

# Metabolic Syndrome in Type 1 Diabetes

## Association with diabetic nephropathy and glycemic control (the FinnDiane study)

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**OBJECTIVE** — The aim of this study was to estimate the prevalence of the metabolic syndrome in Finnish type 1 diabetic patients and to assess whether it is associated with diabetic nephropathy or poor glycemic control.

**RESEARCH DESIGN AND METHODS** — In all, 2,415 type 1 diabetic patients (51% men, mean age 37 years, duration of diabetes 22 years) participating in the nationwide, multi-center Finnish Diabetic Nephropathy (FinnDiane) study were included. Metabolic syndrome was defined according to the National Cholesterol Education Program diagnostic criteria. Patients were classified as having normal albumin excretion rate (AER) ( $n = 1,261$ ), microalbuminuria ( $n = 326$ ), macroalbuminuria ( $n = 383$ ), or end-stage renal disease (ESRD) ( $n = 164$ ). Glycemic control was classified as good ( $HbA_{1c} < 7.5\%$ ), intermediate ( $7.5\text{--}9.0\%$ ), or poor ( $> 9.0\%$ ). Creatinine clearance was estimated with the Cockcroft-Gault formula.

**RESULTS** — The overall prevalence of metabolic syndrome was 38% in men and 40% in women. The prevalence was 28% in those with normal AER, 44% in microalbuminuric patients, 62% in macroalbuminuric patients, and 68% in patients with ESRD ( $P < 0.001$ ). Patients with metabolic syndrome had a 3.75-fold odds ratio for diabetic nephropathy (95% CI 2.89–4.85), and all of the separate components of the syndrome were independently associated with diabetic nephropathy. The prevalence of metabolic syndrome was 31% in patients with good glycemic control, 36% in patients with intermediate glycemic control, and 51% in patients with poor glycemic control ( $P < 0.001$ ). Similarly, metabolic syndrome increased with worsening creatinine clearance.

**CONCLUSIONS** — The metabolic syndrome is a frequent finding in type 1 diabetes and increases with advanced diabetic nephropathy and worse glycemic control.

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**Abbreviations:** AER, albumin excretion rate; eGDR, estimated glucose disposal rate; ESRD, end-stage renal disease; FinnDiane, Finnish Diabetic Nephropathy; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The metabolic syndrome is an important risk factor for cardiovascular disease and early mortality in patients with type 2 diabetes (1) and nondiabetic subjects (2). It is characterized by a clustering of independent cardiovascular risk factors including impaired glucose regulation, central obesity, dyslipidemia, and hypertension (3). In type 2 diabetes, the total cardiovascular risk attributable to the syndrome seems to exceed the sum of the risk from each of the separate components (4). In addition, insulin resistance, itself a key part of the metabolic syndrome, worsens as the number of metabolic syndrome components increases (4). More recently, other disturbances such as microalbuminuria, endothelial dysfunction, abnormalities in fibrinolysis and coagulation, nonalcoholic fatty liver, and elevated markers of chronic inflammation have been linked to the metabolic syndrome (5–9). Both the World Health Organization (WHO) (10) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (11) have proposed their own definitions for the syndrome.

The prevalence and impact of the metabolic syndrome in type 1 diabetes remains to be established. A number of components of the syndrome may be observed in patients with type 1 diabetes and potentially contribute to increased cardiovascular risk. However, metabolic syndrome and insulin resistance are closely correlated with microalbuminuria in patients with type 1 diabetes, as well as in nondiabetic subjects (7,12–14). Patients with nephropathy also have elevated blood pressure, dyslipidemia, low-grade inflammation, and insulin resistance, making the distinction between nephropathy and the metabolic syndrome difficult (13,15–18). Therefore, the aim of this study was to estimate the prevalence of the metabolic syndrome in Finnish type 1 diabetic patients and to assess whether metabolic syndrome is associated with diabetic nephropathy or glycemic control.

## RESEARCH DESIGN AND METHODS

All patients participated in the Finnish Diabetic Nephropathy (FinnDiane) study, a nationwide multicenter study with the aim of identifying genetic and clinical risk factors for diabetic nephropathy in type 1 diabetes. The study protocol is in accordance with the Declaration of Helsinki, and it has been approved by the local ethics committee in each participating study center.

The study design is cross-sectional and includes adult patients with type 1 diabetes from 57 centers from all over Finland. In 2,415 type 1 diabetic patients, complete lipid profiles and clinical data on all of the components of the metabolic syndrome were available by April 2004. Of the patients, 51% were men, the mean age was  $37 \pm 1$  years, and duration of diabetes was  $22 \pm 1$  years.

Data on medication, cardiovascular status, and diabetic complications were registered by a standardized questionnaire, which was completed by the patient's attending physician based upon the medical file. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years and permanent insulin treatment initiated within 1 year of diagnosis.

Coronary heart disease was defined as diagnosed myocardial infarction, coronary revascularization, or pharmacological treatment with long-acting nitroglycerin. Stroke was defined as cerebral infarction or intracerebral hemorrhage. Blood pressure was measured twice with 2-min intervals in the sitting position after a 10-min rest.

Fasting blood samples were collected and analyzed for HbA<sub>1c</sub> (A1C), lipids, and lipoproteins (serum total and HDL cholesterol and triglycerides) and serum creatinine. A1C was determined by standardized assays at each center. Serum lipid and lipoprotein concentrations were measured at the research laboratory of Helsinki University Central Hospital, Division of Cardiology, Finland, by automated enzymatic methods using the Cobas Mira analyzer (Hoffmann-La Roche, Basel, Switzerland). Serum creatinine was assessed by enzymatic methods at a central laboratory. Urinary albumin excretion rate (AER) was determined in 24-h urine collections by radioimmunoassay (Pharmacia, Uppsala, Sweden).

The renal status was defined based on AER in at least two of three collections. Patients were divided by AER categori-

cally into those with normal AER ( $<20$   $\mu\text{g}/\text{min}$  or  $<30$   $\text{mg}/24$  h;  $n = 1,261$ ), microalbuminuria (AER  $20$ – $200$   $\mu\text{g}/\text{min}$  or  $30$ – $300$   $\text{mg}/24$  h;  $n = 326$ ), and macroalbuminuria (AER  $>200$   $\mu\text{g}/\text{min}$  or  $>300$   $\text{mg}/24$  h;  $n = 383$ ). In addition, the presence of end-stage renal disease (ESRD) was defined according to whether patients were either undergoing dialysis or had had a kidney transplant ( $n = 164$ ). Diabetic nephropathy was defined as macroalbuminuria or ESRD. In 281 patients, renal status could not be assessed because of the recent onset of diabetes, too few urine samples, or signs of nondiabetic renal disease. Renal function was further estimated using the Cockcroft-Gault formula for creatinine clearance adjusted for body surface area (19). Creatinine clearance  $>90$   $\text{ml}/\text{min}$  per  $1.73$   $\text{m}^2$  was considered normal,  $60$ – $90$   $\text{ml}/\text{min}$  per  $1.73$   $\text{m}^2$  was considered a mild decrease, and  $<60$   $\text{ml}/\text{min}$  per  $1.73$   $\text{m}^2$  denoted moderate to severe renal impairment (20).

Glycemic control was assessed based on one A1C measurement and classified as good (A1C  $<7.5\%$ ), intermediate ( $7.5$ – $9.0\%$ ), or poor ( $>9.0\%$ ). Data on A1C were not available for 55 patients. As a measure of insulin sensitivity, we used an equation for the estimated glucose disposal rate (eGDR) (21) modified for use with A1C instead of HbA<sub>1c</sub> ( $\text{eGDR} = 24.4 - 12.97 \cdot \text{WHR} - 3.39 \cdot \text{AHT} - 0.60 \cdot \text{A1C}$ ), where WHR stands for waist-to-hip ratio and AHT for antihypertensive treatment and/or blood pressure  $\geq 140/90$  mmHg (yes = 1, no = 0).

### Diagnostic criteria for the metabolic syndrome

The metabolic syndrome was assessed according to the NCEP criteria (11) as follows: waist circumference in men  $>102$  cm and women  $>88$  cm, triglycerides  $\geq 1.70$  mmol/l, HDL cholesterol in men  $<1.00$  mmol/l and in women  $<1.30$  mmol/l, blood pressure  $\geq 130/85$  mmHg or antihypertensive medication, and fasting glucose  $\geq 6.11$  mmol/l. We chose to define all patients in this study to fulfill the criteria for hyperglycemia, whereas three of five criteria were required for the diagnosis of the metabolic syndrome. Lipid-lowering therapy was not included in the criteria. A metabolic score (1–5) was also calculated based on the number of criteria each patient fulfilled.

### Statistical analyses

The significance of difference in categorical variables between groups was tested with a  $\chi^2$  test. Continuous variables were analyzed with ANOVA or a Kruskal-Wallis test when appropriate, and data are presented as means  $\pm$  SEM. A multiple logistic regression analysis was performed with diabetic nephropathy (vs. normal AER) as the dependent variable and age, sex, A1C, and smoking; the metabolic syndrome, its separate components, or the metabolic score were independent variables. The data are presented as odds ratios with 95% CIs. All analyses were performed using SPSS 11.5 (SPSS, Chicago, IL). A  $P$  value  $<0.05$  was considered statistically significant.

**RESULTS**— The prevalence of the metabolic syndrome defined according to NCEP criteria was 38% in men and 40% in women. In these patients, the presence of three or more components of the metabolic syndrome was associated with a threefold increased presence of coronary heart disease. At least four of the five diagnostic criteria were observed in 14% of men and in 13% of women. Patients with the metabolic syndrome were older, had an earlier onset of diabetes, and had a longer duration of diabetes (Table 1). Among patients with the metabolic syndrome, the most frequent combination of different components was hyperglycemia, hypertension, and low HDL cholesterol, which were seen in 30% of those with the metabolic syndrome. Hyperglycemia, hypertension, high triglycerides, and low HDL cholesterol were seen in 15%; hyperglycemia, hypertension, and abdominal obesity were seen in 14%; and hyperglycemia, hypertension, and high triglycerides were seen in 13% of the patients with metabolic syndrome. The frequencies of the rest of the combinations were  $<10\%$  each (1–8%).

The prevalence of metabolic syndrome increased with age. Of the individual components, hypertension and abdominal obesity became more common with increasing age, whereas the prevalence of elevated triglyceride and low HDL cholesterol levels decreased with aging (Table 2). This may partly reflect the use of lipid-lowering therapy, which increased from 1% in patients  $<30$  years of age to 28% in patients  $>50$  years of age.

**Table 1—Descriptive data for patients with and without metabolic syndrome**

	Metabolic syndrome	No metabolic syndrome
<i>n</i>	944	1,471
Men (%)	50	52
Age (years)	38.7 ± 0.4*	36.2 ± 0.3
Age at onset (years)	14.5 ± 0.3*	15.7 ± 0.2
Diabetes duration (years)	24.1 ± 0.4*	20.5 ± 0.3
BMI (kg/m <sup>2</sup> )	26.6 ± 0.1*	24.0 ± 0.1
Waist-to-hip ratio		
Men	0.95 ± 0.01*	0.89 ± 0.01
Women	0.84 ± 0.01*	0.80 ± 0.01
Systolic blood pressure (mmHg)	140 ± 1*	130 ± 1
Diastolic blood pressure (mmHg)	83 ± 1*	78 ± 1
Antihypertensive medication (%)	61*	30
Total cholesterol (mmol/l)	5.21 ± 0.03*	4.82 ± 0.02
HDL cholesterol (mmol/l)	1.10 ± 0.01*	1.43 ± 0.01
Triglycerides (mmol/l)	1.72 ± 0.03*	0.99 ± 0.01
A1C (%)	8.8 ± 0.1*	8.3 ± 0.1
eGDR (mg · kg <sup>-1</sup> · min <sup>-1</sup> )	4.8 ± 0.1*	7.0 ± 0.1
Serum creatinine (μmol/l)	130 ± 4*	94 ± 2
Creatinine clearance (ml/min per 1.73 m <sup>2</sup> )	84 ± 1*	93 ± 1
Creatinine clearance <60 ml/min per 1.73 m <sup>2</sup> (%)	20*	7
ESRD (%)	12*	4
Diabetic nephropathy		
Men (%)	40*	16
Women (%)	34*	11
Coronary heart disease (%)	9*	3
Myocardial infarction (%)	5*	2
Stroke (%)	3†	2
Amputation (%)	6*	1
Retinal laser treatment (%)	53*	26
Current smoking (%)	26†	22

Data are means ± SEM or %. \**P* < 0.001 and †*P* < 0.05 vs. no metabolic syndrome.

**Diabetic nephropathy and metabolic syndrome**

Patients with the metabolic syndrome had more microvascular complications including retinopathy and nephropathy (Table 1). The prevalence of the metabolic syndrome was 28% in those with normal AER, 44% in patients with microalbuminuria, 62% in patients with macroalbumin-

uria, and 68% in patients with ESRD (*P* < 0.001). Patients with the metabolic syndrome had a 3.75-fold (95% CI 2.89–4.85) increased odds ratio for diabetic nephropathy compared with those without the metabolic syndrome when adjusting for age, sex, smoking, and A1C. This risk was strongly correlated with the presence of multiple components of the met-

abolic syndrome such that patients with three, four, and five components of the metabolic syndrome had increased odds for diabetic nephropathy of 2.81 (2.09–3.78), 5.09 (3.45–7.50), and 11.70 (5.74–23.84), respectively, compared with those with one or two components. Notably, all components were independently associated with diabetic nephropathy (data not shown).

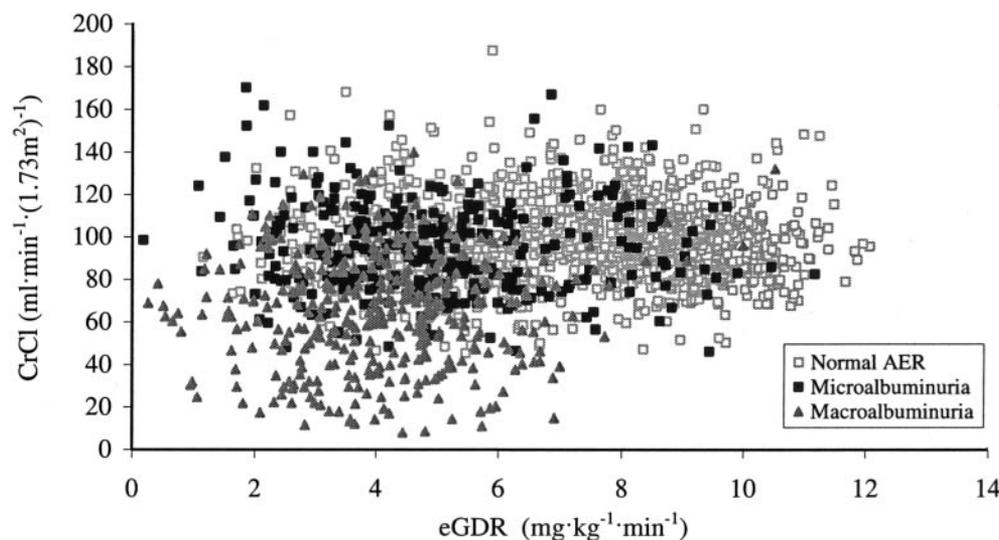
**Effect of renal function and insulin sensitivity**

The prevalence of the metabolic syndrome was 36% in patients with a creatinine clearance in the normal range, 34% in patients with a mild decrease in renal function, and 60% in patients with moderate to severe renal impairment (*P* < 0.001). Patients with ESRD were excluded from the analysis. Figure 1 shows the relationship between insulin sensitivity, as assessed by eGDR and creatinine clearance at different stages of nephropathy. Most patients with type 1 diabetes and normal AER and renal function had normal insulin sensitivity. On the other hand, patients with microalbuminuria were more insulin resistant, whereas decreased renal function was most obvious in those with macroalbuminuria. When patients with normal AER were compared with those with microalbuminuria, there was only a small difference in creatinine clearance (99 ± 1 vs. 95 ± 1, *P* = 0.006), whereas the difference in insulin sensitivity was large (eGDR, 7.3 ± 0.1 vs. 5.0 ± 0.1, *P* < 0.001). When patients with microalbuminuria were compared with those with macroalbuminuria, there was a marked difference in creatinine clearance (95 ± 1 vs. 65 ± 1, *P* < 0.001) and a further decrease in insulin sensitivity (5.0 ± 0.1 vs. 4.1 ± 0.1, *P* < 0.001).

**Table 2—Prevalence of metabolic syndrome and its components by sex, age-group, and glycemic control**

	Total prevalence		Age-group (years)				A1C (%)		
	Men	Women	18–30	30–40	40–50	>50	<7.5	7.5–9.0	>9.0
<i>n</i>	1,241	1,174	727	729	594	365	578	1,087	695
Metabolic syndrome (%)	38	40	33	40	41	47*	31	36	51*
Hypertension (%)	76	63*	51	69	80	90*	60	71	76*
Low HDL cholesterol (%)	28	42*	38	37	34	27*	34	33	40†
High triglycerides (%)	24	14*	19	20	19	17	13	16	28*
Abdominal obesity (%)	12	20*	9	15	20	26*	10	16	21*

Data are % of the total *n* given at the top of each column. \**P* < 0.001, †*P* < 0.01 for men vs. women, age-group difference, and A1C group difference.



**Figure 1**—Insulin sensitivity and renal function in different stages of albuminuria.

**Glycemic control and metabolic syndrome**

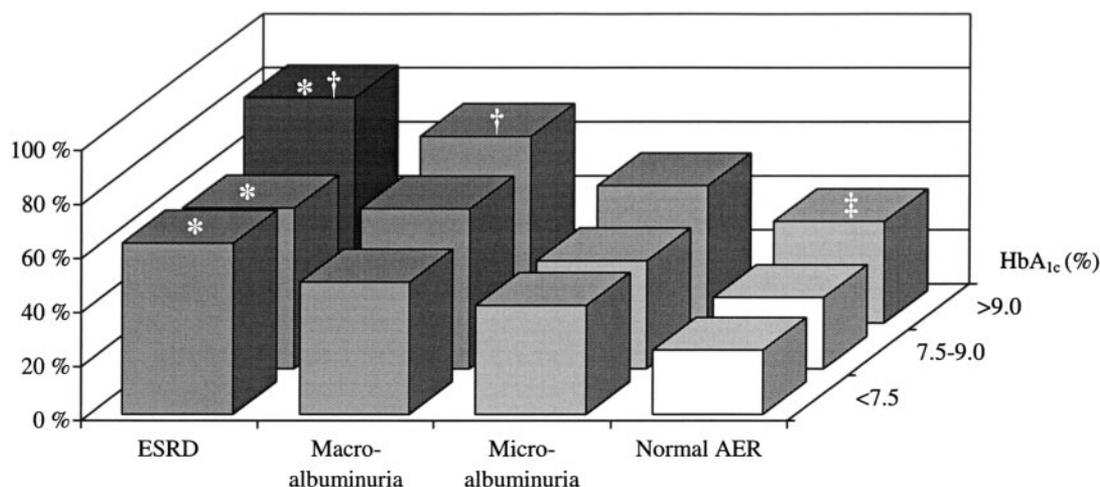
The prevalence of metabolic syndrome was correlated with glycemic control, such that 51% of patients with poor glycemic control had metabolic syndrome, compared with 31% of patients with good glycemic control and 36% in those with intermediate control ( $P < 0.001$ ). This association was seen in all patient groups regardless of renal function. The higher prevalence of the metabolic syndrome in patients with intermediate compared with good glycemic control was largely determined by hypertension, whereas the higher prevalence of the metabolic syndrome in patients with poor compared with intermediate glycemic control was mostly related to an increase in dyslipidemia (Table 2). When patients with normal

AER were analyzed separately with regard to A1C, a similar pattern could be observed (data not shown). A synergistic effect of glycemic control and renal status was also observed in our study. As seen in Fig. 2, the prevalence of metabolic syndrome was lowest in patients with good glycemic control and normal AER (24%) and highest in patients with ESRD and poor glycemic control (83%).

strong association between metabolic syndrome and vascular complications in patients with diabetes (1,4,22–24), these statistics are a matter of concern.

The overall prevalence of the metabolic syndrome in FinnDiane patients (39%) was approximately three times that seen in nondiabetic subjects in the Finnish population but lower than that observed in patients with type 2 diabetes (78–84%) (1,2). This disparity in the prevalence of metabolic syndrome probably reflects differences in population characteristics including duration of diabetes, renal function, and age, which were also independently associated with metabolic syndrome. In addition, there may be different findings depending on the criteria used to define the prevalence of metabolic syndrome (25).

**CONCLUSIONS** — Metabolic syndrome is a common finding in patients with type 1 diabetes. In particular, >50% of patients with poor glycemic control or renal impairment fulfilled the NCEP diagnostic criteria for metabolic syndrome. In addition, ~33% of patients without nephropathy or with good glycemic control met the diagnostic criteria. Given the



**Figure 2**—Prevalence of the metabolic syndrome according to glycemic control and different stages of albuminuria. \* $P < 0.001$  within the A1C groups. † $P < 0.001$  and ‡ $P < 0.05$  within the albuminuria groups.

Of the two most used criteria for metabolic syndrome (NCEP and WHO), we used the NCEP criteria because they are more appropriate to apply in a type 1 diabetic population than the WHO criteria, which include insulin resistance and microalbuminuria (10,11). However, it is possible that metabolic syndrome should be defined differently in type 1 diabetes. In comparison with type 2 diabetes and the general population, hypertension seems to be a more pronounced part of metabolic syndrome in type 1 diabetes, whereas dyslipidemia is more frequent among type 2 diabetic patients (1). Although hypertension was the most prevalent component in addition to diabetes in the present study, when compared with patients fulfilling one or two of the criteria, each additional component further increased the odds ratio for diabetic nephropathy in support of a true syndrome.

It remains to be established whether "metabolic syndrome" as observed in our patients is the same metabolic syndrome as in type 2 diabetes. Certainly, in both type 1 and type 2 diabetes, the role of insulin resistance seems to be equally important as a cardiovascular risk factor (22–24,26). Insulin resistance has also been implicated in the pathogenesis of diabetic nephropathy (17). However, the finding of metabolic syndrome in patients with type 1 diabetes may reflect an epiphenomenon of their inheritance. It is well known that both genetic and environmental factors seem to promote the development of metabolic syndrome (3,27). We have previously shown that type 2 diabetes is more common among parents of type 1 diabetic patients with nephropathy compared with those without nephropathy (28), and offspring of diabetic parents tend to be more insulin resistant (29).

In the present study, insulin sensitivity was more strongly related to AER than creatinine clearance. Indeed, a major change in insulin sensitivity had already occurred in those with microalbuminuria well before the decline in creatinine clearance associated with the late-stage disease. This finding is in disagreement with the findings from a small survey in selected patients with type 1 diabetes in Sweden ( $n = 29$ ), in which albuminuria did not modify insulin sensitivity (30). It is possible that our much larger survey ( $n = 2,415$ ) is more representative be-

cause it includes carefully characterized type 1 diabetic patients recruited from a nationwide multicenter study comprising about 10% of the Finnish adult type 1 diabetic population. In addition, a link between occult nephropathy and insulin resistance is consistent with the Steno hypothesis that microalbuminuria reflects generalized vascular dysfunction (i.e., endothelial dysfunction) (31), which is known to correlate with insulin resistance (32). The onset of nephropathy might also contribute to metabolic syndrome via low-grade inflammation and increased oxidative stress. We have previously shown that increased concentrations of interleukin-6 and C-reactive protein are associated with decreased insulin sensitivity, which worsened in parallel with the severity of the renal disease (16). Although our data are cross-sectional, they provide an interesting hypothesis that should be addressed in a prospective follow-up of this population.

Notably in this survey, in each AER group the prevalence of the metabolic syndrome increased in patients with poorer glycemic control. It is well known that chronic hyperglycemia can modify insulin sensitivity (so-called "glucose toxicity") (33). The increased prevalence of metabolic syndrome may be partly explained by reduced insulin sensitivity in patients with poor glycemic control. In addition, hyperglycemia per se is associated with several of the components of the metabolic syndrome, such as increased triglycerides and decreased HDL cholesterol levels (34). However, in patients with poor glycemic control, the key component leading to the diagnosis of metabolic syndrome was hypertension.

In summary, metabolic syndrome is a frequent finding in type 1 diabetes, especially in patients with advanced diabetic nephropathy and poor glycemic control. Prospective data are needed to finally evaluate whether the current diagnostic criteria for the metabolic syndrome correctly identify type 1 diabetic patients at the greatest risk for cardiovascular complications.

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