The metabolic syndrome as a risk factor for cardiovascular disease, mortality, and progression of diabetic nephropathy in type 1 diabetes

Lena M Thorn MD\textsuperscript{1,2}, Carol Forsblom DMSc\textsuperscript{1,2}, Johan Wadén MD\textsuperscript{1,2}, Markku Saraheimo MD\textsuperscript{1,2}, Nina Tolonen MD\textsuperscript{1,2}, Kustaa Hietala MD\textsuperscript{1}, Per-Henrik Groop DMSc\textsuperscript{1,2}, on behalf of the FinnDiane Study Group

\textsuperscript{1}Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Finland
\textsuperscript{2}Department of Medicine, Division of Nephrology, Helsinki University Hospital, Helsinki, Finland

Corresponding author:
Per-Henrik Groop, MD, DMSc
E-mail: per-henrik.groop@helsinki.fi

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

Submitted 13 November 2008 and accepted 18 January 2009.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
**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 FinnDiane Study (n=3,783), mean age 37±12 and diabetes duration 23±12. Metabolic syndrome was defined according to WHO, NCEP, and IDF definitions. Follow-up time was 5.5 (3.7-6.7) years. 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.

**Abbreviations:** CV-DM-mortality, death from cardiovascular or diabetes-related cause; ESRD, end-stage renal disease; MS_{IDF}, metabolic syndrome according to the International Diabetes Federation definition; MS_{NCEP}, according to the National Cholesterol Education Program Adult Treatment Panel III; MS_{WHO}, according to the World Health Organization; UAER, urinary albumin excretion rate
Type 1 diabetes is associated with 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 was to assess the predictive value of the different definitions of the metabolic syndrome for cardiovascular events, cardiovascular- and diabetes-related mortality (CV-DM-mortality), as well as progression of renal disease in type 1 diabetes.

RESEARCH DESIGN AND METHODS
All patients participated in the Finnish Diabetic Nephropathy Study, initiated in 1997. For this study, the design is prospective and includes 3,783 adult patients with type 1 diabetes, who at baseline had complete lipid profiles and data on the components of the metabolic syndrome available. A more detailed description of the baseline visit has been presented earlier (5). Of the patients 2,270 had 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 the World Health Organization (10) (MS WHO), National Cholesterol Education Programme (11) (MS NCEP), and International Diabetes Federation (12) (MS IDF) definitions (see Table A1 available in the online appendix at http://care.diabetesjournals.org). 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. CV-DM-mortality was used as end-point, defined as underlying or immediate cardiovascular or diabetes-related cause of death. Collection of follow-up data on morbidity is still ongoing and data on cardiovascular morbidity were available in 2,474 (65%), and data on progression of renal disease in 2,594 (69%) of the patients. 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 from 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 characteristics of the patients are presented in Table A2 in the online appendix.

During 5.5 (3.7-6.7) years follow-up, 263 patients suffered a cardiovascular event, and 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 components, all except obesity were independent predictors of a new cardiovascular event, adjusted for the traditional risk factors: MS WHO elevated UAER [2.69 (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\textsuperscript{WHO} obesity 1.28 (0.97-1.68), MS\textsuperscript{NCEP} obesity 0.94 (0.68-1.30), and MS\textsuperscript{IDF} obesity 0.82 (0.63-1.06)]. MS\textsuperscript{NCEP} added to the risk attributed to elevated UAER for cardiovascular events (\textit{P}<0.001). In those with elevated UAER, MS\textsuperscript{NCEP} was associated with a 1.44 (1.06-1.96) hazard ratio for a new cardiovascular event, after adjustment for traditional risk factors and diabetic nephropathy (see Figure A2 in the online appendix).

During 5.7 (4.0-6.9) years follow-up, 238 patients died from either cardiovascular or diabetes-related causes. The predictive value of the metabolic syndrome on CV-DM-mortality is shown in Table 1. Of individual components of the metabolic syndrome, all except obesity were independent predictors of CV-DM-mortality. The predictive value of the metabolic syndrome on the progression of diabetic nephropathy is shown in Table 1. The protective role of MS\textsuperscript{IDF} was largely due to MS\textsuperscript{IDF} obesity [0.39 (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\textsuperscript{WHO} is associated with the highest risk of cardiovascular outcomes, followed by MS\textsuperscript{NCEP}, while MS\textsuperscript{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 when the role of the metabolic syndrome is assessed. The independent risk shown for MS\textsuperscript{WHO} on cardiovascular events and CV-DM-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 microalbuminuria included in the MS\textsuperscript{WHO}. We were however further able to show an additional effect of MS\textsuperscript{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, while 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 since 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 CV-DM-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, the MS\textsuperscript{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.

**ACKNOWLEDGEMENTS**

Authors have no relevant conflict of interest to disclose. Preliminary results have been published in the abstract volume of the
44th European Association for the Study of Diabetes (EASD) Annual Meeting [Diabetologia 51 (Suppl. 1):S544-545, 2008]. The study was supported by grants from the Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Liv och Hälsa Foundation, Finnish Medical Society (Finska Läkaresällskapet), Perklén Foundation, and European Commission (QLG2-CT-2001-01669 and LSHB-CT-2003-503364). The skilled technical assistance of Sinikka Lindh, Anna Sandelin, Susanne Ström, and Jaana Tuomikangas is gratefully acknowledged. The lipid research laboratory of Professor Marja-Riitta Taskinen, including Hannele Hildén, Virve Naatti, Helinä Pertunen-Mio, and Emmi Rautaheimo, is acknowledged for their contribution. Finally, we acknowledge all the physicians and nurses at each center participating in the collection of patients (see Table A3 in the online appendix).
REFERENCES
1. Borch-Johnsen K, Kreiner S: Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *BMJ* 294:1651-1654, 1987
2. Bonora E: The metabolic syndrome and cardiovascular disease. *Ann Med* 38:64-80, 2006
3. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 16:2134-2140, 2005
4. Luk AO, So WY, Ma RC, Kong AP, Ozaki R, Ng VS, Yu LW, Lau WW, Yang X, Chow FC, Chan JC, Tong PC: Metabolic syndrome predicts new onset of chronic kidney disease in 5,829 patients with type 2 diabetes: a 5-year prospective analysis of the Hong Kong Diabetes Registry. *Diabetes Care* 31:2357-2361, 2008
5. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Waden J, Ronnback M, Rosengard-Barlund M, Bjorkesten CG, Taskinen MR, Groop PH: Metabolic Syndrome in Type 1 Diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care* 28:2019-2024, 2005
6. McGill M, Molyneaux L, Twigg SM, Yue DK: The metabolic syndrome in type 1 diabetes: does it exist and does it matter? *J Diabetes Complications* 22:18-23, 2008
7. Bonadonna RC, Cucinotta D, Fedele D, Riccardi G, Tiengo A: The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: results from Metascreen, a multicenter diabetes clinic-based survey. *Diabetes Care* 29:2701-2707, 2006
8. Kilpatrick ES, Rigby AS, Atkin SL: Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "double diabetes" in the Diabetes Control and Complications Trial. *Diabetes Care* 30:707-712, 2007
9. Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes Care* 30:1248-1254, 2007
10. World Health Organization: Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus. Definition, Diagnosis and Classification of Diabetes mellitus and its Complications. *World Health Organization, Geneva*, 1999
11. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
12. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005
13. Martin FIR, Hopper JL: The relationship of acute insulin sensitivity to the progression of vascular disease in long-term Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:149-153, 1987
14. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 55:1560-1567, 1999
### Table 1 – Hazard ratios (HR) for outcomes by different definitions of the metabolic syndrome

|                         | MS\text{WHO} |   | MS\text{NCEP} |   | MS\text{IDF} |   |
|-------------------------|--------------|---|---------------|---|-------------|---|
|                         | HR (95% CI)  |   | HR (95% CI)   |   | HR (95% CI) |   |
| **New cardiovascular event** (n = 263) |              |   |               |   |             |   |
| adjusted for traditional risk factors* | 5.73 (4.14-7.92) | <.001 | 2.45 (1.92-3.14) | <.001 | 1.66 (1.30-2.11) | .001 |
| further adjusted for previous cardiovascular event | 3.65 (2.59-5.14) | <.001 | 1.89 (1.46-2.46) | .001 | 1.09 (0.84-1.41) | .535 |
| further adjusted for diabetic nephropathy | 2.05 (1.38-3.04) | <.001 | 1.31 (0.99-1.72) | .056 | 0.96 (0.74-1.25) | .759 |
| **New myocardial infarction** (n = 161) | 10.29 (6.14-17.25) | <.001 | 2.61 (1.90-3.59) | <.001 | 1.76 (1.29-2.39) | <.001 |
| adjusted for traditional risk factors* | 6.30 (3.68-10.78) | <.001 | 1.85 (1.32-2.59) | <.001 | 1.16 (0.83-1.62) | .375 |
| further adjusted for previous myocardial infarction | 5.80 (3.38-9.97) | <.001 | 1.67 (1.19-2.35) | .003 | 1.11 (0.79-1.54) | .558 |
| further adjusted for diabetic nephropathy | 3.10 (1.70-5.68) | <.001 | 1.17 (0.83-1.65) | .380 | 1.00 (0.72-1.40) | .992 |
| **New stroke** (n = 80) | 7.51 (3.86-14.60) | <.001 | 1.94 (1.25-3.02) | <.001 | 1.10 (0.70-1.73) | .684 |
| adjusted for traditional risk factors* | 4.86 (2.42-9.77) | <.001 | 1.51 (0.94-2.44) | <.090 | 0.73 (0.45-1.20) | .218 |
| further adjusted for previous stroke | 4.49 (2.22-9.07) | <.001 | 1.45 (0.89-2.34) | .133 | 0.65 (0.40-1.08) | .096 |
| further adjusted for diabetic nephropathy | 2.81 (1.29-6.15) | .010 | 1.05 (0.64-1.71) | .859 | 0.66 (0.40-1.07) | .093 |
| **Cardiovascular and diabetes related mortality** (n = 238) | 11.05 (7.25-16.85) | <.001 | 2.87 (2.21-3.73) | <.001 | 1.79 (1.39-2.31) | <.001 |
| adjusted for traditional risk factors* | 7.33 (4.69-11.46) | <.001 | 2.15 (1.63-2.84) | <.001 | 1.20 (0.92-1.58) | .185 |
| further adjusted for diabetic nephropathy | 2.52 (1.53-4.16) | <.001 | 1.31 (0.99-1.73) | .063 | 1.00 (0.76-1.32) | .986 |
| **Progression** |              |   |               |   |             |   |
| from normal UAER to microalbuminuria† (n = 118) | 2.10 (1.42-3.12) | <.001 | 1.13 (0.77-1.68) | .531 | 1.30 (0.88-1.92) | .191 |
| from micro- to macroalbuminuria† (n = 54) | 2.42 (0.96-6.12) | .062 | 1.57 (0.91-2.71) | .102 | 1.65 (0.93-2.92) | .085 |
| from macroalbuminuria to ESRD† (n = 130) | 2.57 (1.13-5.86) | .025 | 1.65 (1.13-2.40) | .009 | 0.52 (0.36-0.75) | <.001 |

Data are hazard ratios (HR) with 95% confidence intervals (CI), derived from Cox regression analyses. *age, gender, smoking, LDL cholesterol, and HbA1c. †adjusted for duration of diabetes, gender, smoking, and HbA1c. UAER = urinary albumin excretion rate, ESRD = end-stage renal disease.