Leptin Predicts Diabetes but Not Cardiovascular Disease

Results from a large prospective study in an elderly population

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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.

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Leptin is a pleiotropic adipokine, and circulating levels correlate with markers of body fat mass (1). Obesity is a known risk factor for the development of both cardiovascular disease (CVD) and type 2 diabetes, and leptin is a candidate mediator of these increased risks. Hyperleptinemia may promote atherosclerosis (2), and dysregulation of leptin signaling in obese individuals results in reduced fatty acid oxidation and glucose uptake (3).

There is evidence for (4–6) and against (7–10) leptin being a prospective risk marker for CVD, whereas there is evidence that leptin predicts diabetes risk independently of other confounders only in men (11–13). We aimed to clarify these risk associations by simultaneous comparison of end points in both sexes individually in a single study.

RESEARCH DESIGN AND METHODS

— Methods of the PROspective Study of Pravastatin in the Elderly at Risk trial (PROSPER) as an ancillary risk association study have been reported (14). Between 1997 and 1999, 5,804 men and women aged 70–82 years were recruited from Scotland, Ireland, or the Netherlands if they had either preexisting vascular disease (coronary, cerebral, or peripheral) or increased risk of such disease because of risk factors. The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent. The primary outcome was definite or suspect death from coronary heart disease (CHD), nonfatal myocardial infarction, or fatal or nonfatal stroke. New-onset diabetes was classified as detailed (14) excluding those with known ($n = 606$) and undiagnosed diabetes ($n = 134$) based on baseline glucose measurements (>95% fasting). CVD events were validated by a committee blinded to the end points.

Fasting morning baseline leptin was measured by an in-house radioimmunoassay validated thoroughly against the commercially available Linco assay. The intra- and interassay coefficients of variation (CVs) were <7% and <10%, respectively. The detection limit of the assay was 0.5 ng/ml. Samples were processed with investigators blinded to the identity of samples.

The distribution of leptin was positively skewed, and a logarithmic transformation was used. Relationships between log-leptin and BMI were assessed using Pearson's correlation coefficient. The influence of leptin on the end points of interest was investigated in each sex using Cox proportional hazards models (using sex-specific standard deviations), adjusting for randomized treatment, age, country, and other risk factors (LDL and HDL cholesterol, triglycerides, blood pressure, smoking, BMI, antihypertensive medications, history of vascular disease, C-reactive protein, and glucose) in models described. Results are reported as hazard ratio (95% CI) for 1-unit increases in log-leptin and corresponding *P* value.

RESULTS

— Plasma leptin levels were available in 5,672 patients. During 3.2 years of follow-up, 864 had a primary CVD end point and 289 were newly diagnosed with diabetes (from 4,934 participants excluding baseline diabetic subjects

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Table 1—*Adjusted hazard ratios, 95% CIs, and P values for association between log-leptin, new-onset diabetes, and various cardiovascular outcomes*

	Men			Women		
	N (*n*)	HR (95% CI)	*P*	*N* (*n*)	HR (95% CI)	*P*
All CVD events*						
Model A	2,738 (493)	1.02 (0.90–1.16)	0.74	2,934 (371)	1.05 (0.91–1.20)	0.52
Model B	2,736 (493)	0.92 (0.77–1.09)	0.34	2,931 (370)	0.94 (0.77–1.15)	0.56
CHD events*						
Model A	2,738 (382)	1.06 (0.92–1.23)	0.40	2,934 (254)	1.10 (0.94–1.31)	0.21
Model B	2,736 (382)	0.93 (0.77–1.14)	0.49	2,931 (254)	0.97 (0.77–1.23)	0.81
Stroke events*						
Model A	2,738 (131)	0.86 (0.67–1.10)	0.23	2,934 (130)	0.88 (0.70–1.09)	0.24
Model B	2,736 (131)	0.81 (0.57–1.14)	0.22	2,931 (129)	0.82 (0.59–1.14)	0.24
New-onset diabetes†						
Model A	2,319 (143)	2.75 (2.14–3.52)	<0.0001	2,615 (146)	1.54 (1.22–1.94)	0.0003
Model B	2,317 (143)	2.54 (1.92–3.35)	<0.0001	2,605 (144)	1.30 (1.00–1.70)	0.05
Model C	2,317 (143)	2.17 (1.57–2.99)	<0.0001	2,613 (146)	0.80 (0.57–1.10)	0.80
Model D	2,305 (141)	1.85 (1.30–2.63)	<0.0006	2,605 (144)	0.89 (0.64–1.26)	0.89

Estimated hazard ratios (HRs) correspond to an increase of 1 unit in log-leptin. *Cardiovascular end points: model A, adjusted for treatment, age, and country; model B, additionally adjusted for LDL and HDL cholesterol, triglycerides, systolic and diastolic blood pressure, smoking, use of antihypertensive medicines, history of CVD, C-reactive protein, and BMI. †Diabetes end points: model A, adjusted for treatment, age, and country; model B, additionally adjusted for LDL and HDL cholesterol, triglycerides, systolic and diastolic blood pressure, smoking, use of antihypertensive medicines, history of CVD, and C-reactive protein; model C, additionally adjusted for BMI; and model D, additionally adjusted for glucose. HR, hazard ratio.

and those with missing values). The baseline characteristics of the population have been reported (14). Leptin levels were slightly lower among those experiencing a primary vascular end point (mean ± SD 12.4 ± 2.43 ng/ml 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.

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