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Glomerular hyperfiltration: A new marker of metabolic risk

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Chronic kidney disease coexists with metabolic syndrome and this relationship may be apparent before overt manifestations of cardiovascular disease. To investigate early stages of the natural history of associations between renal function and metabolic syndrome, we phenotyped 1572 young (mean age = 18.4 years), apparently healthy men for metabolic risk factors and estimated their creatinine clearance based on the Cockcroft–Gault equation. High metabolic risk (clustering of at least three metabolic risk factors) was revealed in 8.7% (137) of the subjects and was associated with a 6.9-fold increase in the odds of glomerular hyperfiltration (95% confidence interval (CI): 3.9–11.5) when compared to reference (from none to two metabolic risk factors). Overweight, elevated blood pressure, and low high-density lipoprotein (HDL) cholesterol increased the multivariate-adjusted odds ratio of glomerular hyperfiltration to 6.6 (95% CI: 3.8–11.6), 1.8 (95% CI: 1.0–3.0), and 2.5 (95% CI: 1.5–4.3), respectively. Systolic and diastolic blood pressures clustered together with leptin in the factor analysis and this blood pressure–adiposity component correlated with estimated creatinine clearance ($r = 0.329$, $P < 0.0001$) and explained on its own 10.2% of the variance in the estimated renal function. Our data reveal the silent epidemics of metabolic risk among young, apparently healthy men. Furthermore, the results indicate that high metabolic risk is associated with glomerular hyperfiltration before overt manifestations of cardiovascular disease.

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Decreased circulating concentrations of high-density lipoprotein (HDL) cholesterol (HDL), increased plasma levels of triglycerides (TG) and glucose, elevated blood pressure and obesity are well-known metabolic risk determinants.[1] Clustering of at least three of these factors fulfills the criteria of metabolic syndrome (MS) according to the Third Report of the National Cholesterol Education Program.[1] MS precedes several common morbidities including cardiovascular disease[2] and type 2 diabetes[3], and the recent studies suggest that it may contribute to chronic kidney disease (CKD).[4] Accumulating data indicate that in subjects recruited from the general population, MS is associated with increased risk of decline in glomerular filtration,[5] whereas in patients with CKD, major metabolic risk factors (such as elevated TG and low HDL-cholesterol) accelerate progression to end-stage renal disease.[6] Furthermore, elevated metabolic risk augments the risk of microalbuminuria[5] and proteinuria.[7] Collectively, these data from middle-aged populations provide compelling evidence that increased metabolic risk may exert a negative effect on renal function and structure.

The increasing prevalence of overweight and type 2 diabetes in young adults and children indicates that metabolic risk continuum begins in young adulthood or indeed in childhood.[8] Consequently, the natural history of the associations between MS and its comorbidities, including CKD, may also begin early in life. Using a well-phenotyped, epidemiologically representative sample of apparently healthy young men, we investigated whether increased metabolic risk could be associated with markers of renal function before overt clinical manifestations of cardiovascular disease.

RESULTS

High prevalence of MS risk factors among apparently young healthy men

General characteristics of the study group are presented in Table 1. Out of five major metabolic risk factors, the most common was decreased HDL-cholesterol, 38.1% (599), followed by elevated blood pressure, 24.1% (380); overweight, 18.4% (290); increased circulating concentrations of

Table 1 | Demographic and clinical characteristics of the subjects

Phenotype	Values
N	1572
Age (years)	18.4±1.3
Weight (kg)	70.8 (65.0–78.0)
Height (m)	1.78 (1.74–1.83)
BMI (kg/m^2)	22.3 (20.6–24.2)
FFM (kg)	56.6 (53.1– 60.2)
SBP (mm Hg)	118.3 (110.0–126.7)
DBP (mm Hg)	73.3 (69.6–80.0)
TC (mmol/l)	4.0 (3.4–4.6)
LDL (mmol/l)	2.4 (1.8–2.9)
HDL (mmol/l)	1.1 (0.9–1.3)
TG (mmol/l)	0.9 (0.7–1.3)
Glucose (mmol/l)	4.7 (4.2–5.1)
Insulin (μU/ml)	7.3 (5.8–10.1)
HOMA-IR	1.5 (1.2–2.1)
Creatinine (μmol/l)	79.4 (72.3–87.0)
Creatinine clearance (ml/min)	137.7 (122.3–155.7)
Smokers	30.0% (526)
Alcohol drinkers	68.0% (1069)

BMI, body mass index; DBP, diastolic blood pressure; FFM, fat-free mass; HDL, high-density cholesterol; HOMA-IR, homeostatic model assessment insulin-resistance index; LDL, low-density cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
Continuous variables are presented as means±s.d. or medians with 25–75% interquartile ranges. Categorical variables are presented as percentages and absolute values in parentheses.

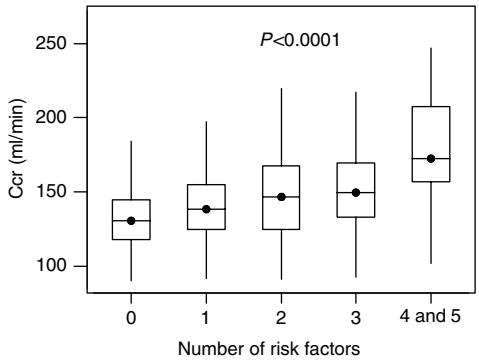

Figure 1 | Absolute creatinine clearance according to the number of metabolic risk factors. Values are medians with 25–75% interquartile ranges. *P*, statistical significance in the Kruskal–Wallis test after adjustment for age, fat-free mass, and insulin-resistance index (based on HOMA-IR). Numbers of subjects in each of the subgroups: 0 risk factors, 631; 1 risk factor, 638; 2 risk factors, 223, 3 risk factors, 62, and 4 or 5 risk factors, 18.

Table 2 | Indicators of cardiovascular and metabolic risk in hyperfiltrators and normofiltrators

Phenotype	Hyperfiltrators	Normofiltrators	*P*-value
N	65	1507	
Age (years)	18.2±1.0	18.4±1.3	0.13
Ccr (ml/min)	207.5 (198.4–222.3)	136.4 (121.6–153.4)	<0.0001
Creatinine (μmol/l)	66.3 (59.7–70.7)	79.8 (73.1–87.3)	<0.0001
BMI (kg/m^2)	26.9 (24.2–30.2)	22.2 (20.5–24.1)	<0.0001
FFM (kg)	64.7 (60.7–68.6)	56.4 (53.1–59.7)	<0.0001
SBP (mm Hg)	128.3 (120–139.3)	118.3 (110.0–125.6)	<0.0001
DBP (mm Hg)	76.7 (69.8–83.3)	72.5 (69.6–80.0)	0.0074
TC (mmol/l)	3.8 (3.0–4.6)	4.0 (3.4–4.6)	0.2656
LDL (mmol/l)	2.2 (1.7–2.9)	2.4 (1.8–2.9)	0.3569
HDL (mmol/l)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	<0.0001
TG (mmol/l)	1.2 (0.8–1.9)	0.9 (0.7–1.3)	0.0007
Glucose (mmol/l)	4.5 (4.0–4.9)	4.7 (4.2–5.1)	0.0215
Log insulin (μU/ml)	0.95 (0.84–1.1/)	0.86 (0.77–1.0)	0.0006
HOMA-IR	1.7 (1.3–2.4)	1.5 (1.2–2.1)	0.0284

BMI, body mass index; Ccr, creatinine clearance; DBP, diastolic blood pressure; FFM, fat-free mass; HDL, high-density cholesterol; HOMA-IR, homeostatic model assessment insulin-resistance index; LDL, low-density cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
Continuous variables are presented as means±s.d. or medians with 25–75% interquartile ranges.

TG, 12.9% (203); and elevated plasma glucose levels, 8.4% (133).

No metabolic risk factors were seen in 35.0% (551) men. One metabolic risk factor was confirmed in 39.4% (619) of subjects. Two, three, four, and five metabolic risk factors clustered together in 16.9% (265), 6.2% (98), 2.2% (35), and 0.3% (4) of subjects, respectively. High metabolic risk (defined as clustering of at least three metabolic risk factors) was revealed in 8.7% (137) of the participants.

Estimated creatinine clearance increases with escalating metabolic risk

There was a gradual increase in absolute estimated creatinine clearance (Ccr) across the cumulating number of metabolic risk factors (Figure 1). Indeed, the 75% percentile of crude Ccr in healthy men (no metabolic risk factors) corresponded to the median and 25% percentile of Ccr in subjects with 3 and 4 or more metabolic risk factors, respectively. Adjustment for obvious cofounders, age and fat-free mass (FFM), did not attenuate this difference ($P<0.0001$). Inclusion of insulin-resistance index (measured by homeostatic model assessment insulin-resistance index (HOMA-IR)) in the adjustment analysis did not abolish the difference in Ccr among the men representing the whole spectrum of metabolic risk ($P<0.0001$).

Hyperfiltration is associated with elevated metabolic risk but not with hyperglycemia

Glomerular hyperfiltration was exhibited by 4.1% (65) of men according to the previously published criteria.[9] High metabolic risk was associated with a 6.9-fold increase in the odds of hyperfiltration (CI: 3.9–11.5, $P<0.0001$) when compared with the low metabolic risk group (subjects with less than 3 metabolic risk factors). Quantitative indicators of metabolic profile were worse in hyperfiltrators when compared with normofiltrators (Table 2). Paradoxically, hyperfiltration was not associated with hyperglycemia; in fact, median plasma glucose levels were lower in men with hyperfiltration compared with normofiltrators (Table 2).

Crude and adjusted odds ratios of glomerular hyperfiltration in relation to individual metabolic risk factors are presented in Table 3. Elevated blood pressure, low HDL, high circulating concentrations of TG (according to the Third Report of the National Cholesterol Education Program criteria[1]), and being overweight were associated with the

Table 3 | Crude and adjusted odds ratios of glomerular hyperfiltration in relation to metabolic risk factors

Variable	Crude		Multivariate-adjusted model 1		Multivariate-adjusted model 2	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
↑BP	2.8 (1.7–4.7)	<0.0001	1.9 (1.1–3.2)	0.026	1.8 (1.0–3.0)	0.047
↑Glucose	1.3 (0.6–3.0)	0.483	0.9 (0.4–2.2)	0.887	0.8 (0.3–2.1)	0.703
↓HDL	3.1 (1.8–5.2)	<0.0001	2.5 (1.5–4.4)	0.001	2.5 (1.5–4.3)	0.001
↑TG	3.2 (1.9–5.6)	<0.0001	1.6 (0.9–2.9)	0.138	1.6 (0.9–3.1)	0.124
↑BMI	8.6 (5.1–14.5)	<0.0001	6.4 (3.7–11.2)	<0.0001	6.6 (3.8–11.6)	<0.0001

↑BMI, body mass index ⩾25 kg/m^2; ↑BP, blood pressure ⩾130/85 mm Hg or antihypertensive treatment; ↑Glucose, serum glucose ⩾6.1 mmol/l; ↓HDL, HDL-cholesterol levels <1.04 mmol/l; ↑TG, triglyceride levels ⩾1.7 mmol/l.
Model 1: BP, glucose, HDL, TG, and BMI included as covariates.
Model 2: BP, glucose, HDL, TG, BMI, age, alcohol consumption, smoking, and log insulin serum concentrations included as covariates.

Table 4 | Factor analysis of the metabolic variables: factor loadings after orthogonal varimax rotation

Variable	Insulin sensitivity factor	Blood pressure-adiposity factor	Lipid factor	Mixed metabolic factor	Communality
Age	−0.347	0.174	0.368	0.080	0.293
SBP	0.125	**0.865**	0.078	0.030	0.771
DBP	−0.029	**0.886**	−0.040	−0.120	0.803
Glucose	0.210	−0.118	−0.191	**0.861**	0.836
HOMA-IR	**0.942**	0.121	−0.033	0.109	0.914
Log insulin	**0.946**	0.148	0.011	−0.006	0.918
TG	0.300	0.218	**0.692**	−0.016	0.616
HDL	0.198	0.055	**−0.828**	0.006	0.728
LDL	−0.228	0.221	0.399	**0.708**	0.761
Leptin	0.125	**0.581**	0.272	0.158	0.452
%Variance	21.6	20.5	15.8	13.0	**70.9**

DBP, diastolic blood pressure; HDL, high-density cholesterol; HOMA-IR, homeostatic model assessment insulin resistance index; LDL, low-density cholesterol; SBP, systolic blood pressure; TG, triglycerides. Bold values represent variables with loadings over 0.4 in factor analysis.

increased odds ratios of glomerular hyperfiltration in the crude analysis (Table 3). After adjustment for other demographic and metabolic variables, only high body mass index (BMI), elevated blood pressure and low HDL remained associated with the increased odds ratio of hyperfiltration (Table 3).

Crude and adjusted associations between leptin and estimated Ccr

Leptin was associated with estimated Ccr ($r=0.538$, $P<0.001$ and $T=7.93$, $P<0.0001$ in Pearson's correlation and regression analysis, respectively), and this association remained significant after controlling for BMI in the multiple regression analysis ($T=2.54$, $P=0.012$). Inclusion of leptin and major elements of metabolic risk in the multivariate factor analysis has resulted in extraction of four major independent components that explained 70.9% of variance in the metabolic risk variables within this stratum of data (Table 4). The insulin sensitivity factor (driven by HOMA-IR and log insulin), blood pressure–adiposity factor (driven by systolic and diastolic blood pressures as well as leptin), lipid factor (driven by HDL-cholesterol and TG), and mixed metabolic factor (driven by glucose and low-density lipoprotein cholesterol) accounted for 21.6, 20.5, 15.8, 13.0% of the variance within the stratum of metabolic risk data, respectively (Table 4). Of these, only the blood pressure–adiposity factor was significantly, linearly correlated with estimated Ccr ($r=0.329$, $P<0.0001$) and explained on its own 10.2% of the variance in Ccr in the multiple regression analysis ($T=4.32$, $P<0.0001$).

DISCUSSION

One of the major findings from this study is the evidence for strikingly high prevalence of major metabolic risk factors among apparently healthy, young men recruited from the general population. Indeed, only less than half of the subjects had no metabolic risk factors. Moreover, at least three metabolic risk factors clustered together almost in one in 10 of the subjects. These data reveal an early beginning of the natural history of MS, way before the manifestations of cardiovascular or renal disease. Furthermore, our results support the notion that overt cardiovascular disease has its roots early in youth. Most importantly, in light of general low awareness of cardiovascular disease risk among young subjects,[10] these alarming data stress the importance of recognizing the silent epidemic of MS among apparently healthy, generally lean men.

We also showed that elevated metabolic risk was associated with renal function. Specifically, the increasing metabolic risk was associated with a progressive elevation in estimated Ccr and conversely glomerular hyperfiltration was related to high cardiovascular risk profile. Both anthropometric and biochemical indices of adiposity and, to a smaller extent, elevated blood pressure were implicated as major determinants of glomerular hyperfiltration. These results are in agreement with well-documented contributions of hemo-

dynamic and metabolic factors to renal hyperperfusion.[11–12] One of the major drivers of this association is likely adipose tissue, a source of bio-molecules with well-documented effects on glomerular structure and function.[13–15] Indeed, several adipocytokines including resistin and adiponectin were associated with glomerular filtration rate (GFR) in patients with CKD and type 1 diabetes.[14–15] Moreover, hyperleptinaemia was linked to glomerular hyperfiltration in experimental model of type 2 diabetes,[16] and the role of leptin as a potent stimulator of proliferation within major cellular compartments of the glomeruli was also well-documented.[13] Finally, adipocytokines genes including the leptin receptor were overexpressed in the glomeruli of patients with biopsy-proven obesity-related glomerulopathy when compared to the normal controls.[17] Collectively, these data suggest that adipocytokines may mediate, at least in part, the observed association between increased total adiposity and glomerular hyperfiltration with a potential to foster the development of glomerular dysfunction and damage.

Association between hypertension and the increased odds of glomerular hyperfiltration, however modest, is not surprising as elevated blood pressure is recognized as a driver of increase in glomerular capillary hydraulic pressure and glomerular filtration.[11,18] Clustering of leptin levels with blood pressure in the factor analysis reflects a common co-existence of overweight and hypertension and suggests that adipose tissue and elevated BP may indeed interact additively in promotion of the pro-hyperfiltrative phenotype in men with high metabolic risk. This concept is indeed supported by previously documented combined effect of overweight and hypertension on increased filtration fraction, and albumin excretion rate in a predominantly male population.[19] However, the mechanistic explanation of this association remains to be elucidated. In addition, future studies are warranted to dissect individual contribution of both systolic and diastolic blood pressure to the pro-hyperfiltrative phenotype. Low number of subjects with exclusively elevated systolic blood pressure and diastolic blood pressure among hyperfiltrators (nine and one men, respectively) did not permit us to address this issue in the current analysis.

Interestingly, elevated plasma glucose levels were not associated with any change in the odds of glomerular hyperfiltration. In fact, circulating concentrations of glucose were lower in hyperfiltrators when compared with normo-filtrators. Thus, it is unlikely that hyperglycemia could be a major driver of glomerular hyperfiltration in young men with high metabolic risk. Although hyperfiltrators in our study exhibited lower insulin sensitivity compared with the control group, adjustment for markers of insulin resistance did not account fully for the difference in Ccr among subjects with different levels of metabolic risk, and insulin sensitivity factor was not associated with Ccr in the factor analysis. These data clearly show that the observed increase in estimated Ccr among men with high metabolic risk is regulated by the mechanisms other than those observed in the early stage of diabetic kidney disease.[20]

The findings of our study provide a unique insight into the natural history of CKD in patients with MS. Major metabolic risk factors increase the risk of CKD[4] and the MS itself is associated with high odds ratio of CKD among middle-aged and elderly subjects.[5] As hyperfiltration is a predictor of microalbuminuria[21] and occurs in patients with obesity-related nephropathy[12] before the end-stage renal disease, increased Ccr in young subjects with elevated metabolic risk may be interpreted as an early, and possibly reversible, marker of target organ damage. However, whether metabolic-related glomerular hyperfiltration early in life is associated with higher risk of CKD in the future remains to be confirmed in prospective studies.

Our study has a number of limitations. It should be acknowledged that weight was present in formulas used to estimate both Ccr and BMI. Consequently, association between the estimated renal function and overweight might be, at least to some extent, explained by the mathematical similarities in the equations. However, the associations between Ccr and total adiposity were replicated in a subsample of subjects in whom leptin concentrations, instead of BMI, were used as a marker of fat mass. Moreover, previous studies based on direct assessment of GFR and indices of adiposity documented that the risk of hyperfiltration was higher in obese subjects compared with the normal controls and weight reduction resulted in a significant decrease in GFR.[22] Therefore, irrespective of the presence of the same parameter in both BMI and Cockcroft–Gault formulas, our findings are biologically meaningful and are supported by previous clinical observations.[12,22] Finally, it should be stressed that Cockcroft–Gault equation was shown previously as a preferred method of estimating filtration in young subjects with normal or supranormal renal function.[23] In contrast, the Modification of Diet in Renal Disease (MDRD) equation was not validated in men aged 18 years or younger and was shown to underestimate GFR in healthy subjects.[24] In fact, compared with the Cockcroft–Gault equation, MDRD formula was associated with a higher underestimation of the measured ^{125}I-iothalamate GFR in healthy kidney donors.[25] In addition, although weight is not included in the MDRD equation, the latter correlates indirectly with body weight measures, including BMI.[26] Therefore, in the absence of direct measurement of renal function and well-validated formula of estimating GFR in apparently young healthy men with normal and supranormal renal function, the Cockcroft–Gault equation may be the least-biased estimator of renal function in the current analysis. Future studies are warranted to validate different methods of estimated GFR against the directly measured GFR in large cohorts of apparently young healthy subjects with normal renal function and hyperfiltration.

We should also stress that as the recruitment of participants in our study began before the publication of the most widely used criteria of MS;[1] the subjects were not

phenotyped for waist circumference, a well-accepted marker of abdominal obesity at present.[1] However, estimates of associations between waist circumference and BMI in adolescents showed their excellent correlations.[27] In addition, previous observations confirmed utility of BMI as a substitute of waist circumference in prediction of MS in men from the West of Scotland Coronary Prevention Study (WOSCOPS).[3]

Finally, the limits of the cross-sectional character of this study do not allow us to attribute causation to the detected associations. Future prospective studies are certainly needed to confirm our findings. Nevertheless, epidemiologically representative sample of subjects, thorough clinical phenotyping, no bias introduced by comorbidities or medication confirm the robust character of our data.

In summary, our study has provided strong evidence for a 'silent epidemic' of metabolic risk factors among apparently young healthy men. We also found that high metabolic risk, in particular elevated blood pressure as well as indices of total adiposity, are associated with glomerular hyperfiltration before overt clinical manifestation of cardiovascular disease. Future studies will focus on confirmation of these findings in long-term prospective observations, dissection of the relationship between adipose tissue and glomerular hemodynamics as well as determination of the precise pathophysiological mechanisms behind these associations.

MATERIALS AND METHODS

A sample of 1754 apparently young, healthy, white subjects included in this project consisted of 1157 men from the previously described Young Men Cardiovascular Association (YMCA) Study cohort[28] and additional 597 young, healthy males recruited later based on the same study protocol from eight additional randomly selected secondary schools in the same southern region of Poland (YMCA extension). The following were criteria of inclusion: age – at least 16 years, self-declared good health, and willingness to provide blood sample for further biochemical and genetic analysis. Out of 1754 men, 182 subjects were excluded from the current analysis either because of incomplete clinical biochemical information or chronic renal disease diagnosed based on the creatinine levels and Ccr. This left 1572 subjects eligible for the current analysis.

Apart from antihypertensive medication (reported by 20 men), no other therapeutics were taken by the participants at the time of recruitment. The study was approved by a local Bioethical Committee and the subjects gave informed consent for participation.

Clinical phenotyping protocol was described in detail in our previous study.[28] In brief, clinical history was taken by standardized, coded questionnaires. Blood pressures were measured in triplicate using a mercury sphygmomanometer according to the standard protocol.[28] Height and weight measurements were taken under standard conditions and used in calculation of BMI, a well-accepted measure of total adiposity.[29] Fat-free mass (FFM) was estimated based on anthropometric data using previously validated equation: $FFM = 5.1 \times \text{height}^{1.14} \times \text{weight}^{0.41}$.[30]

Lipid profile was measured as described elsewhere.[28] Plasma glucose levels were estimated using a hexokinase enzymatic method. Circulating creatinine levels were assessed based on the kinetic Jaffe reaction on a Cobas Bio-Autoanalyzer. Insulin was measured using a radioimmunoassay (DSL) on 1470 Wizard automatic gamma counter. HOMA-IR ((plasma insulin $\times$ plasma glucose)/22.5) was used an indicator of insulin resistance. Circulating concentrations of leptin (a biochemical marker of adipose tissue) were measured according to the protocol described previously[31] on 160 samples of eligible subjects randomly selected from the YMCA population.

All biochemical analyses were performed on fasting samples.

Four major metabolic risk factors (HDL, blood pressure, TG, and glucose) were categorized based on the previously recommended cut-off values from the Third Report of the National Cholesterol Education Program guidelines.[1] Overweight was diagnosed in subjects with $BMI \geqslant 25\,kg/m^2$.[32] We used this lower BMI cut-off in this cohort of generally young, lean men since the higher cut-off of $30\,kg/m^2$ (obesity) would have only captured a minority of individuals with high metabolic risk.

The Cockcroft–Gault equation ((140–age) $\times$ weight)/(72 $\times$ creatinine) was used as an estimator of Ccr – a well-accepted index of predicted renal function.[33] Ccr was expressed in absolute values (ml/min) and not indexed per $1.73\,m^2$ of body surface area, as indexing of GFR by body surface area was shown to obscure a genuine association between renal function and total adiposity.[34] Glomerular hyperfiltration was defined as Ccr over the mean + 2 s.d., as suggested elsewhere.[9]

Statistical analysis

Data are presented as means $\pm$ s.d. or median and 25–75% interquartile range. Kolmogorov–Smirnov test was used as a test for normality. Normally distributed quantitative parameters were analyzed using the parametric one-way analysis of variance. Differences in quantitative variables that did not pass the normality test were assessed by the nonparametric Kruskal–Wallis test. Adjustment analysis was based on comparisons of residuals obtained from the multiple regression models.

χ^2 Test was used to evaluate associations between two dichotomized qualitative parameters. Pearson's linear correlation was employed as a method of computing a coefficient of correlation (r) between two quantitative variables.

To estimate the crude odds ratio of glomerular hyperfiltration, each of five classical metabolic risk factors was included as an independent variable in the binary logistic regression. The adjusted odds ratios of glomerular hyperfiltration were derived from multivariate logistic regression models including all five classical metabolic risk factors simultaneously (model 1) as well as the same combined set of metabolic risk factors together with age, categorized alcohol consumption, categorized smoking, and HOMA-IR (model 2).

Factor analysis, a well-accepted method of studying a range of variables showing a high level of intercorrelation,[35] was used to identify clusters of phenotypes that contribute to the variance within the observed metabolic data in a subset of 160 subjects with available serum leptin levels. Four factors were extracted based on the principal components method and transformed using an orthogonal varimax rotation, as described elsewhere.[35] In brief, each of these factors reflects one of four major clusters of phenotypes identified in the stratum of data from the investigated population. Predominant metabolic variables within each of four factors were identified by individual loadings and used in defining the names of the factors. Accordingly, insulin sensitivity factor, blood pressure–adiposity factor, lipid factor, and mixed metabolic factor refer to the components driven by HOMA-IR and log insulin, systolic blood

pressure, diastolic blood pressure and leptin (blood pressure–adiposity factor), TG, and HDL (lipid factor) as well as glucose and low-density lipoprotein (mixed metabolic factor). Only variables with loadings over 0.4 on the extracted metabolic factors were considered as statistically meaningful. Insulin sensitivity factor, blood pressure – adiposity factor, lipid factor and mixed metabolic factor were tested for association with Ccr in Pearson's linear correlation as well as multiple regression analysis.

Nominal $P<0.05$ were considered as statistically significant.

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