Clin Kidney J (2013) 6: 395–401
doi: 10.1093/ckj/sfs131
Advance Access publication 2 November 2012

Original Article

CKJ

Metabolic syndrome and other cardiovascular risk factors associated with the progression of IgA nephropathy

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Abstract

Background. The metabolic syndrome is associated with modest but independent and additive risk of new onset chronic kidney disease (CKD) in several studies. The purpose of our study was to determine whether metabolic syndrome and other cardiovascular risk factors (hyperuricaemia and smoking) are associated with the progression of IgA nephropathy (IgAN).

Methods. Two hundred and twenty three IgAN patients (107 with and 116 without metabolic syndrome) were examined. The primary renal end point was doubling of serum creatinine; secondary end points were reaching eGFR of ≤ 60 ml/min/1,73m^2 or eGFR of ≤ 30 ml/min/1.73 m^2, and end-stage renal disease, ESRD (the composite of serum creatinine ≥ 500 μmol/l, initiation of dialysis treatment or transplantation). The association of metabolic syndrome with renal end points was examined using the Kaplan-Meier method and Cox models.

Results. Metabolic syndrome established at the diagnosis or during follow-up of IgAN patients was significantly associated with the primary renal end point (unadjusted hazard ratio of doubling of serum creatinine, 95% confidence interval: 1.96 (1.17–1.33, $p = 0.011$). The association remained significant after adjustment for confounders: 1.70 (1.02–3.83, $p = 0.040$). Results were similar for secondary end points except ESRD which was not associated with the presence of metabolic syndrome. Hyperuricaemia and smoking were independent risk factors of progression. Survival curves stratified on metabolic syndrome status showed significant differences for the end points ($p = 0.017$–0.001) except for ESRD.

Conclusions. Early diagnosis and treatment of metabolic syndrome, hyperuricaemia and smoking may be an additional cost-effective strategy for preventing the progression of IgAN.

Keywords: cardiovascular risk factors; chronic kidney disease progression; end-stage renal disease; IgA nephropathy; metabolic syndrome

Introduction

The term metabolic syndrome is commonly used to describe the clustering of cardiovascular risk factors, namely central obesity, hypertension, impaired glucose metabolism and dyslipidaemia. Metabolic syndrome is found in over 25% of adults in the USA and in several other industrialized countries, and there appears to be an increasing prevalence in higher age groups [1]. Individuals with metabolic syndrome are at increased risk for cardiovascular diseases as well as cardiovascular and all-cause mortality [2].

The recent interest of nephrologists in metabolic syndrome increased after the publication of Chen *et al.* [3], demonstrating in a cross-sectional study that metabolic syndrome was associated with a 2.26-fold higher risk (1.68–4.03) of chronic kidney disease (CKD) in a sample representative of the US population. Other cross-sectional studies have also demonstrated a link between metabolic syndrome and CKD (see later). In the only longitudinal study, Kurella *et al.* [4] demonstrated a significantly increased risk of incident CKD in non-diabetic adults with metabolic syndrome. However, the effects of metabolic syndrome on the progression of CKD beyond the contribution of impaired glucose metabolism and hypertension are far from being established with certainty.

IgA nephropathy (IgAN) is the most common primary glomerulonephritis and is an important cause of end-stage renal disease (ESRD) worldwide [5]. Long-term observation in many countries has shown that IgAN causes ESRD in as many as 40% of patients within 20 years after diagnosis [6, 7]. Clinical presentation is usually with haematuria and with variable degrees of proteinuria. Pathologically, IgAN is characterized by the glomerular deposition of polymeric IgA1 mainly in the mesangium accompanied by mesangial hypercellularity, mesangial matrix expansion, and varying degrees of

glomerulosclerosis and interstitial fibrosis. Adverse prognostic indicators include the presence of heavy proteinuria and hypertension, a significant reduction in glomerular filtration rate (GFR) at the time of renal biopsy and the extent of glomerulosclerosis and tubulointerstitial fibrosis on renal pathology [7, 8]. In addition to these known risk factors, other cardiovascular risk factors, such as hypertriglyceridaemia, hyperuricaemia, excessive body weight or cigarette smoking have also been associated with the progression of IgAN in recent studies [9–11]. However, there are no data about the prevalence of metabolic syndrome in IgAN patients, and there have not been any reports of an association between metabolic syndrome and the progression of IgAN.

The purpose of the present study was to determine whether there are differences in the progression of IgAN according to the presence of metabolic syndrome and other cardiovascular risk factors at the time of diagnosis and during the course of IgAN. We emphasized that the clustering of cardiovascular risk factors is associated with a more severe progression of IgAN.

Materials and methods

Study population

We examined 240 biopsy-proven IgAN patients with normal or mild to moderately decreased renal function (CKD Stage 1–3) at the time of the diagnosis of IgAN. All of the patients were diagnosed in the Nephrology Center, Medical Faculty, University of Pécs, Hungary and followed-up in 3- to 6-month intervals by the same two nephrologists, TK and JN. Seventeen patients were not included in the statistical analyses of this study because of insufficient clinical data at the time of the diagnosis of IgAN. Further exclusion criteria were: secondary IgAN cases, rapidly progressive crescentic patients, patients with nephrotic syndrome and immunosuppressive treatment. The analysed cohort included 223 patients.

Definition of metabolic syndrome

All IgAN patients were analysed to determine whether criteria for metabolic syndrome were met by using a modified NCEP ATP III (National Cholesterol Education Programme—Adult Treatment Panel III) definition of metabolic syndrome [12]. Metabolic syndrome was defined as any three or more of the following criteria: (i) fasting plasma glucose level of 5.6 mmol/L or higher or impaired glucose tolerance; (ii) triglyceride level of 1.7 mmol/L or higher or lipid-lowering drug treatment; (iii) high-density lipoprotein (HDL) cholesterol level <1.0 mmol/L for men and <1.3 mmol/L for women or drug treatment; (iv) body mass index (BMI) $\geq$30 kg/m^2; (v) hypertension with blood pressure $\geq$130/85 mmHg or antihypertensive treatment.

Study measurements

Demographic, anthropometric and laboratory data as well as information about lifestyle habits were collected on all participants at the time of diagnosis and at each follow-up visit. Blood was collected by venepuncture after an overnight fast of at least 10 h at all follow-up examinations. The Central Laboratory of Medical Faculty, University of Pécs measured all serum chemistry levels in fresh samples with commercially available reagents. The glomerular filtration rate (eGFR; mL/min/1.73 m^2) was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation [13]. BMI was calculated as weight in kilograms divided by the square of the height in metres.

Definition of progression of IgAN

The primary renal outcome was the doubling of serum creatinine, secondary renal outcomes were the decrease of eGFR to $\leq$60 mL/min/1.73 m^2, or to $\leq$30 mL/min/1.73 m^2 or reaching ESRD (defined as the composite of a serum creatinine $\geq$500 μmol/L or the initiation of dialysis treatment or transplantation).

Statistical analysis

Data analysis was performed using the SPSS software program version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution were expressed as mean ± standard deviation and were compared by using Student's *t*-tests. Variables with non-normal distribution were compared by the Mann–Whitney *U*-test, and categorical variables were expressed as percentage and compared by the χ^2 test. The mean renal survival time until the selected end points was calculated using the Kaplan–Meier method. Differences between the calculated mean renal survival times were compared using the log-rank test. The effect of confounders was assessed by Cox regression analysis.

Confounders were determined *a priori* based on theoretical considerations and by examining baseline covariate associations with metabolic syndrome and with the renal end points [14]. Multivariate models were constructed with sequential adjustments for age and gender as well as for age, gender, uric acid, eGFR, smoking and angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker (ACEis/ARB). A value of $P < 0.05$ was considered statistically significant.

Results

Baseline clinical data

The mean age of the 223 participants included in the analytic cohort was 36.4 ± 13.0 years, 72% were male and 28% were female. Metabolic syndrome was already present in 17% of participants (38 patients) at the diagnosis of IgAN and was diagnosed *de novo* in a further 31% of participants (69 patients) during the follow-up period. Analysing all ($n = 223$) IgAN patients together at the end of the follow-up period, the prevalence of zero, one, two, three and four parameters of the metabolic syndrome was 15 (7%), 48 (22%), 53 (24%), 91 (41%) and 16 (7%), respectively (Figure 2). Sixty-eight (31%) patients were obese and impaired carbohydrate metabolism [impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or diabetes mellitus] was present in 77 (35%) patients, HDL cholesterol was low in 108 (48%) patients, hypertriglyceridaemia was present in 133 (60%) patients and elevated blood pressure or antihypertensive treatment was present in 195 (87%) patients at the end of the follow-up period. Analysing together hypertriglyceridaemia, lower HDL cholesterol and statin treatment, 151 (68%) patients were dyslipidaemic.

Table 1. Baseline characteristics of patients with and without metabolic syndrome

	Metabolic syndrome ($n = 107$)	No metabolic syndrome ($n = 116$)	P-value
Age	37.9 ± 13.8	34.9 ± 12.2	0.089
Follow-up (months)	146.6 ± 112.5	146.1 ± 99.4	0.589
Sex (M/F)	81 (76%)/26 (24%)	80 (69%)/36 (31%)	0.296
Parameters of metabolic syndrome			
BMI (kg/m^2)	30.8 ± 4.8	24.9 ± 3.4	<0.001
Systolic BP (Hgmm)	143 ± 20	136 ± 19	0.005
Diastolic BP (Hgmm)	89 ± 12	85 ± 12	0.014
Hypertension (Y/N)	105 (98%)/2 (2%)	90 (78%)/26 (22%)	<0.001
Triglyceride (mmol/L)	2.18 ± 1.21	1.59 ± 1.55	<0.001
HDL (mmol/L)	1.21 ± 0.48	1.39 ± 0.39	<0.001
Blood sugar (mmol/L)	6.32 ± 1.44	5.10 ± 0.81	<0.001
Uric acid (mmol/L)	390 ± 124	351 ± 118	0.006
Smoking (Y/N)	27 (25%)/79 (75%)	30 (26%)/83 (74%)	0.879
Renal function			
eGFR at the diagnosis (mL/min/1.73 m^2)	73.6 ± 31.8	82.2 ± 27.7	<0.05
eGFR at the end of follow-up (mL/min/1.73 m^2)	46.8 ± 31.6	67.4 ± 35.3	<0.001
Drugs			
ACEi/ARB (Y/N)	92 (86%)/15 (14%)	73 (63%)/43 (37%)	<0.001
Statins (Y/N)	48 (45%)/59 (55%)	19 (16%)/97 (84%)	<0.001

Data expressed as mean ± standard deviations and number of participants (for categorical variables).
BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Comparisons were made by *t*-tests or χ^2 tests.

Baseline characteristics of IgAN patients with and without metabolic syndrome are summarized in Table 1. There were no significant differences in the age, sex, follow-up time or number of smokers between the two groups. Patients with metabolic syndrome had higher uric acid levels in addition to the expected higher values for BMI, triglyceride, glucose and lower HDL cholesterol level that define metabolic syndrome. At the time of the diagnosis of IgAN, the eGFR of patients with metabolic syndrome was lower (73.6 ± 31.8 versus 82.2 ± 27.7 mL/min/1.73 m^2 in patients without metabolic syndrome, $P < 0.05$). However, at the end of the follow-up period, the difference between the eGFR of the two groups was more substantial (46.8 ± 31.6 versus 67.4 ± 35.3 mL/min/1.73 m^2, $P < 0.001$). The systolic and diastolic blood pressures of patients with metabolic syndrome were significantly higher (Table 1), and significantly more patients were treated with ACEi/ARB in the metabolic syndrome group ($P < 0.001$).

Association of metabolic syndrome with progression of IgAN

Survival curves stratified on metabolic syndrome status showed statistically significant differences in the time to reach three different end points for the renal outcome: the doubling of serum creatinine ($P = 0.009$, Figure 1A), eGFR ≤60 mL/min/1.73 m^2 ($P = 0.001$, Figure 1B) and eGFR ≤30 mL/min/1.73 m^2 ($P = 0.017$, Figure 1C). The difference in time to reach the composite end point of ESRD (defined as the composite of a serum creatinine ≥500 μmol/L or the initiation of dialysis treatment or transplantation) was not significant ($P = 0.2$).

Metabolic syndrome was significantly associated with the progression of IgAN in unadjusted Cox models for three different renal end points eGFR ≤60 mL/min/1.73 m^2, eGFR ≤30/mL/min/1.73 m^2 and the doubling of serum creatinine (Table 2). The association remained significant after adjustment for confounders (Table 2). The association, however, was not significant for the end points of ESRD in neither unadjusted nor adjusted Cox models (Table 2). At the analysis of the effect of single traits of metabolic syndrome: obesity (yes/no, Y/N), hypertension (Y/N), dyslipidaemia (Y/N), dysglycaemia (Y/N) and complete metabolic syndrome on the prognosis of IgAN hypertension and complete metabolic syndrome were the two strongest influencing parameters (Table 3).

In Cox regression analysis, higher uric acid level was also an independent risk factor for three different renal end points:

(i) eGFR ≤60 mL/min/1.73 m^2 [hazard ratio (HR) associated with a 1 mmol/L higher serum uric acid level: 1.003; 95% confidence interval (95% CI) 1.001–1.005].
(ii) eGFR ≤30 mL/min/1.73 m^2 (HR 1.002; 95% CI 1.001–1.005) and
(iii) ESRD (HR 1.004; 95% CI 1.001–1.006).

Smoking was significantly associated with ESRD (HR 2.024; 95% CI 1.046–3.920).

Discussion

Our study showed that metabolic syndrome established at the time of diagnosis or during the follow-up of IgAN was significantly associated with the primary renal end point and remained significant after adjustment for confounders. Results were similar for the secondary end points except for ESRD. Hyperuricaemia was also an independent risk factor for all secondary end points, and smoking was an independent risk factor for ESRD. Survival curves stratified on metabolic syndrome status showed significant differences for the association with the various end points except for ESRD.

The criteria for metabolic syndrome diagnosis were set-up originally to identify those individuals most likely to develop cardiovascular diseases [15]. There is no doubt nowadays that the patients with metabolic syndrome are at significantly higher risk for CKD too, as summarized by a number of review articles and by the recent meta-analysis of Thomas *et al*. [16–22]. Most of the observational studies discussed in these papers found a significant association between metabolic syndrome and CKD. The odds ratios for CKD in the different studies were: 2.60 in the National Health And Nutrition Examination Survey III (NHANES III) database [3], 1.43 in the Atherosclerosis Risk in Communities study [4], 1.3 in American Indians [23], 1.54 in Japanese adults [24], 1.88 in the Tehran Lipid and Glucose Study [25], 1.64 in the Inter-Asia study [26], 1.31 in hypertensive African Americans [27], 1.31 in the Hong-Kong Diabetes Registry [28], 1.77 in Korean adults [29], 1.74 [30] and 1.42 [31] in Chinese adults as well as 1.30 in non-diabetic Taiwanese adults [32]. However, the majority of the studies were cross-sectional and, as such, unable to establish a cause-effect

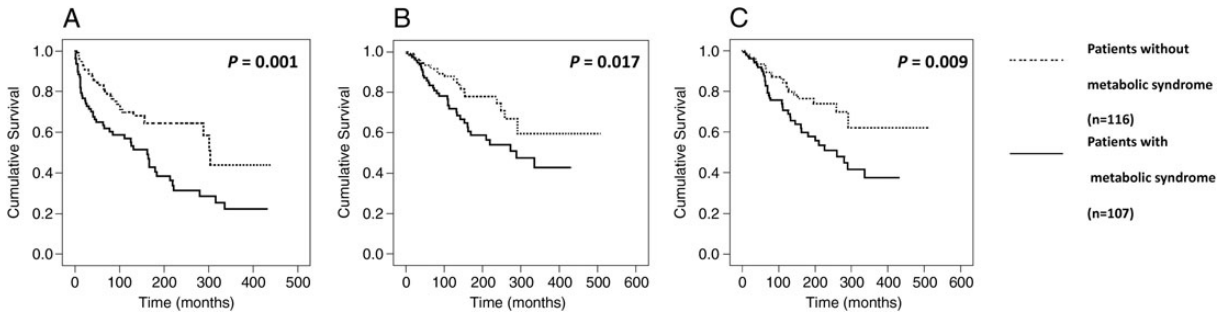

Fig. 1. Time to reach the different end points (Kaplan–Meier analysis). (**A**) Time to doubling of serum creatinine (months). (**B**) Time to reach eGFR ≤60 mL/min/1.73 m^2 (months). (**C**) Time to reach eGFR ≤30 mL/min/1.73 m^2 (months).

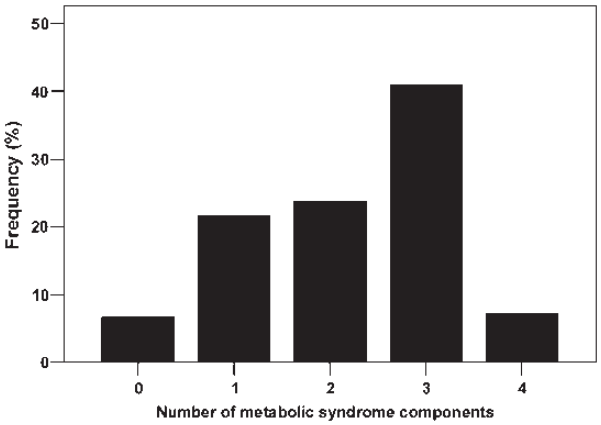

Fig. 2. Frequency of metabolic syndrome components at the end of follow-up.

relationship between metabolic syndrome and the reduction in kidney function, and also unable to determine if metabolic syndrome is associated with longitudinal changes in kidney function. In this study, we detected a significant association between metabolic syndrome and the progressive loss of kidney function except in ESRD, suggesting a potential effect of metabolic syndrome on the early progression of IgAN. The lower eGFR level of patients with metabolic syndrome seen at the time of diagnosis of IgAN suggests a potential effect of metabolic syndrome on the incidence of the renal disease too. Our observation that metabolic syndrome did not associate with the progression of IgAN in the end-stage of IgAN is in agreement with the results of the study of Lee *et al*. [33] on CKD patients participating in the CKD prevention programme regulated by the Public Health Bureau of Taiwan.

Among the components of metabolic syndrome, diabetic and hypertensive injuries, the two major aetiologies of CKD worldwide, have been well studied and described. Concerning the association between IgAN and diabetes, Fliser *et al*. [34] published that insulin resistance and hyperinsulinaemia are already present in patients with incipient renal disease, among others in IgAN patients. In our present study, we found impaired glucose regulation (IGT, IFG or diabetes mellitus) in 77 (35%) patients. It is known that IgAN can also be superimposed on diabetic nephropathy or can be the only renal abnormality of diabetic patients. The association between IgAN and diabetes may not be coincidental, because the intraglomerular hypertension and hyperfiltration as well as biochemical alterations in the glomeruli of diabetic patients may facilitate the deposition of IgA1 immune complexes or aggregates. Furthermore, the abnormalities of the IgA immune system are common in Type 2 diabetes [35].

Hypertension is common in CKD patients and, similar to the general population, it predicts cardiovascular morbidity and mortality. Hypertensive CKD patients with metabolic syndrome have an excess cardiovascular risk. The relationship between blood pressure and mortality is U-shaped; low mean and diastolic blood pressure predicts early mortality [36]. As we already mentioned in the introduction, the progression in IgAN is more severe in the presence of hypertension and strict blood-pressure control portents renal protection in IgAN [37]. In our study, among the parameters of metabolic syndrome, hypertension had the greatest influence on the prognosis of IgAN.

Obesity has been associated with an increased risk for the incidence of CKD and for ESRD in several epidemiological studies [38–41]. In the examined populations, obesity as indicated by the elevated BMI was associated with decreased renal function and ESRD independent of the presence of hypertension and diabetes. Weight loss has a protective effect against the progression of CKD [40]. Higher BMI shows a seemingly paradoxical association with better survival in advanced CKD and in ESRD, which could be related to a better nutritional status in patients with elevated BMI [42].Concerning IgAN patients, obesity was a predictive factor not only for the development of hypertension, but also for chronic renal failure and obese patients have glomerular enlargement and ultrastructural modification of the glomerular basement membrane [9, 43].

Dyslipidaemia, in particular atherogenic dyslipidaemia (high triglyceride and low HDL cholesterol), has been recognized as an independent risk factor for the development and progression of CKD in observational studies and in meta-analyses [44, 45]. Furthermore, the progressive decline in renal function may engender inflammation and oxidative stress, which could in turn induce various metabolic alterations, such as insulin resistance and diabetes, elevation of arterial blood pressure and hypertriglyceridaemia, leading to potential vicious cycles. In the study of Syrjänen *et al.* [10], elevated triglyceride levels were associated with progressive IgAN.

Recent epidemiologic and experimental evidence suggests a role for hyperuricaemia not only as a marker of reduced kidney function but also as a causal risk factor for the development and progression of renal disease [46, 47]. Serum uric acid was a GFR-independent long-term predictor of acute and chronic renal insufficiency in the Jerusalem Lipid Research Clinic cohort study [48].

Table 2. Crude and adjusted hazard ratios (95% CIs) of various renal end points associated with the presence of metabolic syndrome

	Doubling of serum creatinine	GFR		Composite of ESRD
		≤60 mL/min/1.73 m^2	≤30 mL/min/1.73 m^2	
Unadjusted	1.95 (1.16–3.28) P = 0.011	2.04 (1.30–3.10) P = 0.002	1.90 (1.11–3.24) P = 0.019	1.46 (0.80–2.66) P = 0.207
Adjusted for age, gender	1.85 (1.10–3.11) P = 0.019	2.15 (1.37–3.37) P = 0.001	1.84 (1.07–3.14) P = 0.025	1.41 (0.78–2.57) P = 0.251
Adjusted for age, gender, uric acid, eGFR, smoking	1.81 (1.07–3.08) P = 0.027	2.04 (1.28–3.26) P = 0.003	1.81 (1.05–3.13) P = 0.033	1.36 (0.74–2.50) P = 0.320
Adjusted for age, gender, uric acid, eGFR, smoking, ACEi/ARB	1.70 (1.02–2.83) P = 0.040	2.11 (1.31–3.40) P = 0.002	1.64 (0.94–2.87) P = 0.081	1.29 (0.69–2.41) P = 0.419

Table 3. Crude hazard ratios (95% CI) of various end points associated with the presence of single metabolic syndrome components and metabolic syndrome itself

	Doubling of serum creatinine	GFR		Composite of ESRD
		≤60 mL/min/1.73 m^2	≤30 mL/min/1.73 m^2	
Obesity (Y/N)	0.95 (0.54–1.66) P = 0.852	1.52 (1.05–2.20) P = 0.026	1.29 (0.77–2.15) P = 0.334	1.25 (0.67–2.32) P = 0.484
Hypertension (Y/N)	5.73 (1.40–23.46) P = 0.015	4.50 (1.83–11.02) P = 0.001	5.93 (1.45–24,24) P = 0.013	3.89 (0.94–16.07) P = 0.061
Dyslipidaemia (Y/N)	1.65 (0.94–2.92) P = 0.082	1.44 (0.97–2.14) P = 0.073	1.64 (0.95–2.85) P = 0.077	1.32 (0.69–2.53) P = 0.395
Dysglicaemia (Y/N)	0.67 (0.41–1.10) P = 0.116	0.60 (0.42–0.86) P = 0.005	0.67 (0.42–1.09) P = 0.110	0.88 (0.49–1.60) P = 0.680
Metabolic syndrome (Y/N)	1.87 (1.12–3.12) P = 0.016	2.04 (1.42–2.93) P < 0.001	1.98 (1.20–3.25) P = 0.007	1.470 (0.81–2.66) P = 0.207

There is a close connection between hypertension and hyperuricaemia and at the re-evaluation of metabolic syndrome; Reaven [15] suggested to include hyperuricaemia among the criteria of metabolic syndrome. In the only previous study on IgAN patients, hyperuricaemia was found to be a predictor of poor prognosis similarly to our investigation [10].

An association between smoking and CKD has been found in various studies, including in lupus patients, polycystic kidney disease, primary glomerular diseases and diabetic nephropathy [49–52]. In the present study, smoking was significantly associated with the progression to ESRD, similar to the study by Yamamoto *et al*. [11] who, however, examined the smoking status only at time of diagnosis of IgAN.

Our study is notable for the well-characterized nature of the study population and the long follow-up of the patients by the same two nephrologists. Our study also has a number of limitations that have to be considered when interpreting the findings. This was a single-centre study hence the external validity of our findings may be limited. We lacked measurements of waist circumference as a better measure of abdominal obesity. Instead, we used BMI which is an acceptable alternative used in the World Health Organization classification of metabolic syndrome. This modification of the NCEP ATP III classification of metabolic syndrome we used was also used by Lea *et al*. examining the metabolic syndrome and the risk of progressive CKD in hypertensive African Americans [27]. Our study did not involve and discuss proteinuria as a predictor of the progression of CKD, because proteinuria could be a clinical characteristic of IgAN and also a consequence of metabolic syndrome.

This is the first study describing the frequent prevalence of metabolic syndrome at the time of diagnosis and during the follow-up of IgAN patients, and supporting the role of metabolic syndrome in the progression of IgAN. Hyperuricaemia and smoking seem to also be important risk factors of progression in IgAN. In conclusion, the early diagnosis and treatment of metabolic syndrome and hyperuricaemia, and cessation of smoking could be an added beneficial cost-effective strategy in the prevention of the progression of IgAN and in the prevention of the development of cardiovascular diseases, on the basis of the close connection between the progression of CKD and cardiovascular diseases.

Acknowledgements. Part of this material was presented at the American Society of Nephrology Kidney Week 2011 November 10–13, Philadelphia, PA, USA. Dr Kovesdy is an employee of the US Department of Veterans Affairs. The opinions expressed in this paper are those of the authors' and they do not necessarily reflect the opinions of the US Department of Veterans Affairs. Funding. This study was supported by SROP-4.2.2/B-10/1/2010-0029 Supporting Scientific Training of Talented Youth at the University of Pécs.

Conflict of interest statement. None declared.

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Received for publication: 27.6.12; Accepted in revised form: 18.8.12