Trends in obesity and type 2 diabetes; ethnic aspects and links to adipokines

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i sal 933, Tandläkarhögskolan, NUS fredagen den 9 december, kl. 10:00. Avhandlingen kommer att förvaras på svenska.

Objective
The prevalence of obesity and related diseases such as type 2 diabetes mellitus (T2DM) is increasing worldwide, and the Asian Indian population seems to be particularly susceptible to developing T2DM, even at a low body mass index (BMI). In Sweden, the age-adjusted prevalence of diabetes has not increased despite increasing self-reported obesity. However, modern data on the prevalence of obesity and T2DM in Scandinavia are absent. The biochemical links between obesity and subsequent T2DM are unknown, but the adipocyte-derived hormones leptin and adiponectin (adipokines) have been suggested as potential links because they both are related to insulin and glucose physiology. Some studies have found leptin to be an independent predictor of T2DM in men but not in women, although these results are inconsistent. In contrast, adiponectin has more consistently been linked to development of T2DM in both men and women. Furthermore, the leptin–adiponectin ratio may predict incident T2DM better than either of the two hormones separately.

The aims of this thesis were to describe time trends in obesity and T2DM in northern Sweden, to evaluate leptin and adiponectin as predictors of deterioration in glucose metabolism including T2DM, and to evaluate leptin as a risk marker regarding ethnic differences, circ-annual variation, and intra-individual stability.

Materials and methods
Three large population surveys were used, the Northern Sweden MONICA (MONitoring of Trends and Determinants in CArdiovascular Disease) study, the Västerbotten Intervention Programme (VIP), and the Mauritius Non-Communicable Disease Study. Within the MONICA study, six cross-sectional surveys were performed in Sweden’s two northernmost counties, Norrbotten and Västerbotten, between 1986 and 2009. A total of 1000 men and 1000 women ages 25–64 years, also including from 1994 250 men and 250 women ages 65–74 years, were independently chosen for each survey. The overall participation rate was 75%. In 1999, a reinvestigation was performed in 74% of all participants from the three first surveys. Data from the MONICA surveys were used in papers I and IV and data from the reinvestigation survey in paper II.

VIP is an ongoing population intervention program that started in the mid-eighties targeting cardiovascular risk factors and has covered the whole county of Västerbotten since 1991. Inhabitants are invited the years they turn 40, 50, and 60 years old, and the annual participation rate has varied between 48% and 67%. A subset (n=1780) from VIP was used in paper II for the circ-annual leptin analysis, and VIP data linked to the diabetes register in Västerbotten (DiabNorr) were used in a case referent study (640 patients with T2DM) in paper III.

The Mauritius Non-Communicable Disease Study was performed in 1987 in 10 randomly selected (with probability proportional to size) population clusters. All eligible adults ages 25–74 years were invited, and the participation rate was 86% (n=5083). In 1992, a follow-up survey was performed in 49% of the initial participants. The Mauritius survey data were used in paper II.

Results
I. BMI increased in men ages 25–74 years and in women ages 25–44 years in northern Sweden between 1986 and 2004. The prevalence of obesity (BMI ≥30) increased in men ages 25–44 and 55–74 years and in women ages 25–44 years. The prevalence of obesity increased from 10.4% to 19.1% in men and from 12.9% to 17.9% in women ages 25–64 years. Waist circumference (WC) decreased in women of all ages and in men ages 55–64 years between 1986 and
1990. After 1990, WC increased again, and the prevalence of abdominal obesity rose markedly in women ages 25–64 years.

II. Differences in circulating levels of leptin, leptin per BMI unit (leptin/BMI), and leptin per cm in WC (leptin/waist) were tested in men and women of Asian Indian, Creole (African), and Caucasian ethnicity. Asian Indian men and women had the highest leptin concentrations and Caucasian men and women the lowest while Creole men and women had intermediate values for leptin, leptin/BMI, and leptin/waist. No circ-annual variation in leptin concentrations was seen in Caucasians. The intra-individual test–retest stability for leptin was equal in men and women of different ethnicities, over 5–13 years, with an intra-class correlation of 0.65–0.82.

III. High adiponectin concentrations predicted decreased risk of T2DM in both insulin-sensitive and insulin-resistant men and women, whereas high leptin levels predicted increased risk for T2DM only in insulin-sensitive men. A high leptin–adiponectin ratio predicted T2DM in both men and women, and men with a high ratio had a shorter time to diagnosis than those with a low ratio.

IV. In northern Sweden, fasting and post-load glucose increased in women ages 24–65 years with 0.2 mmol/l and 0.7 mmol/l, respectively, between 1990 and 2009. Consequently, the prevalence of impaired fasting glucose and impaired glucose tolerance (IGT) rose from 4.5% to 7.7%, and from 7.8% to 14.5%, respectively. In men, post-load glucose increased at 0.5 mmol/l, and the prevalence of IGT rose from 3.5% to 10.1%. The prevalence of diabetes did not increase. An independent relationship between leptin and changes in fasting and post-load glucose was seen in men but not in women.

Conclusion An increasing obesity and concomitant deterioration in glucose metabolism was seen in northern Sweden in the period studied. High adiponectin concentrations predicted a decreased risk of T2DM in both men and women, whereas high leptin concentrations predicted an increase in fasting and post-load glucose as well as an increased risk of T2DM in men but not in women. Individual insulin resistance status modified the association between leptin and T2DM, and the leptin–adiponectin ratio may add further predictive information beyond the measures of the separate hormones. In relation to traditional anthropometric measures of obesity, Asian Indian men and women had the highest and Caucasians the lowest concentrations of leptin while Creole (African) men and women had intermediate levels. As a risk marker, leptin has a high intra-individual stability, equal in men and women and among different ethnicities over 5–13 years with no circ-annual variation.

Keywords Type 2 diabetes, leptin, adiponectin, obesity, abdominal obesity, epidemiology, ethnicity, fasting glucose, post-load glucose

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