Metabolic Syndrome as a Risk Factor for Cardiovascular Disease, Mortality, and Progression of Diabetic Nephropathy in Type 1 Diabetes

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OBJECTIVE — To assess the predictive value of the metabolic syndrome in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Patients were from the prospective Finnish Diabetic Nephropathy (FinnDiane) Study (n = 3,783): mean age 37 ± 12 years and diabetes duration 23 ± 12 years. Metabolic syndrome was defined according to World Health Organization (WHO), National Cholesterol Education Program (NCEP), and International Diabetes Federation (IDF) definitions. Follow-up time was median 5.5 years (interquartile range 3.7–6.7). Mortality data were complete, whereas morbidity data were available in 69% of the patients.

RESULTS — The WHO definition was associated with a 2.1-fold increased risk of cardiovascular events and a 2.5-fold increased risk of cardiovascular- and diabetes-related mortality, after adjustment for traditional risk factors and diabetic nephropathy. The NCEP definition did not predict outcomes when adjusted for nephropathy but markedly added to the risk associated with elevated albuminuria alone ($P < 0.001$). The IDF definition did not predict outcomes.

CONCLUSIONS — The metabolic syndrome is a risk factor, beyond albuminuria, for cardiovascular morbidity and diabetes-related mortality in type 1 diabetes.

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Type 1 diabetes is associated with an increased risk of cardiovascular morbidity and mortality, which is largely, but not totally, explained by the presence of diabetic nephropathy (1). The metabolic syndrome, a cluster of cardiovascular risk factors, increases the risk of cardiovascular disease and chronic renal disease in the general population and in patients with type 2 diabetes (2–4). The metabolic syndrome is common in patients with type 1 diabetes (5–7), but its role as a predictor of cardiovascular disease and diabetic nephropathy is less clear (8,9). Therefore, the aim of this study was to assess the predictive value of the different definitions of the metabolic syndrome for cardiovascular events, cardiovascular- and diabetes-related mortality, and the progression of renal disease in type 1 diabetes.

RESEARCH DESIGN AND METHODS

— All patients participated in the Finnish Diabetic Nephropathy (FinnDiane) Study, initiated in 1997. The present study is prospective and includes 3,783 adult patients with type 1 diabetes from the FinnDiane Study, who at baseline had complete lipid profiles and data available on the components of the metabolic syndrome. A more detailed description of the baseline visit has previously been reported (5). Of the patients, 2,270 had a normal urinary albumin excretion rate (UAER), 477 microalbuminuria, 543 macroalbuminuria, and 241 end-stage renal disease (ESRD). Diabetic nephropathy was defined as macroalbuminuria or ESRD. In 252 patients, renal status could not be assessed. The metabolic syndrome was assessed according to World Health Organization (MS^{WHO}) (10), National Cholesterol Education Program (MS^{NCEP}) (11), and International Diabetes Federation (MS^{IDF}) (12) definitions (see supplementary Table A1, available in the online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-2022/DC1). All patients with type 1 diabetes fulfilled the criteria for hyperglycemia.

Data on mortality were available for all patients, and death certificates were retrieved from Statistics Finland. Cardiovascular- and diabetes-related mortality was used as the end point, defined as underlying or immediate cardiovascular- or diabetes-related cause of death. Collection of follow-up data on morbidity is still ongoing; data on cardiovascular morbidity were available for 2,474 patients (65%) and data on progression of renal disease for 2,594 patients (69%). The data were collected from follow-up visits (36%) or medical files (64%). Progression of renal disease was defined as a change in category from normal UAER to microalbuminuria (n = 118), microalbuminuria to macroalbuminuria (n = 54), or macroalbuminuria to ESRD (n = 130).

RESULTS

— At baseline, the prevalence of MS^{WHO} was 44%, MS^{NCEP} 35%, and MS^{IDF} 36%. The overlap of the three definitions is shown in Figure A1 in the online appendix. Detailed clinical charac-

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Table 1—*Hazard ratios for outcomes by different definitions of the metabolic syndrome*

	n	MS^{WHO}	*P*	MS^{NCEP}	*P*	MS^{IDF}	*P*
New cardiovascular event	263	5.73 (4.14–7.92)	<0.001	2.45 (1.92–3.14)	<0.001	1.66 (1.30–2.11)	0.001
Adjusted for traditional risk factors*		3.65 (2.59–5.14)	<0.001	1.89 (1.46–2.46)	0.001	1.09 (0.84–1.41)	0.535
Further adjusted for previous cardiovascular event		2.98 (2.10–4.24)	<0.001	1.64 (1.23–2.14)	<0.001	1.03 (0.79–1.33)	0.833
Further adjusted for diabetic nephropathy		2.05 (1.38–3.04)	<0.001	1.31 (0.99–1.72)	0.056	0.96 (0.74–1.25)	0.759
New myocardial infarction	161	10.29 (6.14–17.25)	<0.001	2.61 (1.90–3.59)	<0.001	1.76 (1.29–2.39)	<0.001
Adjusted for traditional risk factors*		6.30 (3.68–10.78)	<0.001	1.85 (1.32–2.59)	<0.001	1.16 (0.83–1.62)	0.375
Further adjusted for previous myocardial infarction		5.80 (3.38–9.97)	<0.001	1.67 (1.19–2.35)	0.003	1.11 (0.79–1.54)	0.558
Further adjusted for diabetic nephropathy		3.10 (1.70–5.68)	<0.001	1.17 (0.83–1.65)	0.380	1.00 (0.72–1.40)	0.992
New stroke	80	7.51 (3.86–14.60)	<0.001	1.94 (1.25–3.02)	0.003	1.10 (0.70–1.73)	0.684
Adjusted for traditional risk factors*		4.86 (2.42–9.77)	<0.001	1.51 (0.94–2.44)	0.090	0.73 (0.45–1.20)	0.218
Further adjusted for previous stroke		4.49 (2.22–9.07)	<0.001	1.45 (0.89–2.34)	0.133	0.65 (0.40–1.08)	0.096
Further adjusted for diabetic nephropathy		2.81 (1.29–6.15)	0.010	1.05 (0.64–1.71)	0.859	0.66 (0.40–1.07)	0.093
Cardiovascular- and diabetes-related mortality	238	11.05 (7.25–16.85)	<0.001	2.87 (2.21–3.73)	<0.001	1.79 (1.39–2.31)	<0.001
Adjusted for traditional risk factors*		7.33 (4.69–11.46)	<0.001	2.15 (1.63–2.84)	<0.001	1.20 (0.92–1.58)	0.185
Further adjusted for diabetic nephropathy		2.52 (1.53–4.16)	<0.001	1.31 (0.99–1.73)	0.063	1.00 (0.76–1.32)	0.986
Progression							
Normal UAER to microalbuminuria†	118	2.10 (1.42–3.12)	<0.001	1.13 (0.77–1.68)	0.531	1.30 (0.88–1.92)	0.191
Micro- to macroalbuminuria†	54	2.42 (0.96–6.12)	0.062	1.57 (0.91–2.71)	0.102	1.65 (0.93–2.92)	0.085
Macroalbuminuria to ESRD†	130	2.57 (1.13–5.86)	0.025	1.65 (1.13–2.40)	0.009	0.52 (0.36–0.75)	<0.001

Data are HR (95% CI), derived from Cox regression analyses. *Adjusted for age, sex, smoking, LDL cholesterol, and A1C. †Adjusted for duration of diabetes, sex, smoking, and A1C.

teristics of the patients are presented in Table A2 in the online appendix.

During median 5.5 years (interquartile range 3.7–6.7) of follow-up, 263 patients suffered a cardiovascular event; of these, 106 had a history of previous events and 173 had diabetic nephropathy at baseline. The predictive value of MS^{WHO}, MS^{NCEP}, and MS^{IDF} for outcomes is shown in Table 1. Of individual metabolic syndrome components, all except obesity were independent predictors of a new cardiovascular event, adjusted for the traditional risk factors: MS^{WHO} elevated UAER (HR 2.69 [95% CI 1.95–3.72]), MS^{WHO} hypertension (1.71 [1.26–2.31]), MS^{WHO} dyslipidemia (1.80 [1.38–2.35]), MS^{NCEP} hypertension (2.00 [1.36–2.93]), MS^{NCEP} low HDL cholesterol (1.35 [1.03–1.78]), MS^{NCEP} high triglycerides (1.83 [1.35–2.48]), MS^{IDF} hypertension (4.25 [2.28–7.92]), MS^{IDF} low HDL cholesterol (1.63 [1.24–2.13]), MS^{IDF} high triglycerides (1.76 [1.31–2.37]), MS^{WHO} obesity (1.28 [0.97–1.68]), MS^{NCEP} obesity (0.94 [0.68–1.30]), and MS^{IDF} obesity (0.82 [0.63–1.06]).

MS^{NCEP} added to the risk attributed to elevated UAER for cardiovascular events ($P < 0.001$). In those with elevated UAER, MS^{NCEP} was associated with an HR of 1.44 (95% CI 1.06–1.96) for a new cardiovascular event, after adjustment for traditional risk factors and diabetic nephropathy (see Figure A2 in the online appendix).

During a median 5.7 years (interquartile range 4.0–6.9) of follow-up, 238 patients died from either cardiovascular- or diabetes-related causes. The predictive value of the metabolic syndrome on cardiovascular- and diabetes-related mortality is shown in Table 1. Of individual components of the metabolic syndrome, all except obesity were independent predictors of cardiovascular- and diabetes-related mortality. The predictive value of the metabolic syndrome on the progression of diabetic nephropathy is shown in Table 1. The protective role of MS^{IDF} was largely due to MS^{IDF} obesity (HR 0.39 [95% CI 0.26–0.57]), which was the only component that was seemingly protective.

CONCLUSIONS — Our main findings support data from two prospective studies on the role of the metabolic syndrome in type 1 diabetes (8,9). Of the current definitions, MS^{WHO} is associated with the highest risk of cardiovascular outcomes, followed by MS^{NCEP}, whereas MS^{IDF} is the weakest predictor.

Diabetic nephropathy is accompanied by the metabolic syndrome (5) and is also the strongest risk factor for cardiovascular outcomes in patients with type 1 diabetes. In the present study, most of the cardiovascular events were seen in those with diabetic nephropathy. Taking these facts into consideration, it is difficult to eliminate diabetic nephropathy where the role of the metabolic syndrome is assessed. The independent risk shown for MS^{WHO} on cardiovascular events and cardiovascular- and diabetes-related mortality, adjusted for diabetic nephropathy, suggests that the metabolic syndrome plays an independent role. It could, however, be argued that the effect is due to the inclusion of microalbuminuria in the MS^{WHO}. We were, however, also able to show an additional effect of MS^{NCEP} beyond elevated UAER alone, suggesting a true role of the metabolic syndrome as a risk factor for cardiovascular outcomes. The results from the present and earlier studies suggest that the role of the metabolic syndrome on progression to microalbuminuria is modest, whereas at later stages the metabolic syndrome plays a larger role.

Of the individual components, abdominal obesity seems to play the weakest role. This is surprising because abdominal obesity is a key feature of insulin resistance, an established risk factor for cardiovascular disease (13). However,

all the other individual components were independent predictors of both cardiovascular events and cardiovascular- and diabetes-related mortality. In patients on dialysis, obesity has been associated with better survival (the obesity paradox), highlighting the importance of optimal nutrition (14). In the present study, MS^{IDF} obesity was seemingly protective of progression to ESRD, suggesting an inverse or U-shaped relationship in patients with macroalbuminuria.

A major limitation was the incomplete follow-up data on mortality, which was due to the ongoing nature of the FinnDiane Study. In conclusion, the metabolic syndrome is an independent risk factor for cardiovascular events and adds to the risk related to albuminuria.

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