Insulin Resistance and the Cluster of Abnormalities Related to the Metabolic Syndrome Are Associated With Reduced Glomerular Filtration Rate in Patients With Type 2 Diabetes

SALVATORE DE COSMO, MD[1]
ROBERTO TREVISAN, MD[2]
ANTONIO MINENNA, MD[1]
MONICA VEDOVATO, MD[3]
RAFFAELLA VITI, MD[1]

STEFANO A. SANTINI, MD[4]
ALESSANDRO R. DODESINI, MD[2]
PAOLA FIORETTO, MD[5]
VINCENZO TRISCHITTA, MD[1,6]

Because of its devastating outcomes, including end-stage renal disease and increased cardiovascular morbidity and mortality (1–3), chronic kidney disease (CKD) is a worldwide public health problem (4). Diabetes is the leading cause of end-stage renal disease in the Western world (5). Several evidences suggest that insulin resistance and the metabolic syndrome are associated with and probably contribute to reduced glomerular filtration rate (GFR) in patients with type 1 diabetes (6,7). At variance, no data are available in type 2 diabetes. The aim of this work was to investigate the role of insulin resistance and the cluster of metabolic syndrome–related (MS-r) abnormalities on kidney function in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Two samples were studied. Selection criteria and clinical features of the first samples have been already published (8). Briefly, 731 type 2 diabetic patients (384 men and 347 women, age 61.4 ± 10 years, diabetes duration 10.8 ± 9 years, HbA$_{1c}$ [A1C] 8.2 ±

1.5%) were consecutively recruited at the Casa Sollievo della Sofferenza Institute in San Giovanni Rotondo. Standardized serum creatinine was measured by the modified kinetic Jaffè reaction. Micro- or macroalbuminuria was diagnosed when albumin-to-creatinine ratio (ACR) was ≥2.5 mg/mmol in men and 3.5 mg/mmol in women; 216 patients (29%) had macroalbuminuria. Estimated GFR was calculated with the abbreviated MDRD (Modification of Diet inRenal Disease) formula (9). CKD was defined as estimated GFR <60 ml/min per 1.73 m^2. The homeostasis model assessment of insulin resistance index was calculated as fasting serum insulin (mU/ml) × fasting plasma glucose (mmol/l)/22.5 (10).

Besides diabetes, cardiovascular risk factors related to the metabolic syndrome such as arterial hypertension, dyslipidemia, and abdominal obesity were considered as reported (8). An individual MS-r score was then assigned ranging from 0 (diabetes only) to 3.

In an independent sample of 86 patients with type 2 diabetes (68 men and 18 women, age 58.4 ± 10 years, diabetes

duration 10.6 ± 7 years, A1C 8.2 ± 1.5%) recruited at the Ospedali Riuniti of Bergamo and at the University of Padova, insulin sensitivity (by euglycemic-hyperinsulinemic clamp) and GFR (by EDTA) were measured.

RESULTS — In the 731 type 2 diabetic patients of the first sample, estimated GFR was 74.3 ± 19 ml/min per 1.73 m^2. A significant association was observed between estimated GFR and sex (being lower in women, $P < 0.001$), duration of diabetes ($r = -0.3$, $P < 0.001$), urinary ACR ($r = -0.3$ $P < 0.001$), retinopathy (being lower in patients with retinopathy, $P = 0.005$), and smoking (being higher in smokers, $P = 0.0001$) but not with A1C ($r = 0.06$, $P = 0.1$). When singly considered, arterial hypertension, dyslipidemia, and increased waist circumference (i.e., the three abnormalities related to the metabolic syndrome) were significantly associated with estimated GFR (P values ranging from 0.002 to 0.00002). MS-r score was 0 in 17 (2.3%), 1 in 86 (11.8%), 2 in 289 (39.5%), and 3 in 339 (46.4%) type 2 diabetic patients; estimated GFR progressively and significantly decreased with increasing MS-r score (82 ± 19, 76 ± 18, and 71 ± 18 ml/min per 1.73 m^2 in patients with score of 0–1, 2, and 3, respectively; $P < 0.001$ by ANOVA) (Fig. 1). The association between MS-r score and estimated GFR was still significant after adjusting for several confounders including sex ($P = 0.001$), duration of diabetes ($P < 0.001$), ACR ($P < 0.0001$), retinopathy ($P < 0.001$), and the four variables considered together ($P = 0.001$). Age was not considered as a possible confounder for which to adjust because it is strongly correlated with duration of diabetes ($r = 0.41$, $P < 0.00001$) (i.e., collinearity), a finding that would have made it difficult to evaluate the independent effect of the two variables (11). The association between MS-r score and estimated GFR was also inde-
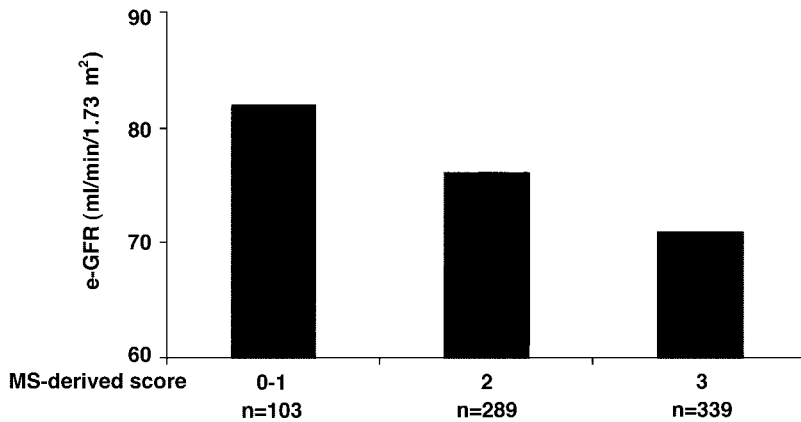
Figure 1—*Estimated GFR values according to the MS-r score in 731 patients with type 2 diabetes.*

pendent of other possible additional confounders, such as A1C ($P < 0.0001$), smoking ($P < 0.0001$), systolic ($P < 0.0001$) and diastolic ($P < 0.0001$) blood pressure, antidiabetic ($P < 0.001$) and antihypertensive ($P = 0.02$) therapy, and treatment with ACE inhibitors and/or angiotensin II receptor antagonist ($P = 0.03$). The MS-r score was significantly associated with estimated GFR in patients without ($n = 508$, $P = 0.002$) or with ($n = 223$, $P < 0.001$) retinopathy. Of note, the association between estimated GFR and MS-r score was strengthened by the presence of retinopathy (P for interaction between metabolic syndrome and retinopathy $= 0.005$). As compared with a MS-r score of 0–1, both MS-r scores of 2 and 3 predicted the risk to be affected by CKD (odds ratio 3.4 [95% CI 1.3–9.2], $P = 0.02$ and 4.6 [95% CI 1.6–12.4], $P = 0.003$, respectively, after adjusting for sex, duration of disease, ACR, and retinopathy).

A significant inverse correlation was observed between estimated GFR and the homeostasis model assessment of insulin resistance index, a surrogate of insulin resistance ($r = -0.2$ $P < 0.001$). In patients of the second sample, a significant correlation was observed between the glucose disposal rate value (at euglycemic clamp) and GFR (by EDTA) ($r = 0.30$, $P = 0.004$; age and sex adjusted).

CONCLUSIONS — In the present study we demonstrate that in patients with type 2 diabetes the cluster of abnormalities related to the metabolic syndrome is associated with reduced kidney function and increases the risk of being affected by CKD (i.e., a GFR <60 ml/min per 1.73 m^2). This association is independent of sex, duration of diabetes, urinary

ACR, and retinopathy. A similar association has been recently reported in the general adult population (12) also including patients affected by type 2 diabetes. Whole-body insulin resistance on glucose handling is likely to underlie most, if not all, features of the metabolic syndrome (13), and this may explain the relationship between insulin sensitivity and kidney function we observed in this study. Since insulin resistance and all other features of the metabolic syndrome are established risk factors of cardiovascular disease, our data suggest that they could, in fact, represent the pathogenic link of the well-known association between advanced renal disease and cardiovascular mortality and morbidity observed in type 2 diabetic patients (14).

It is worth noting that although the association between the metabolic syndrome and kidney function was independent of retinopathy it was nonetheless significantly strengthened by the coexistence of it indicating that microangiopathy interacts with the metabolic syndrome in modulating kidney function in type 2 diabetic patients. These data are compatible with the observation that kidney disease in patients with type 2 diabetes is a quite heterogeneous disease modulated by both microangiopathy (and subsequent diabetic glomerulosclerosis) and atherosclerosis (15).

In conclusion, in patients with type 2 diabetes, insulin resistance, and the cluster of abnormalities related to the metabolic syndrome are strongly associated with kidney dysfunction. Although the study design (i.e., cross-sectional) does not allow us to draw firm conclusions about causality, the results obtained strongly suggest that insulin resistance and the metabolic syndrome affect GFR in

patients with type 2 diabetes. Future prospective studies are urgently needed to understand whether treatment of insulin resistance may positively influence the onset and/or progression of kidney dysfunction in patients with type 2 diabetes.

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