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General Introduction: The epidemiology of microvascular function

Microvascular function

The microcirculation controls tissue perfusion, which regulates substance exchange between blood and target-tissues, as well as blood pressure. Normal responses of the microcirculation follow changes in autonomous nervous system activation and in local and systemic changes in signalling molecules, such as hormones and cytokines. These molecules can have vasodilating or vasoconstricting properties. For example, an increase in plasma insulin concentration is followed by a vasodilatory response in the microcirculation, which facilitates delivery of nutrients to target tissue[1–4].

Fat tissue also secretes cytokines and hormones, some of which are vasoactive. In obese subjects, these cytokine and hormone levels are altered. For example, adiponectin is a vasodilator hormone that is secreted in lower amounts with increased body fatness. Subsequently vasodilator responses may become disturbed in obese subjects. Alterations like these can lead to microvascular (dys)function[1,2,4–7]. A full review of the potential mechanisms underlying microvascular (dys)function is given in chapter 3 of this thesis[8].

Consequences of microvascular dysfunction can be seen in two functions of the microcirculation: nutrient exchange and blood pressure regulation. On the one hand, microvascular dysfunction can increase peripheral resistance, contributing to hypertension[9,10]. On the other hand, microvascular dysfunction can decrease local tissue delivery of nutrients such as glucose, and hormones such as insulin, which eventually could lead to insulin resistance and diabetes mellitus[4,11]. Therefore, microvascular dysfunction, is seen as a predictor or early risk factor for CVD and (gluco-)metabolic disorders[12–14].

A non-invasive method to assess microvascular function, is nailfold capillary videomicroscopy, in short 'capillaroscopy'. Capillaroscopy can be used in epidemiological studies. Even though capillaroscopy is restricted to the skin, it is a proxy of perfusion of muscle tissue[15]. Capillaroscopy is used to assess microvascular function in both cohorts studied in this thesis.

Body fatness

The epidemiology of overweight and obesity, defined as abnormal or excessive body fatness that may impair health, is widely studied[16,17]. The cause of overweight and obesity is straightforward: a disturbed energy balance, in which more energy comes in than is being expended. Prevention or treatment of overweight and obesity are, however, more complicated. A major role is played by psychological aspects, together with environmental factors characterized by widespread availability of energy-dense foods and drinks and few physical challenges. With that overweight and obesity primarily remain a public health challenge, rather than a medical condition[16,17].

A degree of fatness is present in all human beings. Fat tissue has, amongst others, important functions in thermoregulation, protection of internal organs and energy storage. Fat cells not only react to, but also act on surrounding tissue. They can react to local and systemic changes via signalling molecules, such as cytokines and hormones. Also, fat cells can act on the surrounding tissue by secreting cytokines and hormones. As a group these substances are called adipokines, such as leptin and adiponectin, can control functions of body fatness[18]. For example, with increased body fatness, a decreased level of adiponectin is observed. This decrease in adiponectin causes lower vasodilator responses, lowering tissue perfusion, and subsequently affecting the thermoregulatory role of body fatness[19].

Raised body fatness has implications for the health of an individual as it increases the risk of many diseases and conditions, including musculoskeletal, respiratory, psychological and cardiovascular disease[20–22]. Which specific type of body fatness (i.e. more central / abdominal or more diffuse fat accumulation) is most harmful, has been the subject of intense investigations. A more central pattern of body fatness distribution has been suggested to most strongly predict health outcomes[20,21]. Central body fatness, by locally affecting the liver, is associated with systemic low grade inflammation, which appears to be associated with many adverse health outcomes[16,20,22]. Moreover, experimental studies have focussed on the differences between ectopic (accumulation of triglycerides in non-adipose tissue) and visceral (stored inside the abdominal cavity, as well as inside abdominal organs) fat[4,20]. These studies suggest different effects for ectopic fatness and visceral fatness. However, when an obese subject with a more central pattern of body fatness has, for example, increased pancreatic fatness this can be considered both visceral and ectopic fatness.

Methods to assess body fatness range from sophisticated methods, such as the double labelled water method (which is regarded as the gold standard test for years) and Dual Energy X-ray Absoptiometry (DEXA) scan, to older conventional anthropometrics. For epidemiological and clinical purposes, anthropometrics, such as BMI, skinfold thickness, and waist and hip circumference, are widely used[22,23]. These non-invasive measures are used

with the rationale that a high waist circumference or waist-to-hip ratio with a given BMI, represent those subjects who are characterized by high visceral fatness[24]. But in fact it does only represent those who have high abdominal fatness and it can't exclude nor define the proportion of ectopic fatness[22,24,25]. Therefore, in this thesis both anthropometrics and DEXA scan data are used. Also, differences between total body fatness and body fatness distribution are examined.

Study Populations

In this thesis, data from two large observational population-based studies are used.

The Amsterdam Growth and Health Longitudinal Study (AGHLS) is an observational cohort that consist of over 30 years of data[26]. In 1976, approximately 600 first grade school children were included at the age of 13 years. The study started with examination of growth and health among teenagers, but grew into a longitudinal study examining relationships between a wide range of variables such as anthropometrics, physical fitness, cardiovascular risk factors, lifestyle, musculoskeletal health, and psychological health and well-being. Also, methodological issues concerning longitudinal data analyses were extensively examined. Chapter 2 of this thesis illustrates the extensive dataset that emanates from all rounds of measurement over the years of the AGHLS.

The New Hoorn Study (NHS) is a population based cohort examining prevalence and prevention of type 2 diabetes mellitus[27]. The study is a follow-up of the Hoorn Study, and started in 2006, examining approximately 6000 subjects selected from the municipal registry of Hoorn. The study started to examine a group of middle aged apparently healthy subjects, in order to identify subjects with elevated plasma glucose levels (at risk) and undiagnosed cases of type 2 diabetes. Next to measures of oral glucose tolerance, a wide range of health related topics is examined using questionnaires. A new follow-up round has been planned for 2015.

Objective

The general aim of this thesis is to examine whether associations, as found in previous experimental and clinical studies, between body fatness and microvascular function can be observed in apparently healthy subjects. The hypothesis is that body fatness is related to diabetes and hypertension, at least partly by affecting microvascular function. Microvascular dysfunction is apparent in both severely obese subjects[6] and subjects with essential hypertension[286]. These observations, however do not provide evidence for a linear relationship of body fatness with microvascular function.

So far, there are only two population-based studies, both of which were characterized by some degree of subject selection (study populations

selected on insulin sensitivity or blood pressure)[29,30]. First, a recent study by Czernichow et al.[29] studied similar relations in a comparably large study population of healthy insulin-sensitive, but overweight men and women, and found body fatness to be inversely associated with microvascular perfusion. The second comparable study was conducted by Irving et al.[30] In that study, a relationship of microvascular function with BMI was shown. However, that study was restricted to male subjects, selected from a four-corner design based on parental and own blood. Whether the relationships between adiposity and microvascular perfusion found in these studies can be translated to the general population, remains to be seen.

Also, in an epidemiological context, other factors relevant to microvascular function can be explored. Collateral aims of this thesis were to explore predictors of developmental patterns of body fatness, as well as novel associations with microvascular function.

Outline of the thesis

Chapter 2 provides a further introduction to the mechanisms that connect body fatness to microvascular function. Chapter 3 extensively describes the cohort profile of the AGHLS. In chapter 4, the relationship of body fatness with microvascular function is healthy middle-aged adults of the AGHLS study is addressed. Chapter 5 addresses longitudinal developmental patterns of body fatness over time. In chapter 6 we studied adolescent predictors of these developmental patterns body fatness. In chapter 7, the New Hoorn Study population is used to examine the relationship between body fatness and microvascular function within a slightly older and more metabolically perturbed population. Finally, in chapter 8, sleep, which also may be involved in the metabolic syndrome, is studied as risk factor for microvascular dysfunction.