Is Waist Circumference an Essential Component of the Metabolic Syndrome?

Carlos Lorenzo, MD[1]
Manuel Serrano-Ríos, MD[2]
María T. Martínez-Larrad, PHD[2]
Clicerio González-Villalpando, MD[3]
José L. González-Sánchez, PHD[2]
María J. Martínez-Calatrava, PHD[2]
Rafael Gabriel, MD[4]
Steven M. Haffner, MD[1]

The role of obesity for the metabolic syndrome definition is controversial (1,2) even though obesity is strongly related to insulin resistance (fasting insulin levels) (3), chronic inflammation (high-sensitivity C-reactive protein [hsCRP] levels) (4), and coronary heart disease (CHD) (5). Obesity is considered an essential criterion by the International Diabetes Federation definition (1). However, the National Cholesterol Education Program-Adult Treatment Panel III definition accepts any three of five criteria (2). If obesity were essential, significant insulin and hsCRP levels and CHD risk would not be present in lean subjects. We examined this hypothesis in populations from Mexico City and Spain because of their distinct risk factor profile (more cases of type 2 diabetes, low HDL cholesterol, and hypertriglyceridemia in Mexico City vs. more cases of hypertension and hypercholesterolemia in Spain) (6).

RESEARCH DESIGN AND METHODS

The Mexico City Diabetes Study (7,8) from Mexico City and the Spanish Insulin Resistance Study (6) and Segovia Study (9) from Spain were designed as population-based studies. The two studies from Spain were fused in a single dataset because protocols and one of the principal investigators (M.S.-R.) were the same for both studies.

Nondiabetic subjects were considered eligible for analysis (in Spain, n = 1,311; in Mexico City, n = 1,918) because of the absence of a reliable surrogate of insulin resistance for diabetic subjects. Framingham risk equations were used to estimate CHD risk (10) for two reasons: *1*) absence of prospective data in Spain and *2*) small number of both cardiovascular events and lean subjects with multiple metabolic disorders in Mexico City. Specific insulin was measured by radioimmunoassay in Mexico City (interassay coefficient of variation [CV] 3–7%) (Linco Research, St. Louis, MO) (7) and by immunoassay in Spain (9.1–11.4%) (Linco Research); hsCRP was measured by immunoassay in Mexico City (8.9%) (Calbiochem, Darmstadt, Germany) (8) and in Spain (3.3%) (Beckman Coulter, Fullerton, CA).

Components of the metabolic syndrome were defined according to the International Diabetes Federation criteria (1): hypertriglyceridemia (≥1.7 mmol/l), low HDL cholesterol level (<1.0 mmol/l in men and <1.3 mmol/l in women), high blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or pharmacological treatment), fasting hyperglycemia (≥5.6 mmol/l), and elevated waist circumference (≥94 cm in men and ≥80 cm in women).

We used one-way ANCOVA to analyze insulin and hsCRP levels and Framingham risk estimates to account for the effect of age and sex. We performed analyses on the log-transformed values of insulin and hsCRP levels and on the logit transformation of Framingham risk estimates to correct for skewness and kurtosis. These variables were then back-transformed to their natural units for presentation.

RESULTS

In Spain and Mexico City, 26.3 and 55.2% of subjects had three or more metabolic disorders, respectively. Normal waist circumference was present in 5.2% of Spanish subjects with three or more metabolic disorders and in 4.8% of Mexican counterparts.

Among subjects with one or more metabolic disorders, elevated waist circumference was directly related to the number of disorders (Table 1). Insulin and hsCRP levels and CHD risk estimates were not increased in subjects with elevated waist circumference after adjusting for number of metabolic components, except for insulin levels in Mexico City.

Among subjects with three or more metabolic disorders, age- and sex-adjusted estimates of CHD risk were not increased in subjects with elevated waist circumference (yes vs. no) (Spain: 14.5 [13.8–15.3] vs. 14.9% [11.6–19.1], P = 0.836; Mexico City: 7.4 [7.1–7.6] vs. 9.7% [8.4–11.2], $P < 0.001$), and neither were hsCRP levels (Spain: 1.86 ± 0.11 vs. 1.72 ± 0.47 mg/l, P = 0.734; Mexico City: 1.73 ± 0.05 vs. 1.60 ± 0.22 mg/l, P = 0.546). Insulin levels were not increased in subjects with elevated waist circumference (yes vs. no) in Spain (13.5 ± 0.4 vs. 11.1 ± 1.5 μIU/ml, P = 0.171) but were increased in Mexico City (15.3 ± 0.3 vs. 12.5 ± 0.9 μIU/ml, P = 0.004).

CONCLUSIONS

In the U.S. population, 4.6% of men and 6.2% of women with normal weight have three or more metabolic disorders (11). Normal-weight individuals may have insulin resistance. Insulin-resistant, normal-weight individuals have more cardiovascular disease risk factors (12,13), greater CHD and diabetes risks (14–16), and more total and intra-

From the [1]Department of Medicine, University of Texas Health Science Center, San Antonio, Texas; the [2]Department of Medicine, University Hospital San Carlos, Red de Centros de Metabolismo y Nutrición (RCMN) (C03/08), Madrid, Spain; the [3]Center of Studies in Diabetes, Research Center in Public Health, National Institute of Public Health, Mexican Institute of Social Security, American British Cowdray Medical Center, Mexico City, Mexico; and the [4]Research Unit-Clinical Epidemiology, University Hospital La Paz, Red RECAVA, Madrid, Spain.

Address correspondence and reprint requests to Carlos Lorenzo, MD, Department of Medicine, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78284-7873. E-mail: lorenzo@uthscsa.edu.

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Abbreviations: CHD, coronary heart disease; hsCRP, high-sensitivity C-reactive protein.

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

Table 1—*Number of metabolic disorders, insulin and hsCRP levels, and CHD risk estimates stratified by waist circumference category in nondiabetic subjects with one or more metabolic disorders*

	Elevated waist circumference	Normal waist circumference	*P*
Spain			
n	956	187	—
No. of metabolic disorders*	2.21 ± 0.03	1.42 ± 0.07	<0.001
Fasting insulin level (μIU/ml)*	11.2 ± 0.2	9.5 ± 0.5	0.001
Fasting insulin level (μIU/ml)†	11.0 ± 0.2	10.5 ± 0.5	0.335
hsCRP level (mg/l)*	1.60 ± 0.05	1.46 ± 0.12	0.324
hsCRP level (mg/l)†	1.57 ± 0.05	1.58 ± 0.13	0.923
CHD risk estimate over 10 years (%)*	10.5 (10.2–10.9)	10.2 (9.3–11.1)	0.425
CHD risk estimate over 10 years (%)†	10.2 (9.8–10.5)	12.5 (11.5–13.2)	<0.001
Mexico City			
n	1,455	429	—
No. of metabolic disorders*	2.83 ± 0.02	1.56 ± 0.06	<0.001
Fasting insulin level (μIU/ml)*	14.3 ± 0.1	9.4 ± 0.3	<0.001
Fasting insulin level (μIU/ml)†	13.5 ± 0.1	11.4 ± 0.3	<0.001
hsCRP level (mg/l)*	1.62 ± 0.05	1.35 ± 0.07	0.006
hsCRP level (mg/l)†	1.57 ± 0.05	1.46 ± 0.09	0.349
CHD risk estimate over 10 years (%)*	6.1 (5.8–6.3)	5.6 (5.3–5.9)	0.027
CHD risk estimate over 10 years (%)†	5.5 (5.4–5.6)	7.8 (7.4–8.2)	<0.001

Data are means ± SD or median (range) unless otherwise indicated. *Results adjusted for age and sex. †Results adjusted for age, sex, and number of components of the metabolic syndrome.

abdominal fat than insulin-sensitive, normal-weight individuals (14). Similarly, absence of central obesity, as assessed by waist circumference, cannot rule out the presence of multiple metabolic disorders (17). Our results indicate that significant insulin and hsCRP levels and CHD risk estimates may be present in subjects with metabolic disorders other than obesity.

There is much support in the literature for the concept that waist circumference is not an independent predictor of CVD and that risk increases with number of components (18,19). The component most strongly associated with insulin resistance is obesity, but clustering of metabolic disorders greatly exceeds chance association in both obese and lean individuals (3). The cross-sectional design of this study limits our ability to reach conclusions. Nevertheless, our results suggest that the metabolic syndrome is not found exclusively in obese individuals.

References

1. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
2. Grundy SM, Cleeman JI, Daniels SR, et al.: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–2752, 2005
3. Schmidt MI, Watson RL, Duncan BB, et al.: Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. *Metabolism* 45:699–706, 1996
4. Kahn SE, Zinman B, Haffner SM, et al.: Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. *Diabetes* 55:2357–2364, 2006
5. Yusuf S, Hawken S, Ounpuu S, et al.: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 366: 1640–1649, 2005
6. Lorenzo C, Serrano-Ríos M, Martínez-Larrad MT, et al.: Geographic variations of the International Federation of Diabetes and the National Cholesterol Education Program-Adult Treatment Panel III definitions of the metabolic syndrome in nondiabetic subjects. *Diabetes Care* 29:685–691, 2006
7. Haffner SM, Gonzalez C, Mykkänen L, Stern M: Total immunoreactive proinsulin, immunoreactive insulin and specific insulin in relation to conversion to NIDDM: the Mexico City Diabetes Study. *Diabetologia* 40:830–837, 1997
8. Han TS, Sattar N, Williams K, et al.: Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 25:2016–2021, 2002
9. Martinez-Larrad MT, Fernandez-Perez C, Gonzalez-Sanchez JL, et al.: Prevalence of the metabolic syndrome (ATP-III criteria): population-based study of rural and urban areas in the Spanish province of Segovia. *Med Clin* (*Barc*) 125:481–486, 2005
10. Wilson PWF, D'Agostino RB, Levy D, et al.: Prediction of coronary heart disease using risk factor categories. *Circulation* 97: 1837–1847, 1998
11. Park YW, Zhu S, Palaniappan L, et al.: The metabolic syndrome: prevalence and associated risk factor findings in the U.S. population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 163: 427–436, 2003
12. Hollenbeck C, Reaven GM: Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *J Clin Endocrinol Metab* 64: 1169–1173, 1987
13. Zavaroni I, Bonora E, Pagliara M, et al.: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 320:702–706, 1989
14. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S: The metabolically obese, normal-weight individual revisited. *Diabetes* 47:699–713, 1998
15. St-Pierre AC, Cantin B, Mauriège P, et al.: Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ* 172:1301–1305, 2005
16. Meigs JB, Wilson PW, Fox CS, et al.: Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab* 91:2906–2912, 2006
17. Katzmarzyk PT, Janssen I, Ross R, et al.: The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. *Diabetes Care* 29:404–409, 2006
18. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210–1214, 2003
19. Girman CJ, Dekker JM, Rhodes T, et al.: An exploratory analysis of criteria for the metabolic syndrome and its prediction of long-term cardiovascular outcomes: the Hoorn study. *Am J Epidemiol* 162:438–447, 2005