Increased Mortality Associated With the Metabolic Syndrome in Older Women With Diabetes

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About 25% of U.S. adults have the metabolic syndrome (1), a cluster of central obesity; abnormal glucose, insulin, and lipids; and hypertension. Clinicians and the media have increasingly emphasized its diagnosis and treatment (2,3). Several recent prospective studies associate increased cardiovascular disease (CVD) or total mortality risk with the metabolic syndrome in men and younger adults (4–10). Over 90% of CVD mortality in women occurs after 65 years of age (11), and women with diabetes lose sex-protective effects; their CVD relative risk is even greater than men with diabetes (12). Whether the metabolic syndrome increases mortality risk in addition to diabetes is unclear. We prospectively evaluated the syndrome's association with CVD mortality in older women and whether its risk is greater than diabetes alone.

RESEARCH DESIGN AND METHODS — From 1986 to 1988, the Study of Osteoporotic Fractures (SOF) recruited 9,704 community-dwelling women, ≥65 years of age

(>99% Non-Hispanic White) in four U.S. regions: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley near Pittsburgh, Pennsylvania (13). Women unable to walk without assistance and those with bilateral hip replacements were excluded. All participants provided written consent, and SOF was approved by each site's institutional review board.

Waist and hip circumference were measured by standardized protocol (14) to the nearest 0.10 cm with steel tape. Weight was measured by balance beam, height by stadiometer. Blood pressure was measured supine and after standing 1 min; the average of the two measurements was calculated. Measurement and quality control procedures were rigorous (13).

Fasting lipids, including triglyceride and HDL cholesterol levels, were measured at baseline on a random subsample ($n = 1,015$) at one SOF clinic. Cholesterol and triglycerides were measured enzymatically (15,16); HDL was precipitated by heparin and manganese chloride (17).

Metabolic syndrome
We evaluated the risk of mortality in 9,677 participants associated with baseline measures: self-reported diabetes, measured obesity, and hypertension by the National Cholesterol Education Panel (NCEP) and World Health Organization (WHO) criteria for these metabolic syndrome parameters (17–19), and with the metabolic syndrome (positive for diabetes, obesity, and hypertension).

In the lipid subsample, we assessed associated mortality risk with the metabolic syndrome as defined for the entire population and again after counting potentially low HDL or elevated triglycerides as one of the three positive criteria for the metabolic syndrome (18–20); we then stratified by diabetes and the metabolic syndrome.

Mortality/follow-up
More than 98% of follow-up contacts by postcards every 4 months were completed. Cause of death was physician-adjudicated centrally with death certificates and medical records (>95% deaths confirmed) based on ICD-9 for coronary heart disease (CHD) (410–414) (21) and CVD (402,404,410–414,426–445) (21).

Statistical analyses
To test the association between the syndrome and mortality, we used Cox proportional hazards models, adjusted for age and smoking.

RESULTS — At baseline, 682 (7%) of the 9,677 participants had a physician diagnosis of diabetes, about one-third were obese by either NCEP or WHO criteria, more than two-thirds were hypertensive by NCEP criteria (≥130/85 mmHg), and almost half (45%) had hypertension (≥140/90 mmHg) by WHO criteria. During a mean follow-up of 12.2 years, 3,427 (35%) women died, 1,213 from CVD (507 from CHD).

Metabolic syndrome defined without lipid levels
Using the initial definitions (without lipid levels), we found that about 3% of the

Table 1—*Association between parameters for the metabolic syndrome (NCEP and WHO defined) and the metabolic syndrome with associated risk of mortality**

	NCEP			WHO		
	Total mortality	CHD death	CVD death	Total mortality	CHD death	CVD death
N = 9,677						
Metabolic syndrome (diabetes and obesity plus hypertension)	**2.5 (2.2–2.9)**	**4.5 (3.4–6.1)**	**3.3 (2.7–4.1)**	**2.8 (2.4–3.2)**	**4.1 (3.0–5.8)**	**3.7 (3.0–4.7)**
Diabetes†	1.7 (1.4–1.9)	1.9 (1.3–2.7)	1.7 (1.4–2.2)	1.7 (1.5–2.0)	2.0 (1.4–2.8)	1.8 (1.4–2.3)
Obesity‡	1.2 (1.1–1.4)	1.3 (1.0–1.7)	1.5 (1.3–1.8)	1.1 (1.0–1.2)	1.1 (0.9–1.4)	1.2 (1.1–1.4)
Hypertension§	1.3 (1.2–1.4)	1.3 (1.0–1.7)	1.4 (1.2–1.7)	1.3 (1.2–1.4)	1.5 (1.2–1.9)	1.5 (1.3–1.7)
Lipid subsample (*n* = 1,015)						
Metabolic syndrome (diabetes and obesity plus hypertension)	**1.7 (1.1–2.6)**	**3.0 (1.4–6.6)**	**2.3 (1.3–4.3)**	**2.0 (1.2–3.1)**	**3.2 (1.4–7.4)**	**2.2 (1.1–4.5)**
Metabolic syndrome‖¶	**1.5 (1.2–1.8)**	**2.0 (1.3–3.3)**	**1.9 (1.3–2.6)**	**2.0 (1.3–2.9)**	**2.6 (1.2–5.6)**	**2.0 (1.1–3.7)**
Metabolic syndrome vs. diabetes in lipid subsample						
No diabetes, no metabolic syndrome	(reference) *n* = 671	(reference) *n* = 671	(reference) *n* = 671	(reference) *n* = 921	(reference) *n* = 921	(reference) *n* = 921
Metabolic syndrome but no diabetes	**1.3 (1.0–1.7)** *n* = 250	**1.7 (1.0–3.0)** *n* = 250	**1.6 (1.1–2.3)** *n* = 250	NA	NA	NA
Diabetes but no metabolic syndrome	0.9 (0.5–1.9) *n* = 28	0.6 (0.1–4.7) *n* = 28	0.3 (0.0–2.4) *n* = 28	1.2 (0.7–2.0) *n* = 43	1.3 (0.4–4.0) *n* = 43	1.3 (0.6–2.9) *n* = 43
Diabetes plus metabolic syndrome	**2.1 (1.5–3.1)** **n = 66**	**3.3 (1.6–6.9)** **n = 66**	**2.8 (1.6–4.8)** **n = 66**	**2.0 (1.3–2.9)** **n = 51**	**2.6 (1.2–5.7)** **n = 51**	**2.0 (1.1–3.8)** **n = 51**

Data are hazard ratios (95% CI), and significant hazards ratios are bolded. *All models are adjusted for age and smoking. Diabetes is physician diagnosed; measured glucose or insulin are not available. Obesity is defined by *1*) waist circumference >88 cm (NCEP) or by *2*) either waist-to-hip ratio >0.85 or BMI >30 kg/m² (WHO). Hypertension is defined by measured blood pressure ≥130/85 (NCEP) or ≥140/90 mmHg (WHO). Elevated triglycerides are defined by triglycerides ≥150 mg/dl (NCEP and WHO), and low HDL cholesterol is defined by HDL <50 mg/dl (NCEP) and <39 mg/dl (WHO) (see refs. 17 and 19). †Diabetes models are adjusted for age, smoking, hypertension, and obesity by respective criteria. ‡Obesity models are adjusted for age, smoking, diabetes, and hypertension by respective criteria. §Hypertension models are adjusted for age, smoking, diabetes, and obesity by respective criteria. ‖The NCEP metabolic syndrome is defined by any three of the following defined parameters: diabetes, obesity, hypertension, elevated triglycerides, or low HDL; the WHO metabolic syndrome is defined as diabetes plus any two of the following defined parameters: obesity, hypertension, or abnormal lipids (triglycerides or HDL); the two definitions are not mutually exclusive (see refs. 17 and 19). ¶The prevalence of metabolic syndrome with NCEP increased from 4 to 31% by including abnormal lipid measures as one of three positive criteria for the metabolic syndrome and from 3 to 5% for WHO-defined metabolic syndrome (which requires a glucose abnormality).

entire cohort (and about half of those with diabetes) had the metabolic syndrome (317 by the NCEP criteria, 261 by the WHO criteria, and 218 by both). Women with the metabolic syndrome, by either definition, had nearly a twofold increase in total, CHD, and CVD mortality: 61% of the women who met the NCEP criteria and 65% who met the WHO criteria died during follow-up, compared with only 34% without the metabolic syndrome by either criteria set.

After adjustment for age and smoking, total mortality increased almost threefold in women with either syndrome definition (Table 1). The associations of the metabolic syndrome with mortality were even stronger for CVD and CHD deaths. To examine the impact of the three available metabolic syndrome components, we did individual models, ad-

justing for age, smoking, and presence of the other two measured components (e.g., a diabetes model adjusted for age and smoking, as well as hypertension or obesity by respective metabolic syndrome criteria; Table 1). Diabetes and hypertension were independent predictors of both total and CVD mortality. However, only NCEP-defined central obesity (which does not include BMI) was an independent predictor of CHD mortality (Table 1). Importantly, the association of the metabolic syndrome with total mortality was stronger than any of its individual components, including diabetes (Table 1).

Metabolic syndrome defined with lipid levels
In general, the associations with mortality were attenuated in the lipid subsample compared with the same definition in the

entire cohort (Table 1). When the NCEP and WHO definitions were expanded to include counting abnormal HDL cholesterol and triglyceride levels as one of the three necessary criteria for the metabolic syndrome, the associations between the syndrome and mortality did not strengthen and, if anything, were attenuated (Table 1).

Among the lipid subsample, we also compared those without either the metabolic syndrome or diabetes to those with: *1*) only metabolic syndrome, *2*) only diabetes, or *3*) both. Presence of the metabolic syndrome significantly increased the risk of mortality in persons with and without diabetes (Table 1).

CONCLUSIONS — Among older women with diabetes, we found that the metabolic syndrome (diabetes, obesity,

and hypertension) increased the hazard of overall and cause-specific CHD/CVD mortality two- to threefold and was greater than the associated risk of any of the individual components, including diabetes. Including HDL and triglyceride levels in the definition did not strengthen the associations between the metabolic syndrome and mortality in women with diabetes.

To our knowledge, this is the first prospective cohort study to assess the impact of the metabolic syndrome and associated mortality in older women. Several prior studies included younger women in their sample (4–10,22); only a few evaluated sex-specific risks (7,10). In our cohort, followed for a mean of >12 years, 3,427 participants died (nearly one-third of the cohort), including 1,213 from CVD, allowing cause-specific analyses with alternative definitions.

Our findings raise the question of whether all components of the syndrome should be weighted equally in assessing mortality risk. They also support growing clinical and public health emphasis on identifying and treating the metabolic syndrome, particularly in older women.

References

1. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002
2. Brewer HB Jr: Rising to the challenge of the new NCEP ATP III guidelines: exceeding current therapeutic limitations. *Am J Manag Care* 8:S23–S28, 2002
3. Gorman C: Why so many of us are getting diabetes. *Time* 162:59–69, 2003
4. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
5. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
6. Ford ES: The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis* 173:307–312, 2004
7. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP: National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation* 110:1251–1257, 2004
8. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 110:1245–1250, 2004
9. Girman CJ, Rhodes T, Mercuri M, Pyorala K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M: The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol* 93:136–141, 2004
10. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K: Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 164:1066–1076, 2004
11. Anderson RN, Smith BL: Deaths: leading causes for 2001. *Natl Vital Stat Rep* 52:1–85, 2003
12. Hillier TA, Pedula KL: Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. *Diabetes Care* 26:2999–3005, 2003
13. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM: Risk factors for hip fracture in white women: study of Osteoporotic Fractures Research Group. *N Engl J Med* 332:767–773, 1995
14. Lohman TG, Roche AF, Mortorell R: *Anthropometric Standardization Reference Manual.* Champaign, IL, Human Kinetics Books, 1988, p. 177
15. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470–475, 1974
16. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 19:476–482, 1973
17. Warnick GR, Albers JJ: A comprehensive evaluation of the heparin manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res* 29:65–76, 1987
18. World Health Organization: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. In *Report of a WHO Consultation.* Geneva, World Health Organization, 1999
19. Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults: 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
20. Balkau B, Charles MA: Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 16:442–443, 1999
21. American Heart Association: 2002 Heart and Stroke Statistical Update, [article online], 2003. Available from http://www.americanheart.org/statistics/biostats/biowo.htm. Accessed 21 February 2005
22. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. *Diabetes Care* 27:2689–2694, 2004