Obesity and type 2 diabetes : cardiovascular and cerebral aspects

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Chapter 1

General introduction

The prevalence of obesity, defined as a body mass index (BMI) > 30 kg/m^2, is increasing to epidemic proportions. In 2014, 11% of men and 15% of women worldwide were obese. Thus, more than half a billion adults worldwide are classed as obese[1]. The fundamental cause of obesity is an imbalance between energy intake (excessive intake of energy-dense foods) and energy expenditure (reduced physical activity). People with obesity are at risk for a range of chronic conditions including cardiovascular disease (CVD) and nonalcoholic fatty liver disease (NAFLD)[2]. Furthermore, obesity is a major risk factor for the development of type 2 diabetes, which is one of the most common chronic diseases in nearly all countries. According to the World Health Organization, the global prevalence of diabetes in 2014 was estimated to be 9%[1], of which 90% was comprised of type 2 diabetes[3].

Left ventricular (LV) function, central arterial stiffness, and subclinical atherosclerosis are important markers for CVD. NAFLD, or *fatty liver*, is recognized as an amplifier of inflammatory processes which could contribute to the development of CVD. These processes originate in expanded and inflamed visceral adipose tissue (VAT). In addition, increased intrahepatic cytokine expression is suggested to play a key role in the progression of CVD[4]. However, the interrelationships between obesity, markers for CVD, and NAFLD are complex and associations could in part be confounded by the manifestation of multiple metabolic impairments known as the metabolic syndrome.

CVD is one of the major adverse consequences of type 2 diabetes, and chronically elevated plasma nonesterified fatty acid (NEFA) levels in patients with type 2 diabetes are associated with altered myocardial high-energy phosphate metabolism[5]. When evaluating cardiac function most studies focus on the LV, but the right ventricle (RV) is largely overlooked. RV function is an important determinant of outcome in several cardiopulmonary conditions and has proven to be useful for patient risk stratification in heart failure and for prediction of developing atrial fibrillation[6-8]. However, RV anatomy and function have not yet been studied in patients with type 2 diabetes.

The metabolic pathways involved in the pathogenesis of insulin resistance and cardiovascular diseases in patients with type 2 diabetes are complex. Increased lipolysis from adipose tissue causes triglycerides to be stored in different organs outside adipose tissue, known as ectopic fat accumulation. Ectopic fat accumulation in muscle and liver are involved in pathophysiologic insulin resistance[9-11]. Theoretically, limiting organ-specific fat accumulation by exercise training could improve glucose homeostasis and reduce cardiovascular risk.

The brain is another important organ involved in obesity and type 2 diabetes. The hypothalamus plays a key role in the regulation of feeding and the control of glucose metabolism[12]. Moreover, various hypothalamic neuronal circuits are involved in the control of glucose metabolism[13]. It has been shown that the hypothalamic neuronal activity is altered in patients with type 2 diabetes, which may indicate that the hypothalamus inappropriately perceives

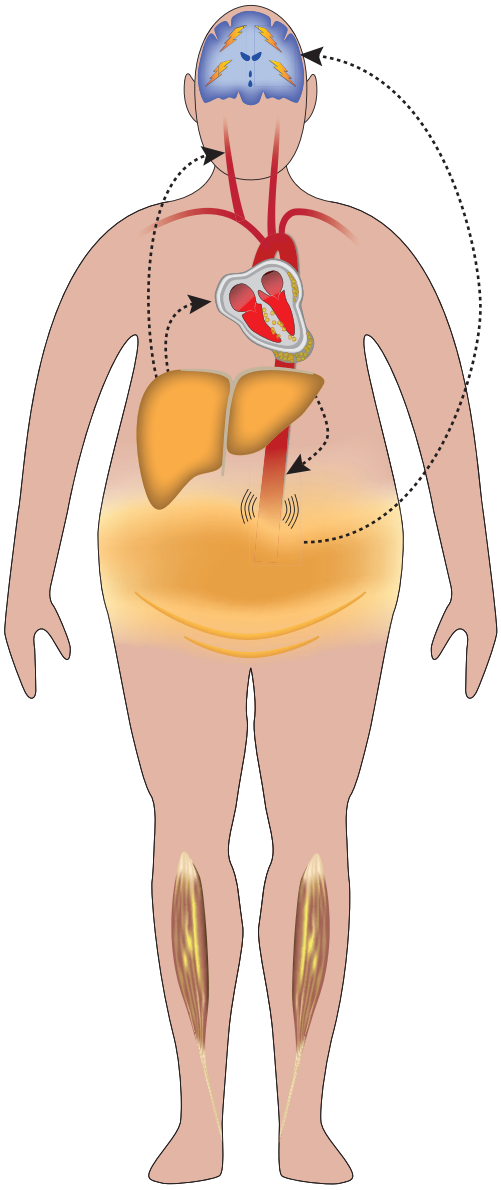

Figure. Schematic overview of the organs and ectopic fat depots studied in this thesis. Expanded visceral adipose tissue is a hallmark of obesity and type 2 diabetes. Several proinflammatory cytokines originate from visceral adipose tissue which may promote aortic stiffness, decreased cardiac function, and microstructural brain damage. The liver is not an innocent bystander, but is recognized as an amplifier of inflammatory processes which could contribute to the development of cardiovascular disease in obesity and type 2 diabetes.

and/or processes signals in response to a nutrient load, reflecting an abnormal perception of the current metabolic status[14]. Caloric restriction is an important therapeutic strategy in type 2 diabetes, but its effect on hypothalamic responsiveness is yet unknown.

Obesity has been associated with structural brain changes, such as brain atrophy[15]. The relationship between obesity and the anatomy of subcortical structures that play a role in human food regulation have not been investigated previously. Such brain structures include the basal ganglia, hippocampus, and thalamus. Furthermore, it can be hypothesized that the inflammatory processes originating from VAT do not only lead to the development of CVD, but could also induce microstructural brain damage.

Magnetic resonance imaging (MRI) is a noninvasive imaging modality that allows for analyzing structural and functional information of the human body. ECG gated cardiac magnetic resonance provides a valuable assessment of cardiac morphology and function[16, 17]. MRI assessment of aortic pulse wave velocity, defined as the velocity of the systolic wave front propagating through the aorta, is a measure for aortic stiffness. It has good agreement with the gold-standard as derived by invasive pressure measurements and can be determined with high reproducibility[18]. Proton (^{1}H) magnetic resonance spectroscopy is the most commonly used magnetic resonance-based method to noninvasively evaluate metabolic changes in the human body. ^{1}H magnetic resonance spectroscopy helps to characterize tissues by assessing biochemistry in vivo. The technique identifies metabolites by observing differences in the resonance frequencies of the ^{1}H signal. Localized ^{1}H magnetic resonance spectroscopy is a sensitive and quantitative method to measure hepatic triglyceride content[19]. Blood oxygen level-dependent (BOLD) functional MRI (fMRI) has been widely applied in spatiotemporal mapping of the human brain function and measuring neuronal activity. The main advantage of BOLD fMRI is its noninvasive nature and local sensitivity combined with a good spatial resolution[20]. Magnetization transfer imaging (MTI) is an MRI technique that is more sensitive to subtle microstructural changes in the brain than conventional techniques[21]. Accordingly, magnetic resonance imaging and spectroscopy are the methods of choice to study the complex interrelationships between visceral obesity, NAFLD, and markers of cardiovascular disease, and to investigate cerebral changes in people with obesity and type 2 diabetes (**Figure**).

OUTLINE OF THIS THESIS

This thesis focuses on cardiovascular and cerebral dimensions and function in people with obesity and type 2 diabetes. State-of-the-art imaging techniques are used to investigate links between the heart, liver, abdominal fat, and brain to elucidate parts of the complex relationships between these organs.

Previous studies have shown a relationship between NAFLD and subclinical cardiovascular measures, but the possible confounding effect of the metabolic syndrome is so far unknown. The association between hepatic triglyceride content and LV diastolic function is evaluated in **Chapter 2** by taking various covariates, including components of the metabolic syndrome, into account. In **Chapter 3** the association between liver fat, the stiffness of the aorta and carotid intima-media thickness is evaluated using a similar approach.

It is known that subclinical LV dysfunction presents in type 2 diabetes, even in the absence of significant coronary artery disease and hypertension. Despite its importance in patient outcome in heart failure, the RV is largely overlooked. **Chapter 4** focuses on the differences of the dimensions and function of the RV between healthy subjects and type 2 diabetes patients. To better understand the changes in RV function, nutritional interventions were applied in a group of healthy subjects to create a physiological and a pathophysiological model of increased plasma NEFA levels. The effects on RV function in these two conditions are evaluated in **Chapter 5**.

Strategies to limit ectopic fat accumulation are rational approaches to improve glucose homeostasis and potentially reduce cardiovascular risk. Most intervention studies have focused on visceral and subcutaneous fat; however, little is known about the effect of exercise alone without diet on ectopic fat accumulation in type 2 diabetes. In **Chapter 6** the effects of an exercise intervention on organ-specific fat accumulation and cardiac function in type 2 diabetes patients is described.

The hypothalamus is critically involved in the regulation of feeding. Type 2 diabetes is a disease of impaired glucose homeostasis and insulin action, with energy imbalance and anomalous fuel flux as metabolic hallmarks. Restoration of the energy balance by reduction of the caloric intake and subsequent weight loss are important therapeutic strategies in type 2 diabetes. The effect of caloric restriction on the hypothalamic neuronal response to glucose ingestion in type 2 diabetic patients is evaluated in **Chapter 7**.

Other brain structures involved in the regulation of human feeding behavior include the basal ganglia, hippocampus, and thalamus. **Chapter 8** focuses on the relationship of the morphometric changes of these structures in obesity. Finally, it has been shown that obesity is associated with brain atrophy, and different fat compartments demonstrate different metabolic and endocrine behaviors. Therefore, **Chapter 9** describes the association of individual associations between abdominal visceral and subcutaneous adipose tissue with microstructural brain tissue damage.

Results of this thesis are summarized in **Chapter 10**.

REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases 2014. http://www.who.int/nmh/publications/ncd-status-report-2014/en. Published 2014.
2. Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab* 2004;89:2583-2589.
3. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications : report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. http://apps.who.int/iris/handle/10665/66040. Published 1999.
4. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;363:1341-1350.
5. Scheuermann-Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P, Radda GK, Neubauer S, Clarke K. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. *Circulation* 2003;107:3040-3046.
6. Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, White M, Aban IB, Mujib M, Dell'Italia LJ, Ahmed A. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. *Circulation* 2010;121:252-258.
7. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001;37:183-188.
8. Aziz EF, Kukin M, Javed F, Musat D, Nader A, Pratap B, Shah A, Enciso JS, Chaudhry FA, Herzog E. Right ventricular dysfunction is a strong predictor of developing atrial fibrillation in acutely decompensated heart failure patients, ACAP-HF data analysis. *J Card Fail* 2010;16:827-834.
9. Krssak M, Falk Petersen K, Dresner A, DiPietro L, Vogel SM, Rothman DL, Roden M, Shulman GI. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. *Diabetologia* 1999;42:113-116.
10. Perseghin G, Scifo P, De Cobelli F, Pagliato E, Battezzati A, Arcelloni C, Vanzulli A, Testolin G, Pozza G, Del Maschio A, Luzi L. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. *Diabetes* 1999;48:1600-1606.
11. Samuel VT, Liu ZX, Qu X, Elder BD, Bilz S, Befroy D, Romanelli AJ, Shulman GI. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J Biol Chem* 2004;279:32345-32353.
12. Liu XH, Morris R, Spiller D, White M, Williams G. Orexin a preferentially excites glucose-sensitive neurons in the lateral hypothalamus of the rat in vitro. *Diabetes* 2001;50:2431-2437.
13. van den Hoek AM, van Heijningen C, Schröder-van der Elst JP, Ouwens DM, Havekes LM, Romijn JA, Kalsbeek A, Pijl H. Intracerebroventricular administration of neuropeptide Y induces hepatic insulin resistance via sympathetic innervation. *Diabetes* 2008;57:2304-2310.
14. Vidarsdottir S, Smeets PA, Eichelsheim DL, van Osch MJ, Viergever MA, Romijn JA, van der Grond J, Pijl H. Glucose ingestion fails to inhibit hypothalamic neuronal activity in patients with type 2 diabetes. *Diabetes* 2007;56:2547-2550.
15. Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R, Fukuda H. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity (Silver Spring)* 2008;16:119-124.
16. Pattynama PM, de Roos A, van der Wall EE, van Voorthuisen AE. Evaluation of cardiac function with magnetic resonance imaging. *Am Heart J* 1994;128:595-607.

17. Paelinck BP, Lamb HJ, Bax JJ, van der Wall EE, de Roos A. Assessment of diastolic function by cardiovascular magnetic resonance. *Am Heart J* 2002;144:198-205.
18. Grotenhuis HB, Ottenkamp J, Westenberg JJ, Bax JJ, Kroft LJ, de Roos A. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. *J Am Coll Cardiol* 2007;49:1660-1665.
19. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, Hobbs HH, Dobbins RL. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005;288:E462-468.
20. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 1990;87:9868-9872.
21. van Buchem MA, McGowan JC, Grossman RI. Magnetization transfer histogram methodology: its clinical and neuropsychological correlates. *Neurology* 1999;53:S23-28.