Decreased kidney function as a risk factor for cardiovascular events in subjects with metabolic syndrome – a pilot study

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Abstract

Introduction: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular events. The aim of the study was to estimate the level of kidney function in subjects with metabolic syndrome (MetS).
Material and methods: The study included 50 subjects (26 males and 24 females) with MetS (diagnosed on the basis of NCEP ATP III criteria) aged 56±12 years and 25 healthy subjects (13 males and 12 females) aged 54±13 years. Glomerular filtration rates (GFR) were estimated using the Cockroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulas. An estimated GFR (eGFR) <60 ml/min/1.73 m^2 was defined as a risk factor for cardiovascular events.
Results: An eGFR <60 ml/min/1.73 m^2 was observed in 5 MetS subjects (10%) (using the CG formula) and in 15 subjects (30%) (using the MDRD formula). Among healthy subjects, an eGFR <60 ml/min/1.73 m^2 was observed in 2 subjects (8%) (using either the CG or MDRD formulas).
Conclusions: Because most patients with MetS are obese, the estimation of eGFR using the MDRD formula, compared with the CG formula, may be more representative. There is also a relationship between the eGFR value calculated with the MDRD formula and the level of triglycerides (TG) in patients with MetS. The decreased MDRD eGFR seen in 30% of patients with MetS may be related to impaired endothelial function and might be connected with the risk factors which are components of MetS.

Key words: metabolic syndrome, glomerular filtration rate, chronic kidney disease, cardiovascular complications.

Introduction

Introducing the concept of the metabolic syndrome (MetS) into clinical practice has important practical consequences. Simple, objective criteria [1] allow early identification of patients at risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease thus allowing the initiation of effective prevention and treatment. These diseases are major causes of premature death in the European population [2].

Several studies have indicated that chronic kidney disease (CKD), which manifests by increased elimination of albumin in urine or decreased

estimated glomerular filtration rate (eGFR), is a strong and independent risk factor for cardiovascular disease. This increased risk is seen in patients with risk factors of atherosclerosis, in those with diagnosed cardiovascular diseases as well as in patients without clinical symptoms [3]. Decreased eGFR increases the rate of development of atherosclerosis and the risk of cardiovascular complications [4].

We conducted a study to estimate eGFR in patients with MetS.

Material and methods

Patient characteristics

Fifty patients [24 women and 26 men, aged 18-75 years (mean 56 ± 12 years)] with MetS diagnosed on the basis of NCEP/ATP III criteria [1] were recruited (Table I). None had been treated for the condition prior to the study. The control group consisted of 25 healthy subjects [12 women and 13 men (mean 54±13 years)]. None of the subjects smoked and none were on any medication including vitamins. The characteristics of the participants are listed in Table I.

All the study participants were volunteers and signed an informed consent form before their inclusion in the study, which was approved by the local Ethics Committee of the Medical University in Lodz (Nr RNN/257/05/KB). The Helsinki Declaration recommendations were observed.

Blood samples (5 ml) were collected from an antecubital vein in the early morning, 12 hours after the previous meal. All the assays were performed within 2 hours of blood collection. The laboratory staff that performed the assays (using established standardized methods) was blind to the group the sample came from.

Methods of glomerular filtration rate (GFR) determination

Glomerular filtration rate was calculated using 2 formulas [5]:

1. Cockcroft-Gault (CG) formula:

$$\text{GFR}\ [\text{ml/min}/1.73\ \text{m}^2] = \frac{(140 - \text{age}) \times \text{body weight}\ [\text{kg}]}{72 \times \text{creatinine level}\ [\text{mg/dl}]} \times 0.85\ (\text{if female})$$

2. Modification of diet in renal disease (MDRD) formula:

$$\text{GFR}\ [\text{ml/min}/1.73\ \text{m}^2] = 186.3 \times \text{creatinine level}\ [\text{mg/dl}]^{-1.154} \times \text{age}^{-0.203} \times 0.742\ (\text{if female}) \times 1.21\ (\text{if African-American})$$

Classification of chronic kidney disease

Classification of CKD stages was based on National Kidney Foundation guidelines – Kidney Disease Outcomes Quality Initiative (NFK-K/DOQI) [6]. Criteria for CKD classification are listed in Table II.

Statistical analysis

The data were analyzed using Student's t-test for independent groups. The comparisons between each measurement were performed using the t-test for paired data. Values were expressed as mean ±SD. A $P<0.05$ was considered significant.

Table I. Characteristics of the patients with metabolic syndrome (MetS) and control subjects included in the study

	MetS	Control group	P
Number [male/female]	50 (26/24)	25 (13/12)	–
Age [years]	56±12	54±13	NS
BMI [kg/m²]	33.1±5.3	25.6±1.6	<0.001
Glucose level ≥110 mg/dl % (No. of subjects)	48 (24)	0 (0)	<0.001
Blood pressure ≥130/≥85 mm Hg % (No. of subjects)	86 (43)	4 (1)	<0.001
Triglycerides ≥150 mg/dl % (No. of subjects)	72 (36)	0 (0)	<0.001
HDL cholesterol <40 mg/dl (males) and <50 mg/dl (females) % (No. of subjects)	44 (22)	12 (3)	<0.01
Abdominal obesity >102 cm (males) and >88 cm (females)	92 (46)	0 (0)	<0.001
Systolic BP [mm Hg]	155.7±27.8	114.8±7.6	<0.001
Diastolic BP [mm Hg]	89.5±17.1	73.4±7.2	<0.01
Fasting blood glucose [mg/dl]	116±36	89±8	<0.01
HDL cholesterol [mg/dl]	47±15	57±9	<0.01
Triglycerides [mg/dl]	201±103	98±16	<0.001
Drugs during the study	No drugs	No drugs	–

BMI – body mass index, HDL – high density lipoprotein, BP – blood pressure

Results

In the patients with MetS, the mean eGFR calculated according to the CG formula was 101±36 ml/min/1.73 m^2 and was significantly higher in males compared with females (104±38 vs. 97±34 ml/min/1.73 m^2, P>0.05). The mean eGFR calculated according to the MDRD formula was 73±18 ml/min/1.73 m^2, 74±15 in males and 71±21 ml/min/1.73 m^2 in females (P>0.05). The eGFR characteristics in patients with MetS are shown in Table III.

Table II. Classification of chronic kidney disease according to National Kidney Foundation guidelines – Kidney Disease Outcomes Quality Initiative (NFK-K/DOQI) [5]

Stage	eGFR [ml/min/1.73 m^2]	Description
1	≥90	Kidney damage with normal or increased eGFR
2	60-89	Kidney damage with mild decreased eGFR
3	30-59	Moderately decreased eGFR
4	15-29	Severe decreased eGFR
5	<15 (or dialysis)	Kidney failure

eGFR – estimated glomerular filtration rate

For healthy subjects, the mean eGFR calculated according to the CG formula was 99±23 ml/min/1.73 m^2 and was higher in females compared with males (101±29 vs. 97±16 ml/min/1.73 m^2, P>0.05). The mean eGFR calculated according to the MDRD formula was 83±14; 85±18 in females and 81±8 ml/min/1.73 m^2 in males (P>0.05). The eGFR characteristics for healthy subjects are listed in Table IV.

Based on their eGFR, subjects were placed into categories of <60, 60-90 and >90 ml/min/1.73 m^2, as calculated by the CG or MDRD formula. For the MetS group, the number of patients falling in each category is shown in Table V. Healthy subjects were categorized by eGFR in the same way as the MetS patients (Table VI).

Comparison of patients with MetS and healthy subjects showed that there were no significant differences between eGFR values calculated with the CG formula (P>0.05). However, there was a significantly lower MDRD eGFR (P<0.02) in patients with MetS compared with healthy subjects.

In patients with MetS a significant negative correlation was seen between eGFR values calculated by the MDRD formula and triglyceride (TG) levels (r= –0.362, P=0.0098).

Discussion

The relationship between impaired renal function and cardiovascular risk has been reported in several studies [7-14]. This relationship was confirmed by a meta-analysis (552 258 patients). A significant

Table III. Characteristics of estimated glomerular filtration rate (eGFR) in patients with MetS

Variable	N	Mean	Median	Minimum	Maximum	Standard deviation
eGFR CG whole group	50	101	101	28	244	36
eGFR CG females	24	97	92	28	172	34
eGFR CG males	26	104	102	55	244	38
eGFR MDRD whole group	50	73	75	29	106	18
eGFR MDRD females	24	71	72	29	103	21
eGFR MDRD males	26	74	75	49	106	15

eGFR CG – estimated glomerular filtration rate according to the Cockroft-Gault formula, eGFR MDRD – estimated glomerular filtration rate according to the MDRD formula

Table IV. Characteristics of estimated glomerular filtration rate (eGFR) in healthy subjects

Variable	N	Mean	Median	Minimum	Maximum	Standard deviation
eGFR CG whole group	25	99	97	51	142	23
eGFR CG female	12	101	106	51	143	29
eGFR CG male	13	97	96	63	127	16
eGFR MDRD whole group	25	83	87	50	103	14
eGFR MDRD female	12	84	92	50	103	18
eGFR MDRD male	13	81	84	65	92	8

eGFR CG – estimated glomerular filtration rate according to the Cockroft-Gault formula, eGFR MDRD – estimated glomerular filtration rate according to the MDRD formula

Table V. Number of metabolic syndrome (MetS) patients categorized by estimated glomerular filtration rate (eGFR)

eGFR CG	Number of patients	Percentage
<60	5	10
60-90	16	32
>90	29	58
eGFR MDRD	**Number of patients**	**Percentage**
<60	15	30
60-90	26	52
>90	9	18

eGFR CG – estimated glomerular filtration rate according to the Cockroft-Gault formula, eGFR MDRD – estimated glomerular filtration rate according to the MDRD formula

Table VI. Number of healthy subjects categorized by estimated glomerular filtration rate (eGFR)

eGFR CG	Number of subjects	Percentage
<60	2	8
60-90	6	24
>90	17	68
eGFR MDRD	**Number of subjects**	**Percentage**
<60	2	8
60-90	15	60
>90	8	32

eGFR CG – estimated glomerular filtration rate according to the Cockroft-Gault formula, eGFR MDRD – estimated glomerular filtration rate according to the MDRD formula

increase in cardiovascular risk was apparent even for stages 1 and 2 of CKD [11]. Renal insufficiency is also associated with heart failure [12, 13].

Several factors are associated with an increased risk of developing CKD; for example, obesity (especially abdominal obesity), diabetes mellitus, hypertension and insulin resistance [15, 16]. Epidemiological studies suggest that insulin resistance is a risk factor for CKD. In NHANES III [17] the frequency of a diagnosis of CKD increased progressively with insulin levels.

The risk of heart failure and death in a population of 1 091 201 patients was estimated in NHANES III [18]. The population was divided into 4 groups: 1 – patients without diabetes mellitus and kidney disease, 2 – patients with diabetes mellitus but without kidney disease, 3 – patients with kidney disease but without diabetes mellitus, 4 – patients with kidney disease and diabetes mellitus. The risk of development of chronic renal insufficiency for each group in 2 years was 8.6, 18.5, 30.7, and 52.3 per 100 patient/years, respectively. Similarly, the risk of death was 5.5, 8.1, 17.7, and 19.9 per 100 patient/years, respectively. Patients with CKD and without diabetes mellitus had 2 times higher risk of developing heart failure and death than patients with diabetes mellitus but without CKD.

The biochemical manifestations of insulin resistance – MetS – are a risk factor for CKD [19, 20]. Compared with patients without MetS, the relative risk for MetS patients of having an eGFR <60 ml/min/1.73 m^2 or microalbuminuria (after ruling out other causes of kidney disease) was 2.6 and 1.89, respectively. The correlation between each component of MetS and CKD was also estimated. After ruling out other causes of CKD, the relative risk of CKD for patients with blood pressure >130/85 mm Hg (but <140/90 mm Hg) was 2.66, for those with a decreased level of HDL cholesterol (HDL-C), 2.11, and 1.8 for those with TG levels >150 mg/dl.

Almost 20 years of observation of the 2585 participants without kidney disease provided information about risk factors for CKD [21]. Apart from age at the beginning of the study and initial eGFR, independent risk factors were diabetes mellitus (relative risk 2.38), hypertension (relative risk 1.57) and a low level of HDL-C (relative risk 0.80). Experimental studies also indicate that insulin resistance is higher than usual in patients with stage 2 CKD [22].

The relationship between dyslipidemia and development or intensification of CKD has been evaluated. In 223 patients with IgA nephropathy, the level of TG was an independent factor for the progression of nephropathy. Compared with patients without hypertriglyceridemia the relative risk of disease progression was 7.3 [23]. A retrospective analysis of data obtained from 4 years of observation of 4326 inhabitants of Okinawa shows that a high level of TG was a risk factor for the development of albuminuria. Relative risk for TG levels was 1.01 for men and 1.03 for women [24]. In the 14 year prospective PHS (Physicians Health Study), the risk factors for having a level of creatinine >1.5 mg/dl or eGFR <55 ml/min/1.73 m^2 were total cholesterol >240 mg/dl (relative risk 1.77), HDL-C <40 mg/dl (relative risk 2.16) and upper quartile of total cholesterol/HDL >6.8 ratio (relative risk 2.16) [25]. The long prospective observation in the Framingham study indicates that a risk factor for CKD development is low levels of HDL-C, in addition to hypertension and diabetes mellitus [26].

We used the CG and MDRD formulas to determine eGFR in patients with MetS and in healthy subjects. Patients with MetS and healthy subjects had almost the same eGFR when calculated by the CG formula. However, there was a significant difference ($P<0.02$) between the groups in eGFR calculated using

the MDRD formula. In the group of patients with MetS we observed a lower eGFR compared with healthy subjects (72±18 vs. 83±14 ml/min/1.73 m^2, respectively, $P<0.05$). An eGFR below 60 ml/min/1.73 m^2 was observed in 8% of healthy subjects (according to the CG and MDRD formulas), but in the group of patients with MetS, a value below 60 ml/min/1.73 m^2 was observed in 10% using the CG formula and in 30% using the MDRD formula. Therefore, the MDRD formula results in a 3-fold higher assignment of patients to a compensated renal dysfunction group (eGFR <60 ml/min/1.73 m^2) compared with the CG formula. The eGFR value calculated using the CG formula may be too high in obese patients [27], and for these patients the MDRD formula (and its modification) may be more representative. The MDRD equation is recommended by the National Kidney Foundation [6].

In the CG formula, weight influences the calculated eGFR; the greater the weight, the higher the eGFR. For this reason a correction was proposed [28] for obese subjects but its use has not been widely accepted. The abbreviated-MDRD equation does not include weight and overestimates the eGFR of underweight patients [29]. The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study reported that the relationship between BMI and GFR showed different directions, depending on the method used to calculate GFR [30]. Because of the interest in CKD and associated cardiovascular risk factors, as well as the CG and MDRD equations not being equivalent, there is a need to reach an eGFR-measurement consensus.

In our study there was a relationship between eGFR value calculated with the MDRD formula and TG level in patients with MetS as predicted from the literature cited above. Furthermore, in a large screened cohort TG concentrations were an independent risk factor for the development of proteinuria in men and women, whereas total cholesterol and low density lipoprotein (LDL) cholesterol (LDL-C) were not. High TG in women and low HDL-C in men also correlated with a decrease in GFR [31] and TG-rich, but not cholesterol-rich, apolipoprotein B-containing lipoproteins are associated with a rapid loss of renal function in CKD [32]. Hypertriglyceridemia was also a significant predictor of poor outcome in patients with IgA nephropathy [33]. In a prospective study of 12,728 subjects, high TG and low HDL-C, but not LDL-C, predicted the risk of increase in serum creatinine [34].

Evidence shows that dyslipidemia per se is a risk factor for progressive renal disease [32-37]. Other researchers reported that the development of focal segmental glomerular sclerosis was correlated with serum TG, but not serum cholesterol level in unilaterally nephrectomized rats [38]. LDL and TG-rich lipoproteins caused proliferation of human mesangial cells [36]. In another study, TG-rich apoB-containing lipoproteins promoted the progression of human renal insufficiency [32]. Oxidized lipoprotein has been found in the glomeruli and interstitial regions [39]. The secretion of interleukin-6, platelet-derived growth factor, transforming growth factor-β and tumour necrosis factor-α by mesangial cells were enhanced when mesangial cells were exposed to lipids [39]. Lipoproteins stimulate production of fibronectin and monocyte chemo-attractant protein-1 expression in mesangial cells [40].

Previous studies showed that statins reduced levels of serum cholesterol and TGs [41, 42]. Other effects of statins include suppression of the inflammatory and fibrogenic pathways of glomerular injury *in vitro* and *in vivo* [43-47]. Athyros et al. showed that in untreated dyslipidaemic patients with CHD and normal renal function at baseline, creatinine clearance declines over a period of 3 years. Statin treatment prevents this decline and significantly improves renal function, potentially offsetting an additional factor associated with CHD risk [48]. They also reported that among CHD patients, those with MetS benefited more from statin treatment than those without MetS. This benefit could be partially attributed to favourable changes in e-GFR level probably induced by statin treatment [49-52].

The decreased eGFR seen in 30% of patients with MetS may be due to impaired endothelial function and be influenced by the numerous abnormal components of the MetS.

Our study has limitations, mainly the small number of patients with MetS categorized by eGFR. However, this is a pilot study, which is still ongoing to increase patient numbers and evaluate the long-term outcomes.

In conclusion, the effects of statins in lowering TG levels and suppressing the pathways for renal injury may be beneficial for patients with hypertriglyceridemia and renal disease. There is a need for a consensus on how to measure eGFR in patients with MetS.

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