Ph.D. thesis
(Summary)

THE NATIONAL CHARACTERISTICS OF IGA NEPHROPATHY AND INVESTIGATION OF RISK FACTORS DETERMINING PROGRESSION – USING A DATABASE SYSTEM

Tibor Vas M.D.

Head of the Doctoral (Ph.D) School: Judit Nagy M.D., D.Sc.
Supervisor: Judit Nagy M.D., D.Sc., Tibor Kovács M.D., Ph.D.

University of Pécs, Medical Faculty
2nd Department of Internal Medicine and Nephrological Center
Pécs, Hungary

2007

Abbreviations

ABPM	- ambulatory blood pressure monitoring
ACE	- angiotensin converting enzyme
ACEi	- angiotensin converting enzyme inhibitor
AGE	- advanced glycation end products
BMI	- body mass index
CCB	- calcium chanel blocker
CML	- N^{ε}-carboxymethyl-lysine
CRP	- C-reactive protein
cTI	- computerised tubulointerstitial index
TI	- tubulointerstitial index
GI	- glomerular index
VI	- vascular index
GN	- glomerulonephritis
IgAN	- IgA nephropathy
NS	- not significant
OGTT	- oral glucose tolerance test
qGSI	- qualitative glomerulosclerotic index
SD	- standard deviation
TBARS	- thiobarbituric acid reactive substances

1. INTRODUCTION

IgA nephropathy – also known as Berger's disease in the literature – is the most common form of primary glomerulonephritides. It occurs in individuals of all ages, but is most common in young adults. Diagnosis requires immunofluorescent examination of kidney tissue. Although the progression is slow and the disease was thought to have a benign course, on the basis of long term follow up 30-40% of patients needs dialysis 20 years after the diagnosis. The investigation and recognition of possible factors contributing to the progression of the diasease are of great importance. Because of the relatively slow progression of the disease, patients are followed up for many years. During the kontroll examinations (2-4 times a year) great amont of information is piled up about the course of the disease. Data needed for controll, treatment and follow up of the patients are available only through the study of the patient's file and other medical documentation. It is an extraordinarily difficult, time consuming method with the possibility of errors. The need for storing, analysing this significantly great amount of data raised the idea of creating a database, which – beyond the storing of the data - can help to recall the stored information according to specific criteria, to summarise and export the data for different statistical and matematical softwares for more comlex analysis. Softwares used until recently were not able to completely fulfill this need. Our aim was to create a database system using all available medical files of IgAN patients, which can considerably speed up safley and this work. Until the end of 2007, medical documentation of 320 IgAN patients was processed this way. The database is updated regularly.

Structure of the database

Each patient in the database has a so-called „static" and a „variing" table consisting of different parts with continuously growing amount of the following data:

„Static" table: Personal data, onset of the first symptoms, the diagnosis of IgAN (time of renal bipsy), anamnesis, diagnosis of the patient with onset of the diseases, risk factors, family history.

„Variing" table (each time the patient is admitted to the clinic): Changes in the patient's anamnesis, vital signs, laboratory tests (blood and serum), renal funtion, urine analysis, diagnostic interventions, data about administered drugs and diet.

The database enables the investigation of connenctions between these data with the help of biostatistical methods. This is made easier by the fact, that the database is compatible with the

most widespread statistical and presentation creating programms, can be updated almost without any limitation, even with new types of data if required. The data stored can be called back according to special conditions, groupped, or exported for statistical analysis, creating presentations etc.

The complex examination of potential factors playing a role in the progression of the disease is possible with analysing the data obtained during the long term observation of IgAN patients. The importance of the examinations shows the fact, that the cause and the exact pathomechanism of the disease is not yet known. It is especially important in the light of the fact, that the disease's prevalence is high and 30-40% of the patients need dialysis after 20-25 years follow up.

2. HYPOTHESIS AND AIMS

2.1. Epidemiological data of IgAN patients cared at our clinic.

Our work is the first national survey on epidemiology and characteristics of IgAN based on the database consisting of great amount of data. The following epidemiological questions were addressed with the help of the IgAN database:

- the incidence and prevalence of the disease in county Baranya
- the frequency of the diasease in renal biopsies
- the age of the patients at the time of renal biopsy
- the frequency and characteristics of clinical symptoms at onset of the disease

2.2. Investigations of factors influencing the progression of the disease

2.2.1. Recurrent urinary tract infections.

Because of the decreased protection of mucous membranes it can be supposed, that the prevalence of chronic urinary tract infections with or without symptoms or that of the significant bacteriurias is increased in IgAN. The urinary tract infections may contribute to the progression of IgAN due to the damage of the tubulointerstitium. The following questions were addressed:

- the frequency of significant bacteriurias and urinary tract infections among IgAN patients
- what are the pathogens
- to what degree are urinary tract infections presented with symptoms?

- is the progression of the disease influenced by urinary tract infections?
- may the unfavourable effect of urinary tract infections on the progression be fended off by antibiotic treatment

2.2.2. Tonsillectomy

The frequent upper respiratory tract infections of IgAN patients often paralell with macroscopic haematuria and the frequency of chronic tonsillitides observed even among our patients raised up the potential role of tonsills in the pathogenesis of the disease. On the basis of these observations tonsillectomy may exert favourable effect on the pathogenesis of the disease by eliminating the antibodies. We looked for aswers for how the

- urine (proteinuria and haematuria)
- renal function (creatinin clearance)
- progression
- has changed after tonsillectomy.

2.2.3 The 24-hour blood pressure monitoring and the progression of IgAN.

The early diagnosis and effective treatment of high blood pressure is of special importance in chronic glomerulonephritides, even in IgAN, because the connection between the progression of renal diseases and hypertension is well known. Numerous investigators found, that renal survival of IgAN patients with hypertension is worse compared to patients without hypertension. Ambulatory blood pressure monitoring provides a better picture about the daily blood pressure compared to casual measurements, even the „white coat effect" and the decrease of diurnal rythm is recogniseable. Analysing the data obtained by ambulatory blood pressure monitoring of IgAN patients, we were looking answers for the following questions:

- Are there any differences between the mean blood pressure values obtained by ambulatory blood pressure monitoring and casual measurements?
- Diurnal rythm in IgAN patients
- Prevalance of white coat effect in IgAN
- Effectiveness of antihypertensive therapy.
- Is there any connection between results obtained by ambulatory blood pressure monitoring (effect of white coat hypertension, presence or absence of diurnal rythm) and the progression of IgAN.

2.2.4 Antihypertensive drugs with different pathomechanism and the progression of IgAN.

The secunder hypertension developed paralell with the destruction of active renal parenchyma, the increased intraglomerular pressure and hyperfiltration causes further damage to the already active nephrons. Thus, normalising blood pressure is of special importance among factors slowing the progression of IgAN. Angiotensine converting enzyme inhibitors (ACEi) and the non-dihydropyridine type calcium channel antagonists (CCB) are very advantageous from this point of view, because it's renoprotective effect is more expressed compared to other types of antihypertensive drugs with the same blood pressure lowering ability.

Long acting drugs (administered 1-2 times a day) have numerous advantages compared to the short acting drugs (administered 3-4 times a day): better patient's compliance, more uniform drug effect, resulting in decreased target organ damage. We wanted to investigate the following:

- effect of short and long acting ACE inhibitors and CCBs compared to each other at the same patient
- comparison of the renoprotective effect of short-, and long acting antihypertensive drugs

2.2.5 Connection of oxidative stress and non-enzymatic glycation in IgAN.

During non-enzymatic glycation advenced glycation endproducts are formed in human body. They play an important role in the progression of renal diseases. AGEs (so the N^{ε}-carboxymethyl-lisine, CML) are produced because of oxidative stress also, but their serum level may increase due to decreased elimination (decreased renal function). Oxidative stress presented during the oxidation of LDL is of special importance in the pathogenesis of vascular diseases. But relatively few data is available about serum AGE levels and oxidative stress in IgAN until now. We were looking for answers for the following questions:

- Level of non-enzymatic glycation in IgAN (through measuring the circulating serum level of fluorescent AGEs and CML)
- Oxidative stress in IgAN (measuring TBARS)
- The oxidative resistance and oxidative modification of LDL (change of its TBARS és α-tocopherol etc. content)

2.2.6 Histomorphological and histomorphometrical examinations and progression of IgAN.

The histological findings using light microscopy in IgAN are not uniform: it may vary from minimal lesions to focal or diffuse proliferative glomerulonephritides even with crescents. Connection between histological findings, renal function and progression of the disease was investigated by lot of investigatiors. The following questions were addressed:

- is there any connection between the different hisomorphological classifications of IgAN and renal function at the time of renal biopsy.
- what is the connection between histological findings and the change of renal function.

2.2.7 Metabolic syndrome and the progression of IgAN

Parts of the metabolic syndrome are cardiovascular risk factors on their own, but their common effect is much more harmful. Aim of our study was to investigate:

- the prevalence of the metabolic syndrome and it's components in IgAN.
- connection between the components of metabolic syndrome and progression of IgAN.

3. METHODS AND RESULTS

3.1. Epidemiological data of IgAN patients cared at our clinic.

IgAN was diagnosed in 17.5% of renal biopsies at our clinic between 2002 and 2005 (32.4% among primary glomerulonephritides). It meant 61 newly diagnosed IgAN patients.

Mean follow up was 12 ± 7 years. Until the end of 2006, our database consisted of 287 patient's data (209 male, 78 female), female/male ratio 1/2.68.

The distribution of IgAN patients at renal biopsy according to their age was: 0-20 years, n=37 (12,89%), 21-30 years, n=76 (26,48%), 31-40 years, n=78 (27,17%), 41-50 years, n=57 (19,86%), 50-60 years, n=30 (10,45%), 61-70 years, n=6 (2,10%), 71-80 years, n=3 (1,05%). Follow up time: 0-5 years, n=134 (46,69%), 6-10 years, n=54 (18,81%), 11-15 years, n=29 (10,10%), 16-20 years, n=32 (11,15%), >20 years fölött, n=38 (13,24%). Proteinuria: <0,5 g/day, n=61 (29,47%), 0,5-3 g/day, n=124 (59,91%), >3 g/day, n=22 (10,62%). Haematuria at the diagnosis: haematuria, n=183 (63,76%), no haematuria, n=104 (36,24%). Hypertension at the diagnosis: known hypertension, n=99 (34,49%), hypertension, not yet known, n=20 (6,97%), no hypertension, n=168 (58,54%).

3.2. Investigations of factors influencing the progression of the disease

3.2.1. Recurrent urinary tract infections.

Microbiological tests of the urine were made at each control examination (every 3-6 months) independently of the patient's symptoms. The controll group consisted of 19 IgAN patients without urinary tract infection. During the follow up the following parameters were recorded every 6-12 months: serum creatinin, serum carbamid nitrogen, creatinine clearance, blood sedimentation rate, serum potassium, blood pressure, presence of haematuria, proteinuria. Data were analysed retrospective.

76 patients file was analysed, bacteriurias were found in 19 patients (1-5 times). Frequency of bacteriurias was 0,21/pts/year. Total number of bacteriurias were 37 (29 presented without symptoms). The recurrent infections were caused by the same bacteria in 10 cases. Creatinine clearance decreased in both groups during the 8,42 years follow up (UTI group: from 102,82 ± 37.6 ml/min to 88,07 ± 30.47 ml/min, controll group: from 98,69 ± 37,74 ml/min to 72,49 ± 34,21 ml/min, not significant).

3.2.2. Tonsillectomy

The history of 50 IgAN patients with tonsillectomy was investigated. The controll group consisted of 60, age, sex, renal function, follow up time matched IgAN patients with chronic tonsillitis. The mean survival time from renal biopsy to creatinin clearance<80 ml/min/1,73m^2 was 143,8±13,9 months in patients with tonsillectomy, and 117,9±12,4 months without tonsillectomy. The mean survival time to ESRD was 229,9±8,4 and 208,2±9,2 months in the two groups. Differences were not significant.

Using Cox-regression analysis, tonsillectomy and decreased proteinuria had favourable influence on time to creatinin clearance<80 ml/min/1,73m^2, but tonsillectomy had no favourable, significant effect on time to ESRD.

3.2.3 The 24-hour blood pressure monitoring and the progression of IgAN.

126, biopsy proven IgAN patients were involved in the study. Ambulatory blood pressure monitors (Meditech, type 02-03) were used for 24 hours (daytime: every 15 minutes, nighttime: every 20 minutes). Casual measurements were made on three times, in sitting position after 5 minutes rest. 55 patients were normotensive (36 male/19 female, mean age 37.7 ± 10 years), 71 patients hypertensive (57 male/14 female, mean age 46.4 ± 12 years).

Comparison of the blood pressure values measured by ABPM and casual measurements. The mean blood pressure levels in IgAN patients were higher (135.7±14.0 / 87.8±8.8 mmHg) compared to 24-hour (126.3±10.2 / 82.3±8.8 mmHg), daytime (127.2±10.2 / 83.3±9.5 mmHg) and nighttime (123.6±14.8 / 79.1±11.5 mmHg, $p<0.005$) blood pressure values obtained by ABPM.

The diurnal rythm of blood pressure. The 82 % of the normotensive IgAN patients were „dipper" (41/55) and 93 % (66/71) of hypertensive IgAN patients were „non-dipper".

White coat hpertension. Ten normotensive patients was thought to have hypertension on the basis of casual measurement (mean blood pressure 149±7/96±8 mmHg), but significantly lower blood pressure levels were found using ABPM (mean: 127±6/83±5 mmHg, $P<0.05$). White coat hypertension was observed at 14 treated hypertensive patients (mean blood pressure: 152±8/98±6 mmHg, ABPM: 130±4/85±8 mmHg, $P<0.05$).

Effectiveness of the antihypetensive treatment. No difference was found between the mean daytime blood pressure of normotensive and treated hypertensive IgAN patients measured by ABPM. Normotensive patients had signifficantly lower nightime blood pressure compared to treated hypertensive IgAN patients.

3.2.4 Antihypertensive drugs with different duration time and pathomechanism and the progression of IgAN.

Data of 22, hypertensive, biopsy proven IgAN patients were analysed (male/female: 18/4, mean age at onset: 32.45 ± 9.53 years, mean follow up time 7.25 ± 2.36 years). After treatment with short acting ACE inhibitors (captopril, n=20) and/or dihydropyridine type CCBs (nifedipine, n=13) for at least 3 years, long acting ACE inhibitors (enalapril, n=18, cilazapril, n=4) and/or CCBs (diltiazem hydrochlorid, n= 16) were used. Short acting drugs were administered three times, long acting ones two times a day. At each controll examination the values of seum creatinin, creatinine clearance and the level of proteinuria was recorded. Just before the shift to the long acting drugs and three years after that shift ABPM examinations were made. Proteinuria and creatinine clearance was measured at the same time.

To estimate the progression of IgAN patients we calculated the slope of 1/creatinine values during the years of both short and long acting administration of drugs. After the shift to the administration of long acting drugs the slope of the 1/creatinine values and the level of proteinuria significantly decreased. Creatinine clearance values did not change significantly.

3.2.5 Connection of oxidative stress and non-enzymatic glycation in IgAN.

88 IgAN patients were involved in the study. They were devided into two groups according to their renal function. Patients with normal renal function (creatinine clearance ≥ 80 ml/min) made up the first group (creatinin clearance 106 ± 22 ml/min, n=54) and patients with decreased renal function (creatinin clearance 51 ± 19 ml/min, n= 34) made up the second one. Healthy volunteers with normal renal function made up the control group (creatinin clearance 102 ± 24 ml/min, 18 female, 44 male, mean age 32 ± 11 év). OGTT was made at the same time.

Serum AGE level was measured by determination of AGE-FL and CML levels. The level of AGE-FL was measured using fluorescent spectrofotometer (Hitachi F-4500, with excitation wave lenght of 370 nm, and emission wave lenght of 440 nm). CML was measured by competitive ELISA method. The mean values of three measurements on each sample were used at our calculations.

To determine the level of the oxidative stress, the level of TBARS was measured using fluorescent spectrofotometer described by Jentzsch (with excitation wave lenght of 532 nm, and emission wave lenght of 553 nm).

Oxidative stress/glycation parameters and renal function. Significantly elevated TBARS levels were found in both the plasma and in the LDL particles of patients with normal and elevated renal function ($p < 0.001$), parelell with the decreased oxidative resistance of LDL ($p < 0.04$). AGE-FL and CML levels did not differed significantly in IgAN patients with normal renal function compared to controll group. But these levels were significantly elevated in patients with decreased renal function.

Oxidative stress/glycation parameters and glucose metabolism. The AGE levels and parameters of oxidative stress were influenced only to a minor degree by the initial disorder of glucose metabolism. The oxidative resistance was significantly decreased in patients with both normal and disturbed glucose metabolism compared to controll group after adjustment for age and renal function.

Among IgAN patients with disturbed glucose metabolism AGE-FL and CML levels were elevated only in patients with decreased renal funcion compared to controlls. But TBARS levels were significantly elevated in IgAN patients with both normal and decreased renal function compared to controll group. In the same way, among IgAN patients with normal glucose metabolism (n=67), the AGE-FL and CML levels were higher only in patients with decreased renal

fnction, when compared to contolls. In IgAN patients with normal glucose metabolism TBARS levels were elevated in patients with both normal and decreased renal function.

Connection between AGE-s and renal function. In all of the IgAN patients (n=88) significant correlation was found between creatinine clearance and AGE-FL, CML levels.

Correlation between oxidative resistance of LDL and it's α-tocopherol content. IgAN patients were devided into two groups: patients with α-tocopherol content below (< 8.34 mol/mol ApoB, mean: 7.32 ± 1.02 mol/mol ApoB, n = 49) and above (> 8.34 mol/mol ApoB, mean 9.54 ± 1.39 mol/mol ApoB, n = 39) the mean value of α-tocopherol level. The oxidative resistance was significantly lower and the TBARS content of LDL was significantly higher in IgAN patients with low α-tocopherol content, compared to patients with high α-tocopherol content and controlls. The TBARS content of LDL was significantly higher in patients with high α-tocopherol compared to controlls.

3.2.6. Connection between histomorphological and histomorphometrical findings and progression of IgAN.

Only biopsies with at least 6 glomeruli were examined. This criteria was fulfilled in 128 cases among biopsies executed between 1975 and 2000 at our clinic. WHO classification was applied for histomorphological examinations. Histomorphometrical examinations were made according to Risdon (tubulointerstitial index), Kusumoto (glomerular index) and Bader (vascular index). The qGSI index was determined by the modification of the method described by Vleming.

During the computerised analysis of the interstitium (cTI) photos of the slides stained by Masson-trichrom were recorded using a digital kamera (Ikegami, 10 field of view each case, 400x magnification). No glomeruli, arteries, dilated tubuli were recorded. At each picture blue colour showing the interstitium was marked using the Adobe Photo Shop computer programm, and it's area calculated by the Scion Image program. To obtain the cTI, the calculated values were averaged (10-10 photo at each case). The above measurements were made by a pathologist without any information obout the patients clinical or laboratory data.

Patients were grouped by the histological indices (WHO: 4 groups, TI: 4 groups, GI: 5 groups, VI: 3 groups, qGSI-A és qGSI-B: 4-4 groups). Time from the diagnosis of the disease to the endpoints (serum creatinine>200 umol/l, serum creatinine>500 umol/l, creatinin clearance <80 ml/min) was calculated by Kaplan-Meier analysis and the difference was analysed by log-rank test

between the groups. Factors influencing the time until the endpoints were analysed by Cox-regression analysis.

Data of patients grouped on the basis of the WHO classification and time to the different end points are shown in Table 1.

	WHO 1	**WHO 2**	**WHO 3**	**WHO 4-5**
No of patients (n=)	14	31	42	39
Age (year)	36.79 ± 9.10	31.87 ± 12.82	30.07 ± 8.86	37.77 ± 12.73
Serum creatinine (umol/l)	95.86 ± 16.10	94.16 ± 23.38	97.33 ± 21.00	123.61 ± 93.70
Creatinine clearance (ml/min/1.73 m2)	93.43 ± 16.30	92.13 ± 23.25	95.68 ± 19.65	75.45 ± 30.40
Time until creatinine clearance < 80 ml/min/1.73 m2 (months)	158 ± 135	146 ± 139	125 ± 116	71 ± 112 [a]
Time until serum creatinine > 200 umol/l (months)	- [+]	234 ± 128	206 ± 130 [b]	231 ± 175 [b]
Time until serum creatinine > 500 umol/l (months)	- [+]	256 ± 95	228 ± 123	256 ± 180

[a] vs. WHO 1-3, $p < 0,05$, [b] vs. WHO 1, $p < 0,05$, [+] all of the patients are censored

Table 1. Data of patients grouped on the basis of the WHO classification at renal biopsy and time to different end points.

Paralell with the worsening of the tubulointerstitial changes the time to different endpoints were gradualy decreased. The same tendency was found in case of the vascular index. In the different GI groups only the group with modest histological changes showed significantly better outcome compared to the other GI groups.

Completely scarred glomeruli was found in 43 out of the 98 cases. Examinations were made involving (qGS.I.-B) and excluding (qGS.I.-A) these glomeruli. Paralell with the worsening of qGS.I., the time until endpoints decreased. Significantly poorer outcome at each endpoint was found only in patient group with the worst qGS.I. (both qGS.I.-B and qGS.I.-A) compaired to other qGS.I. groups.

Time from renal biopsy to serum creatinine >265 umol/l („point of no return") was significantly infuenced by T.I. ($p<0.001$), V.I. ($p=0.03$), qGS.I.-A ($p<0.001$), qGS.I.-B ($p<0.03$) and the cTI. ($p=0.001$), and time to creatinine clearance <80 ml/min was influenced by V.I.

(p=0.005), qGS.I.-A (p<0.02), and qGS.I.-B (p<0.05). Only tubulointerstitial index exerted significant influence on time to ESRD (p<0.001).

4.2.7 Metabolic syndrome and the progression of IgAN.

The folowing parameters of 163 IgAN patients were determined: blood pressure, serum triglicerid, HDL, cholesterol, LDL, uric acid, fasting glucose, serum creatinine, creatinine clearance. The number of metabolic syndrome components were calculated at each patients at renal biopsy.

- *Impaired glucose metabolism* (impaired fasting glucose, impaired glucose tolerance, diabetes mellitus).
- *Hypertension* (treated or repeated casual blood pressure ≥ 140/90 mmHg based on WHO criteria).
- *Dyslipidaemia* (serum triglycerid ≥1.7 mmol/l, total cholesterol > 5.2 mmol/l, LDL > 3.4 mmol/l, or HDL < 1.0 mmol/l).
- *Obesity* (body mass index ≥ 27 kg/m2).

Fifty out of the 163 patients (30.7%) had already metabolic syndrome. Its importance is underlined by the fact, that their mean age at diagnosis was only 33.4±10.2 years. At the diagnosis og IgAN, 68.1% of patients had at least 2 metabolic syndrome components. In patients with 2-4 metabolic syndrome components the time to both examined endpoints (creatinine clearance<80 ml/min and serum creatinine>500 umol/l) was significantly shorter compaired to patients with 0-1 components.

4. DISCUSSION

4.1 Epidemiological data of IgAN patients cared at our clinic.

IgAN usually starts at younger ages. No national data about the incidence of IgAN based on renal biopsies was avaiable so far. From 1977, 314 IgAN patients were diagnosed at our clinic. 66 percent of these patients were younger, than 40 years old, and only 3.13% were older, than 60 years at the time of diagnosis. Because of the relatively slow progression of the disease, the long term follow up of patients has great importance. More, than half of our patients (53.3%) has been followed up for more than 5 years, and 24.4 % of patients has been followed up for more than 15 years.

The microscopic and macroscopic haematuria followed 1-2 days after infections is characteristic for the disease. Similar to other publications, microscopic or macroscopic haematuria was found at 63.76% of patients examined first time at our clinic. Presence of heavy proteinuria is not typical, only 7.66% of cases presented with expressed (>3g/day) proteinuria at diagnosis. Considerably, almost half of our patients (41.46 %) has had hypertension at onset.

4.2. Investigations of factors influencing the progression of the disease

4.2.1. Recurrent urinary tract infections.

Decreased protection of mucous membranes observed in IgAN, the more frequent urinary tract infection without symptoms may exert an unfavourable influence on the progression of the disease due to damage of the interstitium. Urinary tract infection was observed in 25 % of patients followed up for at least 3 years, caused mainly by Gramm negativ bacteria. The progression of IgAN in these patients was not faster compared to the age, sex, follow up time matched controll group. The early treatment with antibiotics (for 7-10 days or continuously for months if they offen recur) may have fended off the unfavourable effect of chronic urinary tract infections causing tubulointerstitial damage. Although not signifficant, the decrease in creatinine clearance during follow up was suprisingly smaller in urinary tract infections group, arising the old assumption, that antibodies causing IgAN originate from infections. Treatment with antibiotics may decrease the amount of antigens, and thus the immuncomplexes.

4.2.2. Tonsillectomy

On the basis of our data, tonsillectomy had no statistically relevant favourable effect on the prgression of the disease. The minor difference in survival time until the endpoint of serum creatinin<80 ml/min/1.73 m2 practically disappeared if time to ESRD was investigated. Similarly, tonsillectomy had favourable effect in Cox regression analysis, only if endpoint was the time to serum creatinin<80 ml/min/1.73 m2. We can assume, that tonsillectomy has no significant effect on the outcome of IgAN, despite the short term (1-2 years) favourable effect on haematuria/proteinuria.

4.2.3 The 24-hour blood pressure monitoring and the progression of IgAN.

On the basis of our data, the dipper/non-dipper ratio in normotensive IgAN patients and healthy controlls are similar, but 93 % of hypertensive IgAN patients are non-dipper.

The unfavourable cardiovascular effect of non-dipper blood pressure values is well known. The „white coat hypertension” was described even in the mild forms of essential hypertension.

This phenomenon was observed even in 18% of our normotensive patients. This is similar to the frequency of „white coat hypertension" observed in essential hypertension. We found „white coat hypertension" in 20% of our treated hypertensive patients. Neglecting this fact may lead to administration of antihypertensive drugs to otherway normotensive patients, or the dose in hypertensive patients may be overestimated. Hypotension may lead to decrease in GFR due to the decreased intraglomerular filtration pressure. Even the psychological effect of the awareness of hypertension and the cost of unnecessary administered drugs can not be neglected.

The daytime blood pressure in normotensive and treated hypertensive IgAN patients did not differ significantly, but the night time blood pressure decrease was absent in treated hypertensive patients, partially explaining the faster deterioration of renal function in treated hypertensive patients. The early, effective antiyhpertensive treatment, the re-establishment of diurnal rythm of the blood pressure may deleay the developement of ESRD.

4.2.4 Antihypertensive drugs with different duration and pathomechanism and the progression of IgAN.

The effect of short-, and long acting drugs on the disease' progression was not investigated in the same IgAN patients so far. Long acting antihypertensive drugs are more favourable compared to short acting ones, due to better compliance of patients and their more uniform effect. The change of the slope of 1/creatinine regression lines after administration of long acting antihypertensive drugs supports these assumptions.

On the basis of our data, during the administration of long acting antihypertensive drugs blood pressure values were lower, independently of the part of the day, but only 24 hour diastolic blood pressure, the 24 hour hypertensive time index, and 24 hour diastolic hyperbaric impact showed signifficant difference. The effect of long acting drugs on the decrease of night time blood pressure is more expressed, the mean value of the diurnal index was elevated in our study.
During the administration of long acting antihypertensive drugs the proteinuria and the progression of IgAN significantly decreased.

4.2.5 Connection of oxidative stress and non-enzymatic glycation in IgAN.

Oxidative stress is caused by free radicals formed during oxidation-reduction reactions. Under normal conditions specific enzimatic and non-enzymatic reactions eliminates the free radicals. The imbalance between the production and elimination of free radicals may lead to damage of different organs. Using numerous markers of oxidative stress many publications

proved, that under uraemic conditions oxidative stress is increased. According to some data, increased oxidative stress may be observed even before the developement of ESRD.

We found significantly elevated amount of TBARS in serum and in LDL, and decreased oxidative resistance of LDL in IgAN patients compared to healthy controlls. This increased level of oxidative stress was not influenced neither by the renal function nor the glucose metablism of the patients.

The AGE levels were not investigated in IgAN patients so far. The AGE-FL and CML levels were not higher in IgAN patients with normal renal function, but these levels were significantly elevated in IgAN patients compared to patients with normal renal functions, or to contolls.

These observation supports the idea, that decreased renal function is responsible for the elevated AGE-FL and TBARS levels in IgAN. The LDL of IgAN patients with higher LDL α-tocopherol content had increased oxidative resistance independently of renal function.

Increased oxidative stress seems not to be specific for IgAN, because the same observations were made in the early stages of other glomerulopathies. On the basis of our present and previous examinations the elevated AGE levels in decreased renal function is independent of the underlying kidney disease.

5.2.6. Connection between histomorphological and histomorphometrical findings and progression of IgAN.

In patients grouped by the WHO classification the WHO I-II-III groups showed a tendency for deteriorating renal function, but without significance. No difference was observed between WHO group IV-V. On the basis of our data, from prognostic point of view, WHO I-V. classification may be replaced by two groups: patients with good prognosis (WHO I-III), and with poorer one (WHO IV-V).

On our opinion the progressive renal insuffitiency is the consequence of glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. On the basis of our results in early stages of renal disease glomerular and tubulointerstitial changes plays an equal role, but in the developement of ESRD the tubulointerstitium plays a definite role. Taking scared glomeruli into account did not influenced the assessment of the progression.

5.2.7 Metabolic syndrome and the progression of IgAN.

The syndrome is important partly because of their frequency, and partly the increased oxidative stress, the associated atherosclerosis, and target organ damages as a consequence. The components of metabolic syndrome are itself independent cardiovascular risk factors.

The early diagnosis of the syndrome or their components is the basis of it's treatment. Metabolic syndrome resembles an iceberg, where the peaks (the components of the metabolic syndrome) are targets of the therapeutic interventions.

The increased incidence of metabolic syndrome, similarly to the hungarian population, was observed also in our IgAN patients. It is worth mentioning, that in 30 % of IgAN patients metabolic syndrome was observed already at the time of diagnosis.

Considering the low age of patients at diagnosis and the increasing prevalence of metabolic syndrome paralell with time, it may considerably contribute to the deterioration of renal function, to the increased cardiovascular morbidity and mortality.

On the basis of our observations, the unfavourable effect of the metabolic syndrome on the progression of IgAN was proved, resulting in decreased renal survival time to both mild renal damage and ESRD.

This effect was already obsereved not only in patints with metabolic syndrome, but in patient having at least two metabolic syndrome components.

5. LIST OF THE Ph.D. THESES:

1. Our work is the first national survey on epidemiology and characteristics of IgAN based on the database consisting of great amount of data.

2. The early diagnosis and treatment of recurrent urinary tract infections in IgAN may account for the fact, that these patient's prognosis don't differs from the prognosis of patients without urinary tract infections.

3. Tonsillectomy made because of frequent upper respiratory tract infections has no influence on the long term progression of the disease.

4. The early diagnosis and treatment of hypertension is of special importance in the decrease of the progression.

a) With our ABPM examinations we described at the first time the mean characteristics of IgAN patient's hypertension. Among these factors the absence of the diurnal rythm (in both normotensive and hypertensive patients), and the presence of „white coat hypertension" are most important.

b) We proved at the first time in IgAN, that the shift from short-, to long acting antihypertensive drugs can decrease the progression of the disease paralell with the more uniform antiyhpertensive effect.

5. We proved for the first time (together with our previous observations), that oxidative stress is increased already in patients with normal renal function, but the serum level of AGEs tends to increase only paralell with the decrease of renal function. The oxidative resistance of LDL is increased in patients with higher LDL α-tocopherol content, independently of renal function.

6. Using different morphometrical and morphological methods, glomerular, tubulointerstitial, vascular changes were analysed. Even our new observations have proved the role of the tubulointerstitial damages in the IgAN's long term prognosis.

7. 30% of patients has metabolic syndrome already at the time of diagnosis, other patients develop the syndrome during the course of the disease. Patients with metabolic syndrome has clearly poorer outcome.

ACKNOWLEDGEMENT

I am very thankful to professor Judit Nagy for the human support, clinical, scientific advices and instructions. I am thankful for helping me through the hours of dispair with her professional vocation and enormous working capacity.

I pay gratitude and respect to professor István Wittmann for their scientific and clinical knowledge he gave me, and especially for the considerable and practical help in the field of oxidative stress.

I am very thankful to my supervisor, to Tibor Kovács for the enourmous and selfless proffesional support and guidance he gave me from the first steps in my experimental work.

I am grateful to Zoltán Wagner for the measurements of oxidative stress parameters and advanced glycation endproducts in the serum of our IgAN patients, and to Zsuzsa Varga for the measurements of LDL's oxidative resistance.

I am thankful to Peter Degrell for the professional help in the field of renal pathology and for the thorough and time consuming analyis of our IgAN patient's renal biopses, making our clinical investigations about histological findings and progression of the diseases possible.

I am thankful to Matild Schmelczer, who gave me encouraging words and practical advices when I was a medical student.

I am grateful to László Pótó for the practical help in statistical analysis.

Many thanks for Tamás Szelestei, István Pintér, László Wagner and István Mazák for the comments on this work, for Sámikné Ilona Varga, Heitmanné Anikó Lendvai and Enikő Bodor and for the others, not mentioned above, but helping me in this work.

6. LIST OF PUBLICATIONS USED FOR THE THESES.

Publications

I. **Vas T.**, Wagner Z., Jenei V., Varga Zs., Kovács T., Wittmann I., Schinzel R., Balla Gy., Balla J., Heidland A., Nagy J.: Oxidative stress and non-enzymatic glycation in IgA nephropathy. Clin Nephrol. 2005, 64 (5), 343-351.

II. Wagner Z., Molnár GA., Mazák I., **Vas T**., Wagner L., Tamaskó M., Laczy B., Nagy J., Wittmann I.: Az előrehaladott glikációs végtermékeke akkumulációja krónikus vesebetegségekben – a vesefunkció romlás, mint az atherosclerosis rizikófaktora. Metabolizmus, 2004, 4, 166-169.

III. Wittmann I., Wagner Z., Mazák I., Pótó L., Wagner L., Kovács T., **Vas T.**, Molnár GA., Nagy J: A vesefunkció határozza meg az öregedést? Hypertonia és Nephrológia. 2002, 6, 222-227.

IV. **Vas T.** Wagner Z., Kovács T., Wittmann I., Schinzel R., Heidland A., Kientsch-Engel R., Nagy J.: Nem enzimatikus glikáció és oxidatív stress IgA-nephropathiában. Hypertonia és Nephrológia. 2002, 6, 273-277.

V. Nagy J., Kovács T., **Vas T**., Wittmann I.: Az IgA nephropathiás betegek kezelési lehetőségei. Hypertonia és Nephrológia. 2001, 5 (1), 3-8.

VI. **Vas T.,** Kovács T., Szelestei T., Csiky B., Nagy J.: A rövid és a hosszúhatású antihypertensiv szerek renoprotectiv hatásának összehasonlító vizsgálata IgA nephropathiás betegekben. Orv Hetil 1999, 140(36), 1991-1995.

VII. Csiky B., Kovács T., Wagner L., **T. Vas**, Nagy J.: Ambulatory blood pressure monitoring and progression in patients with IgA nephropathy. Nephrol Dial Transplant 1999, 14, 86-90. IF: 1,752

VIII. **Vas T.**, Kovács T., Kocsis B., Nagy J.: A visszatérő szignifikáns bakteriúriák és az IgA nephropathia progressziója. Orv Hetil 1998, 139 (7), 349-352.

7. OTHER PUBLICATIONS

Book chapter

1. Nagy J., **Vas T.**, Wagner L.: „Minimal change" nephrosis syndroma és focalis segmentalis glomerulosclerosis. In: Rosivall László, Kiss István (ed.): Nephrológia – Elmélet és klinikum, dialysis, transplantatio. Budapest, Medintel, 2003, 519-528.

Publications

2. Kovács T., Harris S., Vas T., Seres I., Short C.D., Wittmann I., Paragh G., Mackness M.I., Mackness B., Durrington P.N., Nagy J., Brenchley P.E.C: Paraoxonase gene polymorphysm and serum activity in progressive IgA nephropathy. J Nephrol 2006, 19, 732-738.
3. Wagner Z., Degrell P., Mazák I., **Vas T**., Molnár G., Wagner L., Laczy B., Tamaskó M., Nagy J., Wittmann I.: A metilglioxál sejtkárosító hatásának vizsgálata izolált vörösvértestekben - a glomeruláris típusú vörösvérsejtek képződésének modellje. Hypertonia és Nephrológia 2005, 9, 24-29.
4. Szőnyi L., Dobos M., Vásárhelyi B., Hénonger E., **Vas T.**, Nagy J., Kovács T.: Prevalence of α1-antitripsin phenotypes in patients with IgA nephropathy. Clin. Nephrol. 2004. 62 (6): 418-422.
5. Kovács T, **Vas T**, Késői I, Nagy J: Újabb adatok az IgA-nephropathia pathogenesiséhez. Hypertonia és Nephrológia, 2004, 8 (3-4), 157-161.
6. Wagner Z., Molnár G., Mazák I., **Vas T**., Wagner L., Tamaskó M., Laczy B., Nagy J., Wittmann I.: A nem-enzimatikus glikáció aterogén hatásának mechanizmusa diabetes mellitusban és veseelégtelenségben. Metabolizmus 2004, 3, 130-134.

7. Wittmann I., Molnár G., Wagner Z., **Vas T.**, Wagner L., Meleg B., Laczy B., Nagy J.: Is ACE gene insertion/deletion polymorphysm one of the common determinants of the carbohydrate metabolism and hypertension in patients with type 2 diabetes mellitus? Diabetologia. 2003, 46 (S2), 139-140.
8. Wagner Z., Degrell P., **Vas T**., Wagner L., Mazák I., Molnár G.A., Laczy B., Nagy J., Wittmann I.: Glomeruláris haematuriára jellemző vörösvértest-morfológia kialakulása in vitro karbonil-stressz hatására Magyar Belorvosi Archivum Supplement 2003, S2, 119
9. Degrell P., Grama L., Kovács T., **Vas T.,** Kellermayer M.S.Z., Wittmann I., Nagy J.: A fibrinogén-fibrin pontos lokalizálása lézer pásztázó konfokális mikroszkóppal IgA nephropathiában és más vesebetegségekben Hypertonia és Nephrológia 2003.7 (S3), 66.
10. Wagner Z., Degrell P.,**Vas T.,** Wagner L., Mazák I., Molnár G. A., Laczy B., Nagy J., Wittmann I.: Carbonyl stress in vitro induces dysmorphic red blood cell formation seen in glomerular haematuria. Nephrology Dialysis Transplatation 2003, 18 (S4), 640-644.
11. Mazák I., Wittmann I., Wagner L., Wagner Z., Degrell P., **Vas T**., Molnár GA., Nagy J.: Cigarette smoke and its formaldehyde component inhibit bradykinin-induced calcium increase in pig aortic endothelial cells. Endothelium 2002, 9, 103-108. IF: 1,512
12. Wagner L., Wittmann I., Kovács T., Wagner Z., Mazák I., **Vas T**., Csiky B., Molnár G., Nagy J.: Az L-arginin anyagcsere lehetséges útvonalai. Hypertonia és Nephrológia, 2002, 6 (2), 104-112.
13. Wagner L., Wittmann I., Kovács T., Wagner Z., Mazák I., **Vas T.,** Csiky B., Molnár G., Nagy J.: Az L-arginin adásának és megszorításának hatása egészséges és beteg vesére. Hypertonia és Nephrológia, 2002, 6 (2), 113-120.
14. Wittmann I., Mazák I., Pótó L., Wagner Z., Wagner L., **Vas T**., Kovács T., Belágyi J., Nagy J.: Role of the iron in the interaction of red blood cells with methylglioxal. Modification of L-arginine by methylglyoxal is catalysed by iron redox cycling. Chem Biol Interact 2001, 138, 171-187. IF: 1,706
15. Kovács T., **Vas T**., Wagner L., Schmelczer M., Kocsis B., Nagy J.: The effect of smoking on urinary NOx and cGMP excretion in IgA nephropathy and in health. Contrib Nephrol 2000, 130, 124-129. IF: 1,707
16. Szelestei T., Bähring S., Kovács T., **Vas T**., Salamon Cs., Busjahn A., Luft F.C., Nagy J.: Association of a utheroglobin polymorphism with rate of progression in patients with IgA nephropathy. Am J Kid Dis, 2000, 36, 468-473. IF: 3,646
17. Kovács T., Wagner L., **Vas T**., Schmelczer M. Kocsis B., Nagy J.: A nitrogén monoxid, endothelin és a vérnyomás kapcsolata IgA nephropathiás betegekben. Magy Belorv Arch 1998, 51, 9-16.
18. Késői I., Sági B., Vas T., Kovács T., Wittmann I., Nagy J.: Korai artériás érfalmerevség krónikus IgA-nephropathiában – a metabolikus paraméterek szerepe. Hypertonia és Nephrológia 2007, 11 (2), 77-84.

Number of congress abstracts and posters

English language, author: 7 ; Hungarian language, author 16 ; English language, co-author: 28 ; Hungarian language, co-author: 34.