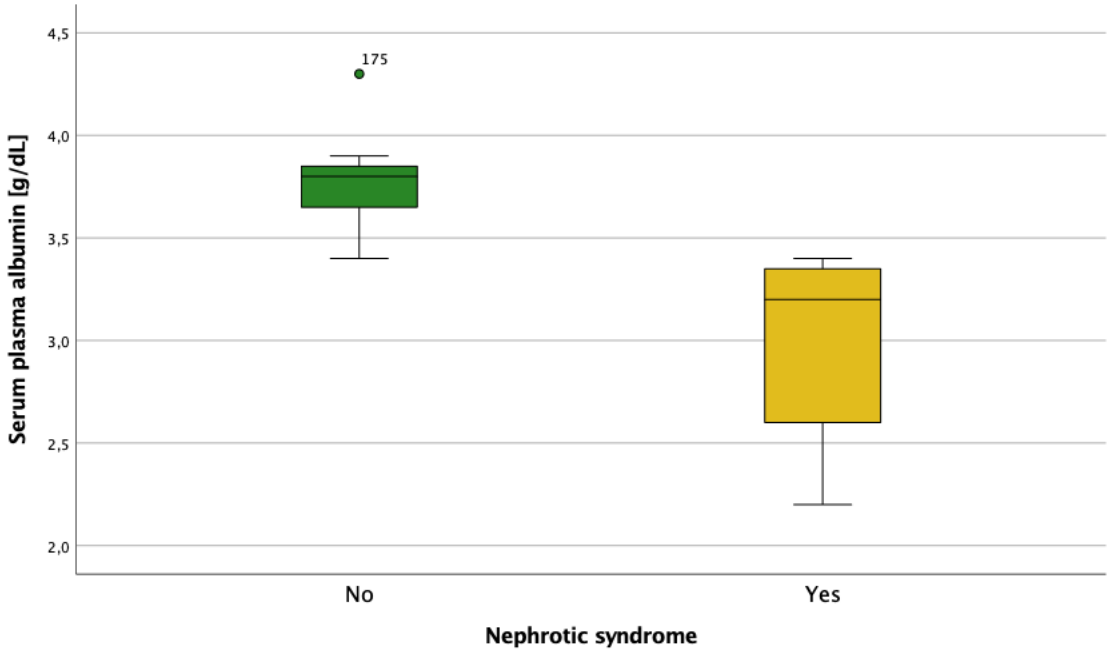

Figure 23. Boxplot displaying serum plasma albumin and nephrotic syndrome for the disease type diabetic kidney disease

A significant difference was seen performing a Mann-Whitney-U test for NS in patients with diabetes mellitus and serum albumin witth p value of 0,000 an effect size of 0,81977. Perfoming a Mann-Whitney-U test no sifnificant difference was found looking at age-gender, serum albmunin-gender, PCR-gender, BMI-gender, PCR-NS in the DKD disease type.

8.6 Amyloidosis

Monoclonal plasma serum components were found in 9 patients in the AL disease type group (9/14, 1 Unknown). Performing a Spearman test a positive correlation was found between PCR (mg/g) and ACR (albumin-creatinine ratio) (mg/g) with a p value of < 0,001 and a correlation coefficient (CC) 0,923. No significant correlation between PCR/ACR and serum albumin has been found. Perfoming a Mann-Whitney-U test a sifnificant difference was found looking at PCR and nephrotic sydrome for the amylodisis disease group with a p = 0,026 and an effect size of 0,6. No significance was seen performing a Mann-Whitney-U test for KRT and PCR. Median PCR was 8106 mg/g (IQR 5063-13398) and median ACR 6570 mg/g (IQR 3512-8770). In 6 patients we found elevated kappa free light chains with a maximum of 95,2 mg/L and in 8 patients lambda free light chains where elevated with a maximum of 235 mg/L.

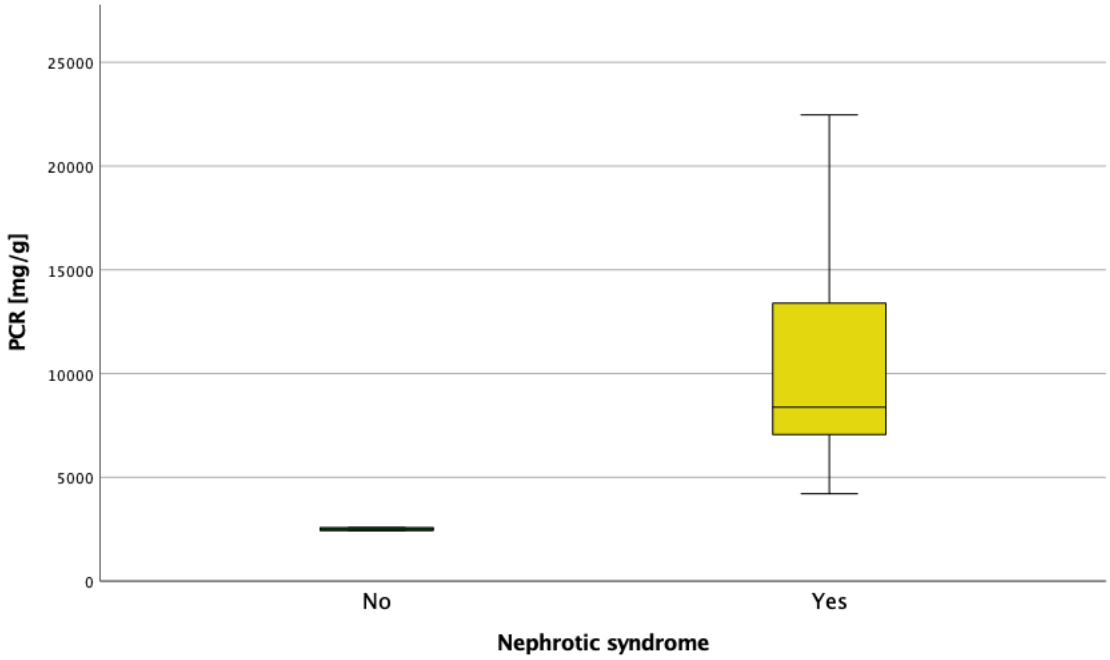

Figure 24. Boxplot displaying PCR (protein-creatinine ratio) and nephrotic syndrome for the disease type amyloidosis

9.0 Discussion

In this thesis we obtained clinical data from 243 patients at the division of nephrology at the Medical University of Graz from 2007 to 2017 and divided the patients into disease type groups regarding the histologically proven glomerular disease. Further we statistically analysed the patient cohort regarding nephrotic syndrome, patient characteristics, clinical characteristics, laboratory findings, outcome, and the disease types.

Focusing on the patient characteristics, the oldest patient group regarding the median age was found in the amyloidosis disease type group with 64,5 years. The most nephrotic patients with 29 (85,2%) and the highest PCR with 8317 mg/g were in the MCD disease type group, as seen by comparing it to the work of Waldman with a 9,93 g/d ±0,71(25). The disease type group AKI showed highest median creatinine values at biopsy 3,62 mg/dL. The AL disease type group displayed the lowest median serum albumin of 2,3 g/dL compared to the other disease type groups. A positive correlation performing a Spearman test was found between CRP and nephrotic syndrome for the MN (p= 0,002) and DM (p= 0,029) disease type group.

We observed a high percentage of renal haematuria and nephritic sediment in the MCD and DN disease type group. For the MCD disease type group a high percentage of renal haematuria 22 (64,7%) and nephritic sediment 17 (50%) was discovered. Focussing on renal haematuria and nephritic sediment, we found that renal haematuria is most present in the DN disease type group with 17 (89,5%). Looking at the literature, renal haematuria and nephritic sediment are often vaguely defined or it is not clear if the refer to haematuria of renal origin. Renal haematuria can be defined as a presence of dysmorphic or glomerular type red blood cells in the urine (e.g. acanthocytes, ringforms or doughnut-shaped), Buchkremer defines it as such: it is definite glomerular haematuria if more than 30% of ringforms are present.(26)

Additionally, a chi-quadrat test was performed showing a weak correlation between the nephrotic and haematuria patient group looking at the total data, expressing that those variables are depending. The fact that the MCD disease type group has the most nephrotic patients could underline this statistical finding. Further a strong correlation was seen between those groups for the AL disease type group.

Further for the MCD disease type group looking at the figure 12 an accumulation of MCD patients from the age 40-60 can be observed which raises the question of a second peak of MCD in older patients. The median age at biopsy for the MCD patients lays at in the

interquartile ratio (IQR) 35,8-64,3, this could be described as a peak in the adult onset of MCD. Compared to a study from Chen et al. the average age at biopsy of the adults lays in between IQR = 30,0-58,0 (27) , also Fenton et al. describe the average adult-onset age with an age range from IQR = 31-63 (28), similar findings Waldman et al. report 45,1 ± 1,6 years (29)

A difference has been seen between gender and serum albumin in plasma for the MCD disease type group. After performing a Mann-Whitney-U test the difference between gender and serum albumin in plasma can be described as significant (p = 0,006, medium effect size of 0,4747), in the literature nothing like this was previously described, Fenton et al. analysed it but found no association.(28)

By looking at the ATH drug therapy two patients were found that received a triple RAAS inhibition one each for the MCD and FSGS disease type group.

Looking at the antihypertensive drug therapy we found two patients, one in the MCD and one in the FSGS disease type group were treated with a triple RAAS inhibition which is not state of the art and does not refer to the standard set by the KDIGO 2021 guidelines. Either it must be an off-label use to treat a therapy resistant hypertension, or it was a sampling error due to the fact that it is a retrospective study and the gathering of data is biased it that way. We concluded that if those patients received the triple RAAS inhibition it was for a short time, probably for a few days and then later switched to a double RAAS inhibition.

A strong significant negative correlation between PCR (mg/g) to serum albumin (g/dL) was found for the FSGS disease type group (p = 0,000). It suggests that great proteinuria causes hypalbuminaemia due to urinary loss, but the mechanism behind hypalbuminaemia is not completely understood and one observation which argues against our findings is the fact as Praga et al. observed that patients with massive proteinuria often do not suffer from hypalbuminaemia. (11)

Clinical classification for FSGS was assessed but will not be further discussed due to just one patient diagnosed with a confirmed primary FSGS, so no differences between primary and secondary FSGS will be analysed.

A significant difference between age and nephrotic syndrome has been described for the MN disease type group and in the same disease type group the most patients receiving a RAAS inhibition with a total of 40 patients were observed.

One point that is worth mentioning is by preforming a Mann-Whitney-U test we find a significant difference (p = 0,001, effect size of 0,44216) between age and nephrotic

syndrome for the MN disease type group. Due to older patients maybe comorbidities (hypertension, diabetes) influence the glomerular structure and favour the development of nephrotic syndrome. Although in the study from Paolo et al they did not focus on the nephrotic syndrome itself they divided their patient group by age with the cut off laying by the age of 60 and postulate that older patients benefit from biopsy and diagnosis and further from therapy as such as younger patients. (30)

RAAS inhibition plays a very important part in the management of glomerular diseases especially in the initial treatment of MN as Bomback et al postulate(31) and additionally the state of the art by following the KDIGO guidelines for MN. In this thesis a total of 40 patients were treated with at least one RAAS inhibition, the most patients of all the disease type groups. Some could argue that number wise it is also the biggest patient group of the whole dataset and therefore also has the most patients receiving a RAAS inhibitions.

Focussing on the DKD disease type group, the patient characteristics showed the highest BMI and the maximum amount of ATH drugs taken. A study from Lu et al. suggests that a higher BMI is associated with an increased risk of developing DKD and decreased eGFR levels (32). With the results shown in our thesis we can underline those findings examining that the DKD disease type group showed the highest BMI with 28,1 kg/m2 [IQR 24,2-32,5] compared to the other groups and further after the AKI disease type group it showed the lowest eGFR levels such as 31,4 [IQR 24,6-39,1].

The disease type group DKD shows the highest amount of ATH drugs taken compared to the other disease type groups with 4,0 (IQR 3,0-5,0) and does raise the question if the ATH therapy is due to nephroprotective effects and treating DKD itself or it is a treatment for other comorbidities such as hypertension. From our point of we view we can’t say it for sure due to limitations of our retrospective study and evaluating the ATH therapy with the difficulty to determine the reason. Skof et al state in their review that the blood pressure management in DKD patients is very important mainly for the protective properties of the RAASI drugs, but another much more important pilar of therapy is the glycaemic management of DKD patients(33).

Analysing the markers of chronicity, the highest percentage in tubular atrophy is displayed in the histological images for the HN and DKD disease type group further by looking at the variation over time prevalence of those disease type groups seem to decrease. The outcome regarding the kidney replacement therapy shows the highest number in KRT patients for HN disease type group with 19 (41,3%).

Looking at the variation over time data a slight decrease in the prevalence for HN and DKD is seen in our data, this might be due to better treatment, more established primary prevention work, and earlier diagnosis of the underlying cause such as diabetes mellitus and hypertension. By analysing the 2017 annual report of the ÖGN the Austrian nephrology society we see a relatively small decrease of DKD in Austria, but no decrease or rather a small increase of HN can be observed in comparison to the trend seen in our data from 2007-2017. Here needs to be mentioned that our data differs since we are just one centre and are comparing the rest of Austria some slight differences are expected. The outcome regarding the kidney replacement therapy shows the highest number in KRT patients for HN with 19 (41,3%) and by also comparing it to the 2017 annual report of the ÖGN the Austrian nephrology society lists the HN disease type group as the second most common cause of ESRD in the year 2017. Keeping in mind that our data reflects the years from 2007 to 2017 in our department and the report refers just to the year 2017 including our data.

Data regarding complications of biopsy were collected and the complication most patient suffered from was haematoma. In our patient group in 15 cases (6,2%) the complication haematoma occurred, compared to the systematic Review by Poggio et al. in the most frequent complication in the overall studies was haematoma with 11%. (34) A reason why in our study the percentage is only around 6,2% can be explained by the fact that we in this thesis collected data just from a fraction of the total number of biopsies, by just including the nephrotic and other categorised patients and that the total number of complications for patients collected from 2007-2017 might be higher and probably close to 11%. Another explanation could be that due to our department intern elaborate SOP (standardized operation procedures), we can achieve lower complication rates.

Concluding the main findings of this study are probable the observation of a second age peak between 40 to 60 years of adult MCD patients, but further research is needed. Furthermore a relatively high percentage of the patients with nephrotic syndrome examined showed a nephritic sediment for the MCD disease type group, although a uniform definition of nephritic sediment cannot be found in the literature and should be defined more precisely.

10.0 Limitations

The main limitations is the definition of nephrotic for this thesis, we excluded the criteria oedema, due to the fact that retrospectively in this study the mentioning of oedema in the medical history was inconsistent. Other limitations can be found in the study format of a retrospective study, where we can't have been sure if the data was collected correctly, due to relying on the work of others. It needs to be mentioned that just the outcome was analysed not the therapy itself which limits the study. A further limitation is the number of patients itself, some of the disease type groups have only a small sample number, so the data is not as representative as in other bigger groups.

11.0 Bibliography

1. Agrawal S, Zaritsky JJ, Fornoni A, Smoyer WE, Katz H, Discovery D. Dislipidemias En Niños Tratamiento. 2018;14(1):57–70.
2. Cameron JS, Hicks J. The origins and development of the concept of a "nephrotic syndrome." Am J Nephrol. 2002;22(2–3):240–7.
3. Pal A, Kaskel F. History of nephrotic syndrome and evolution of its treatment. Front Pediatr. 2016;4(MAY):1–6.
4. Kelepouris E, Rovin BH. Overview of heavy proteinuria and the nephrotic syndrome. Glassock RJ, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
5. Hausmann R, Kuppe C, Egger H, Schweda F, Knecht V, Elger M, et al. Electrical forces determine glomerular permeability. Journal of the American Society of Nephrology. 2010;21(12):2053–8.
6. Reiser J, Von Gersdorff G, Loos M, Oh J, Asanuma K, Giardino L, et al. Induction of B7-1 in podocytes is associated with nephrotic syndrome. Journal of Clinical Investigation. 2004;113(10):1390–7.
7. Schnenberger E, Ehrich JH, Haller H, Schiffer M. The podocyte as a direct target of immunosuppressive agents. Nephrology Dialysis Transplantation. 2011;26(1):18–24.
8. Gbadegesin R, Lavin P, Foreman J, Winn M. Pathogenesis and Therapy of Focal Segmental. Pediatric Nephrology. 2013;26(7):1001–15.
9. Kaysen GA, Kirkpatrick WG, Couser WG. Albumin homeostasis in the nephrotic rat: nutritional considerations [Internet]. Available from: www.physiology.org/journal/ajprenal
10. Kaysen GA, Gambertoglio J, Jimenez I, Jones H, Hutchison FN. Effect of dietary protein intake on albumin homeo stasis in nephrotic patients. Vol. 29, Kidney International. 1986.
11. Praga M, Borstein B, Andres A, Arenas J, Oliet A, Montoyo C, et al. Nephrotic Proteinuria Without Hypoalbuminemia: Clinical Characteristics and Response to Angiotensin-Converting Enzyme Inhibition. American Journal of Kidney Diseases. 1991;17(3):330–8.
12. Radhakrishnan J. Pathophysiology and treatment of edema in adults with the nephrotic syndrome. Glassock RJ, Fervenza FC, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
13. Xiao M, Bohnert BN, Aypek H, Kretz O, Grahammer F, Aukschun U, et al. Plasminogen deficiency does not prevent sodium retention in a genetic mouse model of experimental nephrotic syndrome. Acta Physiologica. 2020;(May):1–15.
14. Radhakrishnan J. Lipid abnormalities in nephrotic syndrome. Glassock RJ, Rovin BH, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
15. Meyrier A, Radhakrishnan J. Etiology, clinical features, and diagnosis of minimal change disease in adults. Glassock RJ, Fervenza FC, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
16. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. Clinical Journal of the American Society of Nephrology. 2017;12(2):332–45.
17. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clinical Journal of the American Society of Nephrology. 2017;12(3):502–17.
18. Fervenza FC, Sethi S. Focal segmental glomerulosclerosis: Epidemiology, classification, clinical features, and diagnosis. Glassock RJ, Rovin BH, Lam AQ, editors. Waltham, MA: UpToDate; 2020.

19. Fervenza FC, Sethi S. Focal segmental glomerulosclerosis: Pathogenesis. Glassock RJ, Rovin BH, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
20. Beck LH, Salant DJ. Membranous nephropathy: Epidemiology, pathogenesis, and etiology. Glassock RJ, Fervenza FC, editors. Waltham, MA: UpToDate; 2020.
21. Couser WG. Primary membranous nephropathy. Clinical Journal of the American Society of Nephrology. 2017;12(6):983–97.
22. Kronbichler A, Oh J, Meijers B, Mayer G, Shin J Il. Recent Progress in Deciphering the Etiopathogenesis of Primary Membranous Nephropathy. Biomed Res Int. 2017;2017.
23. Beck LH, Salant DJ. Membranous nephropathy: Clinical manifestations, pathology, and diagnosis. Glassock RJ, Fervenza FC, Lam AQ, editors. Waltham, MA: UpToDate; 2020.
24. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et al. Authors Current Mailing address: 8. Paul Eggers Kidney & Urology Branch, NIDDK, National Institutes of Health, 6707 Democracy Blvd. 2081.
25. Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: Clinical characteristics, treatment, and outcomes. Clinical Journal of the American Society of Nephrology. 2007 May;2(3):445–53.
26. Florian Buchkremer M. Urine Sediment of the Month: Dysmorphic RBCs, the Hallmark of Glomerular Hematuria [Internet]. 2019 [cited 2023 Feb 3]. Available from: https://www.renalfellow.org/2019/03/09/urine-sediment-of-the-month-dysmorphic-rbcs-the-hallmark-of-glomerular-hematuria/
27. Chen DP, Helmuth ME, Smith AR, Canetta PA, Ayoub I, Mucha K, et al. Age of Onset and Disease Course in Biopsy-Proven Minimal Change Disease: An Analysis From the Cure Glomerulopathy Network. American Journal of Kidney Diseases [Internet]. 2023 Jan 3 [cited 2023 Jan 26]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638623000021
28. Fenton A, Smith SW, Hewins P. Adult minimal-change disease: Observational data from a UK centre on patient characteristics, therapies, and outcomes. BMC Nephrol. 2018 Aug 16;19(1).
29. Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: Clinical characteristics, treatment, and outcomes. Clinical Journal of the American Society of Nephrology. 2007 May;2(3):445–53.
30. Paulo RPMB, Jorge LB, Yu L, Woronik V, Dias CB. Diagnosis and course of membranous nephropathy in adults: comparison by age group. Kidney Blood Press Res. 2022 Oct 20;
31. Bomback AS, Fervenza FC. Membranous Nephropathy: Approaches to Treatment. Vol. 47, American Journal of Nephrology. S. Karger AG; 2018. p. 30–42.
32. Lu J, Liu X, Jiang S, Kan S, An Y, Zheng C, et al. Body Mass Index and Risk of Diabetic Nephropathy: A Mendelian Randomization Study. Journal of Clinical Endocrinology and Metabolism. 2022 Jun 1;107(6):1599–608.
33. Skov J, Christiansen JS, Poulsen PL. Hypertension and diabetic nephropathy. Endocr Dev. 2016;31:97–107.
34. Poggio ED, McClelland RL, Blank KN, Hansen S, Bansal S, Bomback AS, et al. Systematic review and meta-analysis of native kidney biopsy complications. Clinical Journal of the American Society of Nephrology. 2020 Nov 1;15(11):1595–602.