Leptin Predicts Diabetes but Not Cardiovascular Disease

Results from a large prospective study in an elderly population

OBJECTIVE — To clarify the association of circulating levels of leptin with risk for cardiovascular disease (CVD) events and new-onset diabetes in men and women.

RESEARCH DESIGN AND METHODS — We related baseline leptin levels to CVD events (n = 864) and incident diabetes (n = 289) in an elderly population (n = 5,672) over 3.2 years of follow-up.

RESULTS — In treatment-, age-, and country-adjusted models, leptin was not associated with risk of CVD in men (hazard ratio 1.02 [95% CI 0.90–1.16]) per unit log-leptin increase) or women (1.05 [0.91–1.20]) but was associated with risk of diabetes in men (2.75 [2.14–3.52]) and women (1.54 [1.22–1.94]). After adjusting for classic risk factors and BMI, C-reactive protein, and glucose, the diabetes association retained significance in men (1.85 [1.30–2.63]) but not in women (0.89 [0.64–1.26]).

CONCLUSIONS — Leptin, similar to other markers of adiposity in general, is more strongly related to risk of diabetes than CVD in the elderly.
and those with missing values). The baseline characteristics of the population have been reported (14). Leptin levels were leptin in this study was BMI (12.4 ± 2.43 vs. 13.5 ± 2.43 ng/ml, \( P = 0.0095 \)). The strongest correlate of leptin in this study was BMI (\( r = 0.59 \), \( P < 0.0001 \)).

Leptin showed no association with CVD risk in minimally adjusted models or in other multivariable analyses in men or women (Table 1). This was also true when examining associations separately with CHD and stroke. The findings were similar in those with first-time versus secondary CVD events in either sex (data not shown).

For diabetes, risk associations were significant in both men and women after adjusting for basic confounders (model A). Stepwise adjustment for additional confounders (model B) and BMI (model C) revealed that BMI mediated a significant proportion of the risk association in women. The association of leptin with diabetes risk was not significant in women in model C but persisted in men, even after adjusting for both BMI and glucose (model D). Leptin had a greater association with diabetes in men than in women; the 95% CIs do not overlap in any model. In all models, there was no significant interaction by treatment allocation, although this variable was adjusted for in any case.

**CONCLUSIONS** — Recent findings (7,10) reported no association of leptin with CHD risk in women. Investigators suggested a need to confirm these findings in both sexes in larger studies (10). Our study does this in the largest study of leptin and CVD risk associations to date. PROSPER findings contrast with those of the West of Scotland Coronary Prevention (WOSCOP) study, although the association reported in that study was modest (univariable relative risk 1.25 per SD increase) (4). We suggest that leptin is not likely to be an important risk marker for CVD events.

In agreement with other reports (11–13), we report that leptin is a risk marker of diabetes, but the association is significantly stronger in men. The sex difference in terms of leptin’s diabetes risk associations is not well understood but, speculatively, may reflect differing distributions of adipose tissue in men versus women. Women have more total and subcutaneous fat (a major producer of leptin) and, accordingly, higher leptin levels. Men have a greater percentage of visceral fat mass and are at greater risk of diabetes than women per unit of circulating leptin increase. Adjustment models not including insulin resistance leave residual associations with risk for diabetes in men (13) but not in women. However, in etiological terms, adjusting leptin’s association with diabetes risk for insulin resistance may be an over-adjustment.

Strengths and limitations of the study have been considered (14). The study stems from a statin trial (14), but we observed no interaction by treatment for leptin’s associations with end points of interest, and all analyses were adjusted for treatment allocation. The participants were elderly, but associations with end points were broadly similar to those observed (separately for CVD and diabetes) in younger populations (10,12). Thus, our results have external validity. The present study, however, cannot establish whether hyperleptinemia per se or leptin resistance explains the reported association between circulating leptin and incident diabetes.

In summary, circulating leptin levels are unlikely to be a unifying link between obesity, CVD, and diabetes risk. Leptin, like other markers of adiposity (BMI and waist circumference) in middle-aged and elderly populations (14), is more strongly related to risk of diabetes than CVD in the elderly.

**Acknowledgments** — Funding for leptin assays was provided by the Stroke Association.

No potential conflicts of interest relevant to this article were reported.

We thank Anne Kelly for performance of the leptin assays.

**References**

1. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R,
Leptin, diabetes, and CVD risk associations

Ranganathan S, Kern PA, Friedman JM: Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1:1155–1161, 1995

2. Beltowski J: Leptin and atherosclerosis. *Atherosclerosis* 189:47–60, 2006

3. Steinberg GR, Parolin ML, Heigenhauser GJ, Dyck DJ: Leptin increases FA oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. *Am J Physiol Endocrinol Metab* 283:E187–E192, 2002

4. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N: Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation* 104:3052–3056, 2001

5. Wallerstedt SM, Eriksson AL, Niklason A, Ohlsson C, Hedner T: Serum leptin and myocardial infarction in hypertension. *Blood Press* 13:243–246, 2004

6. Wolk R, Berger P, Lennon RJ, Brilakis ES, Johnson BD, Somers VK: Plasma leptin and prognosis in patients with established coronary atherosclerosis. *J Am Coll Cardiol* 44:1819–1824, 2004

7. Brennan AM, Li TY, Kelesidis I, Gavrilas A, Hu FB, Mantzoros CS: Circulating leptin levels are not associated with cardiovascular morbidity and mortality in women with diabetes: a prospective cohort study. *Diabetologia* 50:1178–1185, 2007

8. Couillard C, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ, Despres JP: Leptinemia is not a risk factor for ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Diabetes Care* 21: 782–786, 1998

9. Thogersen AM, Soderberg S, Jansson JH, Dahlén G, Boman K, Nilsson TK, Lindahl B, Weinehall L, Lundberg V, Johnson O, Ahren B, Hallmans G: Interactions between fibrinolysis, lipoproteins and leptin related to a first myocardial infarction. *Eur J Cardiovasc Prev Rehabil* 11: 33–40, 2004

10. Lawlor DA, Smith GD, Kelly A, Sattar N, Ebrahim S: Leptin and coronary heart disease risk: prospective case control study of British women. *Obesity (Silver Spring)* 15:1694–1701, 2007

11. McNeely MJ, Boyko EJ, Weigle DS, Schofer JB, Chessler SD, Leonetti DL, Fujimoto WY: Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. *Diabetes Care* 22:65–70, 1999

12. Soderberg S, Zimmet P, Tuomilehto J, Chitsion P, Gareeboo H, Alberti KG, Shaw JE: Leptin predicts the development of diabetes in Mauritian men, but not women: a population-based study. *Int J Obes (Lond)* 31:1126–1133, 2007

13. Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N: Adipokines and risk of type 2 diabetes in older men. *Diabetes Care* 30:1200–1205, 2007

14. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, Ford I, Forouhi NG, Freeman DJ, Jukema JW, Lennon L, Macfarlane PW, Murphy MB, Packard CJ, Stott DJ, Westendorp RG, Whincup PH, Shepherd J, Wannamethee SG: Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. *Lancet* 371:1927–1935, 2008