Preface

The aim of this thesis is to investigate the effects of Roux-en-Y gastric bypass (RYGB) on energy expenditure and appetite and to investigate the roles of GLP-1 and PYY in postoperative alterations. This is explored through two studies. All clinical experiments were carried out at the Department of Nutrition, Exercise and Sports (NEXS), Faculty of Science, University of Copenhagen. The first study was carried out from June 2009 to April 2013, and included patients from Hvidovre University Hospital. The second clinical study was carried out from March 2011 to January 2012.

Both studies, as well as one year of my employment, were predominantly funded by UNIK: Food, Fitness & Pharma for Health and Disease, University of Copenhagen. Additional sponsorships, funding, and collaborators related to the studies are specified in the papers. My employment was further sponsored by the Faculty of Science (one year) and NEXS (one year), University of Copenhagen.

The thesis is based on three scientific papers in preparation for submission.

Paper I: **Effects of RYGB on energy expenditure and appetite: a randomized controlled Study**
Julie Berg Schmidt, Nikolaj Ture Gregersen, Sue D Pedersen, Lone Vestergaard, Mette Søndergaard, Christian Ritz, Dorte Lindqvist Hansen, Dorte Worm, Sten Madsbad, Trine Ryberg Clausen, Arne Astrup, Jens Juul Holst, Anders Sjödin
(Original paper in manuscript)

Paper II: **Effects of PYY_{3-36} and GLP-1, as Mono- and Coinfusions, on Energy intake, Energy Expenditure and Appetite in Overweight Men**
Julie Berg Schmidt, Nikolaj Ture Gregersen, Sue D Pedersen, Johanne L Arentoft, Christian Ritz, Thue W Schwartz, Jens Juul Holst Arne Astrup, Anders Sjödin
(Original paper in manuscript)

Paper III: **Does gastric bypass surgery affect energy expenditure?**
Julie Berg Schmidt, Louise Wulf, Nikolaj Ture Gregersen, Sue D Pedersen, Anders Sjödin
(Review in manuscript)

Summary

Following a weight loss, mechanisms designed to protect body weight are activated, involving both an increase in appetite and a decrease in energy expenditure (EE). Such compensatory responses may predispose individuals to a lesser degree of weight loss and to weight regain. It has been proposed that gastric bypass (GBP) surgery attenuates these processes, explaining the superiority of this weight loss intervention. However, the effect of GBP on EE has never been investigated independently of acute changes in energy balance. After GBP, decreased motivation to eat coincides with hormonal changes, but how these hormones, separately and in combination, explain the substantial effects on appetite, energy intake, and, potentially, EE is poorly understood.

This thesis aimed to examine whether GBP can attenuate the decrease in EE normally associated with negative energy balance, as well as the roles of the hormones and signaling molecules peptide YY (PYY), leptin, fibroblast growth factor 19 (FGF19), and bile acids in these alterations. This was investigated in a clinical study with subjects randomized to either GBP or to a 'pair-fed' control group and was supported by a critical review of the existing literature. In the same study, it was explored how PYY, glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), leptin, and ghrelin contribute to postsurgical alterations in appetite. The possibility of GLP-1 and PYY exerting overlapping, additive, or even synergistic effects on energy intake and appetite was examined in a randomized, double-blinded, placebo-controlled, four-arm crossover study, wherein subjects received either mono- or coinfusion of GLP-1 and PYY.

Findings from the clinical studies do not support the preservation or increase of EE as a plausible explanation for the pronounced weight loss seen acutely after GBP, nor does the existing literature provide evidence for such roles. On the contrary, basal metabolic rate and total EE were suppressed more in GBP patients compared to pair-fed control subjects. This suppressive effect was associated with an additional decrease in leptin. Despite an exaggerated postprandial response of PYY, bile acids, and FGF19, no stimulating effect of GBP was found on meal-induced thermogenesis, nor did single- or coinfusion of GLP-1 and PYY affect EE. However, it remains to be determined whether RYGB affects EE after energy balance is restored, and whether it particularly affects meal-induced thermogenesis merits further investigation.
In spite of progressive weight loss, GBP decreased motivation to eat. This effect was partly explained by a simultaneous postprandial increase in GLP-1, a suppression of ghrelin, an increase in nausea, and to a lesser extent, an increase in PYY. Leptin and CCK, however, were not involved in reductions in motivation to eat after GBP. When GLP-1 and PYY were coinfused, the reduction in energy intake clearly exceeded the summed effects of the hormones when given separately. This suggests a synergistic effect, which has not previously been demonstrated in human studies.

In summary, GBP-induced stimulation of EE is unlikely to explain the larger weight loss after this procedure compared to other weight loss strategies. Rather, a reduction in motivation to eat,

mediated at least partly by GLP-1, PYY, and ghrelin, as their complex interactions, seems to be a major contributor to early postoperative weight loss.

Dansk sammendrag

Som konsekvens af et vægttab aktiveres mekanismer der er designet til at beskytte kroppens energidepoter. Disse mekanismer involverer både en øgning af appetitten, samt et fald i energiforbruget. Et sådan kompensatorisk respons modvirker vægttab og prædisponerer individer til at tage den tabte vægt på igen. At fedmekirurgi, og specifikt gastric bypass (GBP), kan forhindre dette respons kan være en af forklaringerne på hvorfor denne intervention på nuværende tidspunkt er den eneste effektive behandling mod svær fedme. Det er dog uklart hvordan energiforbruget påvirkes af GBP uafhængigt af den akutte negative energibalance, der uundgåeligt følger med denne operation. GBP er desuden påvist at kunne medføre en lang række hormonelle ændringer, men hvordan disse kan forklare ændringer i appetit, energiindtag og energiforbrug er uafklaret.

Denne afhandling har til formål at undersøge, om GBP kan forhindre et vægttabs-medieret fald i energiforbruget, og om ændringer i niveauer af hormonerne PYY, leptin, FGF19 og galdesyrer kan forklare potentielle effekter. Dette blev undersøgt i et klinisk studie hvor forsøgspersoner blev randomiseret til enten GBP eller til en såkaldt par-fodret kontrolgruppe, samt ved en kritisk gennemgang af den eksisterende litteratur. I samme studie blev det undersøgt, hvordan PYY, GLP-1, CCK, leptin og ghrelin bidrager til de postoperative ændringer i appetitfølelse. Hvorvidt GLP-1 og PYY udøver deres effekter på appetit og fødeindtag gennem overlappende, additive og/eller synergiske effekter blev undersøgt i et randomiseret, dobbeltblindet, placebokontrolleret overkrydsningsstudie med fire arme, hvor forsøgspersoner modtog enten mono- eller co-infusioner af GLP-1 og PYY.

Hverken de kliniske studier eller den eksisterende litteratur kunne levere evidens for at en stigning i energiforbruget bidrager til det postoperative vægttab. Derimod var reduktionen i basalstofskiftet og i det totale energiforbrug efter GBP større end i kontrolgruppen. Det yderligere fald i energiforbruget hos GBP-opererede kunne forklares ved et fald i leptin. Til trods for et markant øget postprandialt respons af PYY, galdesyrer og FGF-19 sås der ingen effekter på den måltidsinducerede thermogenese. Hvorvidt GBP har effekter på energiforbruget ved energibalance vides ikke, og særligt den måltidsinducerede thermogenese vil være interessant at undersøge i fremtidige studier.
Til trods for et intensivt vægttab var motivationen til at spise reduceret efter GBP. Dette kunne delvist forklares ved en postprandial stigning i GLP-1, en undertrykkelse af ghrelin, en stigning i kvalme og i mindre grad af en stigning i PYY. Derimod kunne leptin og CCK ikke forklare ændringer i appetit. Ved co-infusion af GLP-1 og PYY var reduktionen i energiindtaget større end summen af effekterne ved mono-infusion af GLP-1 og PYY. Dette tyder på en synergistisk virkning, hvilket ikke tidligere er blevet påvist i humane studier.

Det konkluderes, at det er usandsynligt at det postoperative vægttab er medieret af en stigning i energiforbruget. Snarere er nedsat appetit en plausibel forklaring for vægttab efter GBP og synes delvist medieret af GLP-1, PYY og ghrelin, samt ved komplekse interaktioner mellem disse.