Metabolic hormones and ethnic aspects in obesity

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CHAPTER 9

APPENDICES

SUMMARY

Obesity is a chronic disease defined by excessive fat deposits caused by a positive balance between energy intake and expenditure. It is a worldwide problem, with the prevalence of obesity having tripled since the early 1980s and is expected to rise further. Obesity imposes a significant burden on individuals, including stigma, physical limitations, and the difficulty of achieving and maintaining weight loss. It also can lead to many related diseases such as cardiovascular disease and type 2 diabetes mellitus (T2DM). Furthermore, certain ethnicities are more susceptible to developing obesity and related diseases, notably South Asians having a fourfold higher risk of developing T2DM compared to Europids. This thesis aims to i) unravel additional underlying causes of the disadvantageous metabolic profile of South Asians, and ii) comprehensively understand how different (non-)pharmacological interventions can modulate circulating levels of various hormones and regulate overall energy metabolism in humans with different comorbidities.

Chapter 1 introduced the epidemiology, the underlying, and sustaining factors of obesity, as well as a detailed description of the physiology of adipose tissue and energy metabolism. It introduces potential underlying mechanisms for the increased risk of developing obesity and cardiometabolic diseases in the South Asian population. Finally, it discusses the targets for preventing and treating obesity and related diseases.

Chapter 2 explored differences in circulating levels of inflammation-related proteins in South Asians and Europids with T2DM using a panel of 73 inflammation-related proteins from Olink Proteomics. The relative plasma levels of six proteins were higher, and six were lower in South Asians compared to Europids. Relative plasma levels of fibroblast growth factor 21 (FGF21) were most notably different and lower in South Asians, especially in females. To validate these findings, we measured circulating FGF21 concentrations in the serum samples of the same cohort and found a lower concentration of circulating FGF21 in both males and females. Lower FGF21 levels and concentrations in South Asians may align with their pro-inflammatory phenotype, given FGF21's known anti-inflammatory properties. Future research is needed to determine if decreased FGF21 levels and concentrations are a cause or consequence of the increased T2DM risk in South Asians.

In addition to inflammation, another factor contributing to the unfavorable metabolic profile of South Asians could be differences in hormone regulation. Therefore, in **Chapter 3,** we compared the effect of a single mixed meal tolerance test (MMTT) on the excursion of incretin hormones as well as glucagon in young and lean Dutch South

Asian and Dutch Europid males and females in relation to the excursions of glucose and insulin. After an overnight fast, we measured incretin hormones (i.e., total and active glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide-1 (GIP)), glucagon, glucose, insulin and parameters involved in lipid metabolism at baseline and six time points up to 240 minutes post-meal. While Europids exhibited a single glucose peak, South Asians showed an second glucose peak. Potentially as a consequence, especially South Asian females had a higher second peak of active GLP-1 and GIP compared to Europid females. Moreover, this was accompanied by a biphasic insulin response with a higher area under the curve (AUC) of insulin in males. These effects may result from biphasic gastric emptying in South Asians, though the consequences for the disadvantageous metabolic phenotype of South Asians remains to be determined. We further explored differences in hormone regulation between South Asians and Europids in **Chapter 4**, by analyzing the excursion of the hunger and satiety hormones peptide YY (PYY), ghrelin, and leptin in response to an MMTT in the same participants as in **Chapter 3**. While PYY levels did not differ before and during the MMTT between males and females of both ethnicities, South Asian males exhibited lower ghrelin levels before and during the MMTT, and both South Asian males and females had higher levels of leptin at before and during the MMTT compared to Europids. Baseline leptin levels correlated positively with fat mass and fat percentage in South Asians, suggesting leptin could potentially serve as a biomarker for body fat in South Asians.

Next, we aimed to understand how (non-)pharmacological interventions can modulate the concentration of different hormones and regulate overall metabolism in humans with different comorbidities. To do so, in **Chapter 5** we investigated the effect of cold exposure on FGF21 and growth differentiation factor 15 (GDF15) in healthy lean individuals and examined whether cold-induced changes in FGF21 and GDF15 levels before, during, and after 90 minutes of stable cold exposure differ between morning and evening. The potential metabolically beneficial effects of cold exposure are likely mediated through the activation of brown adipose tissue (BAT), partly through the secretion of hormones such as FGF21 and GDF15. We found that cold exposure increased FGF21 levels only in the evening, without affecting GDF15. The changes in FGF21 were not correlated with the change in cold-induced energy expenditure, indicating that the timing of cold exposure influences FGF21 levels independently of energy expenditure changes. These findings could be significant for improving metabolic health through cold exposure.

Cold exposure may not suit everyone and therefore pharmaceutical activation of BAT may be of interest. In rodents, BAT is activated via the adrenergic beta-3 receptor (ADRB3); however, in humans, ADRB2 is responsible for the noradrenergic activation

of human BAT, at least *in vitro.* Therefore, in **Chapter 6**, we aimed to investigate whether the ADRB2 agonist salbutamol intravenously activates human BAT *in vivo.* In a randomized double-blinded crossover trial involving healthy young males, we compared glucose uptake in BAT after intravenous salbutamol administration with or without propranolol, an ADRB1 and ADRB2 blocker. The activation of BAT was measured by the increase in glucose uptake in BAT using a dynamic [^{18}F]fluoro-D-deoxy glucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT scan). We found that intravenous salbutamol increased glucose uptake in BAT, an effect that was diminished when combined with propranolol. The increase in glucose uptake was positively associated with increased energy expenditure. Our findings demonstrate that ADRB2 activates human BAT; however, the long-term effects of pharmacological stimulation of BAT require further investigation.

We next investigated both the intervention options and potential metabolic differences in the South Asian population with Europids in **Chapter 7**. Here, we investigated whether GDF15 may be involved in satiety induction by GLP-1 receptor agonism in patients with T2DM, and whether GDF15 levels differ between South Asians versus Europids. In a randomized control trial, we measured GDF15 levels at baseline and after 26 weeks of daily treatment with the GLP-1 agonist liraglutide compared to placebo in South Asians and Europids with T2DM. At baseline, we found no significant difference in GDF15 levels between South Asians and Europids. Additionally, liraglutide did not modify GDF15 levels in either ethnicity. Our findings suggest that liraglutide induces satiety independent of the GFRAL/GDF15 pathway, suggesting that other mechanisms likely explain the weight loss induced by liraglutide.

Finally, in **Chapter 8**, we discussed all findings described in this thesis in the context of the latest scientific literature. We explored the potential implications of our findings for clinical practice and addressed remaining future challenges. Moreover, we elaborated on the role of inflammation and hormone dysregulation as an underlying role in the metabolic profile of South Asians, with a particular focus on GLP-1, the stress system, and sex hormones. We proposed new criteria to combat the challenges during the matching of cohorts of South Asians. Furthermore, we discussed the implications of our findings for the optimization of interventions by incorporating the timing for BAT activation, exploring the pharmacological activation of BAT, and considering the possible combinations of other hunger- and satiety-related factors like FGF21 and GDF15 with the current GLP-1 agonists. These findings could potentially lead to new therapeutic options for combating obesity and obesity-related diseases. Future research is essential to translate these discoveries into practical clinical applications.