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Leptin in Patients with Type 2 Diabetes

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Leptin is a hormone that is secreted by adipose tissue that regulates metabolism and reduces appetite. Serum levels of leptin in humans are log-linearly related to obesity and lack of leptin in humans induces severe obesity, demonstrating that leptin signalling is necessary for normal feedback control of body weight [1,2]. The positive log-linear relationship with body weight also implies that the appetite suppressing effects of leptin are reduced in obesity. In non-diabetic subjects as well as in pre-diabetes serum leptin levels have been linked with increased risk for cardiovascular disease and also with several risk factors for such incidents [1,3,4]. In the study "Serum leptin levels are independently related to the incidence of ischemic heart disease in a prospective study of patients with type 2 diabetes" by Camilla Vavruch et al. we aimed to identify new and clinically useful markers of risk related to cardiovascular disease in patients with type 2 diabetes [5]. We used baseline characteristics from 476 men and 244 women with type 2 diabetes in a dedicated cohort (Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care study, acronym CARDIPP). The patients were 55-66 years old at recruitment and the follow-up period was 6 years, during which 47 men and 10 women died or were hospitalized for ischemic heart disease. We found that levels of serum leptin were positively related to the hazard ratio of ischemic heart disease in both men and women, and that this relationship was independent of age, HbA1c, BMI, systolic blood pressure, smoking, known duration of diabetes, and LDL/HDL-cholesterol ratio. Leptin levels were also found to be positively correlated with the inflammatory marker CRP. In men, leptin levels also provided information about risk that was independent of yet another two particularly strong non-invasive markers of cardiovascular disease; carotid intima-media thickness and carotid-femoral pulse-wave velocity (see Figure 1). However, we could not show these independent relationships in women which likely was an effect of lower statistical power since this sample was smaller and since there were numerically fewer cardiovascular incidents in women. Indeed, similar trends for the risks were seen in women as in the men.

Thus, we found that information about serum leptin levels gave additional information of the risk to develop ischemic heart disease complications independently of the degree of adiposity i.e. BMI. We believe this to be in line with the idea that "leptin resistance", meaning insensitivity to feedback-signalling of adipose stores to the CNS, is linked with an increased risk for ischemic heart disease. We did not, however, include an intervention aimed to affect leptin levels, thus our study does not provide definite proof of causality of leptin or leptin-resistance. In a previous study by Brennan et al. leptin levels were not related to cardiovascular disease in women with an average age of 58 years [6]. However, we theorize that less efficient treatment to reduce risk for complications in diabetes might have obscured specific actions of leptin in that study, as it was carried out in the 1990's and LDL-cholesterol levels were higher in the study by Brennan et al. than in our trial [6].

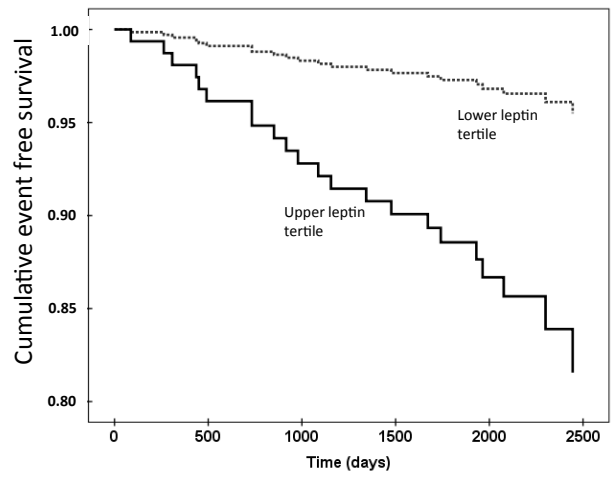

Figure 1: Serum levels of leptin in relation to ischemic heart disease incidents in men with type 2 diabetes.

Strengths in our study include use of registry data with high quality and no patients were lost to follow-up. The rather short follow-up time and consequently low rates of mortality and morbidity are weaknesses. However, the short follow-up time also improves clinical relevance since the patients were indeed being cared for in a manner that is in accordance with current standards. It is possible that our findings were indeed made possible by the good controls of glycaemia, blood pressure and cholesterol, as this might have increased the chance to detect the risk specifically related to levels of leptin that might act through other mechanisms than traditional risk factors. Indeed, our findings support the use of serum leptin for estimation of risk for ischemic heart disease since it was independent of major traditional risk factors. Our findings support further assessment in larger cohorts of the role of measuring leptin levels as a predictive marker of ischemic heart disease in the care of patients with type 2 diabetes.

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