Pathogenesis of Obesity and Effects of Treatment

Clinical and Molecular Studies on Body Fat, Energy Balance, and Weight Loss

UNIVERSITY OF GOTHENBURG

Akademisk avhandling

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av

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Leg. läkare

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Avhandlingen baseras på följande delarbeten:

I **Relations of Adipose Tissue CIDEA Gene Expression to Basal Metabolic Rate, Energy Restriction, and Obesity: Population-Based and Dietary Intervention Studies.**
Gummesson A, Jernås M, Svensson PA, Larsson I, Glad CA, Schéle E, Gripeteg L, Sjöholm K, Lystig TC, Sjöström L, Carlsson B, Fagerberg B, Carlsson LM.
J Clin Endocrinol Metab 2007;92:4759-65.

II **Cell death-inducing DFF45-like effector C is reduced by caloric restriction and regulates adipocyte lipid metabolism.**
Magnusson B, Gummesson A, Glad CA, Goedecke JH, Jernås M, Lystig TC, Carlsson B, Fagerberg B, Carlsson LM, Svensson PA.
Metabolism 2008;57:1307-13.

III **Increased intestinal permeability is associated with visceral and hepatic fat accumulation.**
Gummesson A, Carlsson LM, Storlien L, Bäckhed F, Lundin P, Löfgren L, Stenlöf K, Fagerberg B, Carlsson B.
Submitted for publication.

IV **Effects of Bariatric Surgery on Cancer Incidence in Swedish Obese Males and Females.**
Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonen M, Wedel H, Bengtsson C, Bouchard C, Carlsson B, Dahlgren S, Jacobson P, Karason K, Karlsson J, Larsson B, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Carlsson LM, for the Swedish Obese Subjects Study.
Submitted for publication.

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Abstract

Obesity is common and related to many health problems including various forms of cancer. The condition arises from the imbalance between food intake and energy expenditure, and is strongly influenced by genetic factors. Weight loss has several health benefits, but for many of the obesity-related diseases such as cancer, the impact of obesity treatment is not clarified. Unfortunately, weight loss is in most cases difficult to sustain, and obesity treatment today is insufficient. The adipose tissue and the gastrointestinal tract play active roles in the regulation of whole-body energy balance, and therapeutic targets for the treatment of obesity may be found within these sites. Also, these organs may be responsible for mediating some of the adverse effects of obesity. Special attention has been drawn to visceral adipose tissue, i.e. the fat surrounding the intestines, as being particularly harmful. The aim of this thesis was to increase our understanding of the mechanisms behind human obesity and the consequences of obesity treatment. We used population-based cross-sectional studies, as well as longitudinal intervention studies with short- and long-term weight loss.

CIDEA and CIDEC are two genes with putative functions in adipose tissue, and we therefore studied their transcriptional regulation in relation to energy balance and body composition as an attempt to elucidate their role in human obesity. The genes were predominantly expressed in adipose tissue as compared to other human tissues, both CIDEA and CIDEC gene transcription were highly responsive to changes in energy availability, and CIDEA correlated with body fat and insulin levels. CIDEA expression also correlated with basal metabolic rate and uncoupling protein 1, suggesting a role in the regulation of energy expenditure. In gene silencing experiments in cultured adipocytes, we showed that CIDEC is involved in the regulation of basal as well as stimulated lipolysis, and mitochondrial fatty acid oxidation. Together, our results support a role of CIDEC and CIDEA in human obesity.

There are indications that impaired intestinal barrier with increased passage of gut-derived antigens may drive visceral adipose tissue accumulation, and we therefore investigated if increased intestinal permeability is associated with visceral obesity in humans. Study subjects were recruited from a population-based cohort of Swedish women. Intestinal permeability was assessed using the urinary excretion of orally ingested sucralose and mannitol. We used computed tomography to measure visceral and liver fat. Intestinal permeability of the large intestine correlated with visceral fat area ($P=0.0003$) and liver fat content ($P=0.004$). The results indicate that gut leakiness should be further explored as a possible cause of visceral fat accumulation.

The Swedish Obese Subjects (SOS) study in combination with the Swedish National Cancer Register makes it possible to, for the first time, study the effects of bariatric surgery on cancer incidence in a prospective, controlled study setting. The SOS study started in 1987 and involves severely obese subjects, 2010 of which underwent bariatric surgery, and 2037 contemporaneously matched obese controls who received conventional treatment. Bariatric surgery resulted in a sustained weight reduction, whereas the average weight change in the control group was minimal. In women, the number of first-time cancers during on average 11 years after inclusion was lower in the surgery group compared to the control group (HR= 0.58, 95% CI: 0.44-0.77, $p<0.001$). In men, we could not detect any difference between treatment groups (HR=0.97, $p=0.91$).

In summary, the results of this thesis suggest that the CIDEA and CIDEC genes play a role in obesity, impaired intestinal barrier function contributes to visceral fat accumulation, and bariatric surgery reduces the risk of developing cancer in severely obese women.

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