Chapter 1

General introduction
Chapter 1

The Metabolic Syndrome

The metabolic syndrome refers to a clustering of metabolic risk factors, including (abdominal) obesity, hypertension, glucose intolerance and dyslipidemia which confers an increased risk for type 2 diabetes and cardiovascular disease (1). The metabolic syndrome is viewed as one of the most challenging health issues of the present century due to the ongoing global obesity epidemic. In the Netherlands 34% of men and 24% of women (National institute for health and the environment, the Netherlands (RIVM); data 26 January 2012; http://www.rivm.nl and 20 – 25 percent of the world’s adult population meet the criteria of the metabolic syndrome (2). The mechanisms underlying the clustering of components of the met syndrome are incompletely understood. Obesity-associated microvascular dysfunction explains part of this clustering, predisposes obese subjects to CVD and is therefore viewed as a possible therapeutic target underlying the causes of the metabolic syndrome (3,4).

Microvascular (dys)function
Morphologically, the microcirculation encompasses all vessels <150 μm in diameter, including arterioles, capillaries, and venules. Its major function is to regulate tissue perfusion to ensure adequate delivery of nutrients, oxygen and hormones and to provide endothelial exchange surface area between the plasma compartment and muscle interstitium. A second important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries causing disturbances in capillary exchange (4). Microvascular dysfunction is a broad term that includes both structural and functional changes. An important structural change is “microvascular rarefaction” which refers to the reduction in the number of arterioles and/or capillaries within vascular beds. Functional changes comprise of impaired microvascular endothelium-dependent responses to various vasoactive agents of which the response of the endothelium to insulin seems to play a crucial role.

Microvascular effects of insulin
Insulin, in addition to its essential metabolic action, also plays an important role in the regulation of vascular tone and tissue perfusion. Insulin can bind directly to endothelial cells, where it stimulates intracellular signaling intermediates (including phosphatidylinositol 3-kinase (PI3K)) leading to NO release, and subsequent vasodilation (5). Insulin, however, also activates the intracellular mitogen-activated protein kinase pathway (MAPK), which enhances the generation of the vasoconstrictor endothelin-1 (ET-1) (5). In the healthy microcirculation, the vasodilatory signal predominates, but if the PI3K pathway is inhibited, pharmacologically or downregulated by insulin resistance, this lead to impaired insulin-mediated vasodilation or even insulin-stimulated vasoconstriction. This phenomenon is referred to as vascular insulin resistance (6-8).
Microvascular dysfunction and hypertension
It is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs, and the microcirculation is therefore important in determining systemic vascular resistance (SVR). Previously it has been shown that both microvascular endothelium-dependent vasodilation, and capillary density correlate inversely with blood pressure in hypertensive and normotensive subjects (9,10). Furthermore microvascular rarefaction can already be demonstrated in subjects with mild hypertension and in normotensive subjects with a genetic predisposition to high blood pressure, suggesting abnormalities in the microcirculation precede and thus may be a causal component of high blood pressure (11,12). In humans, however, the effects of insulin on SVR have rarely been examined directly.

Microvascular dysfunction and insulin resistance
In healthy humans it has been shown that insulin increases tissue perfusion of target organs while this effect is impaired in obese insulin-resistant subjects (9,13). This is has been established with contrast enhanced ultrasound (CEU), a technique for measuring microvascular blood volume of organs such as muscles and by directly visualizing capillaries in human skin. It has been hypothesized that if insulin increases microvascular perfusion this enhances the access of both insulin and glucose to cells, thereby augmenting glucose uptake. The validity of this hypothesis has been underscored by human and animal studies, including one showing that when insulin signaling is selectively impaired in endothelial cells using conditional mutagenesis in mice, this impairs transcapillary insulin transport, insulin-stimulated glucose uptake in muscle, and results in mild glucose intolerance (14).

Microvascular dysfunction: organ specific or part of a generalized microangiopathy?
Microvascular dysfunction is central to many forms of end-organ damage associated with the metabolic syndrome, including those involving the eye, kidneys, heart, and brain (4,6). The microcirculations of different organs, however, exhibit considerable differences, and different segments of the microcirculation within a given organ differ as well. Especially the microcirculation of the brain is different from other organs as this is part of the so-called “blood-brain barrier.” The endothelium of brain capillaries is highly impermeable to passive transport of even the smallest solutes and strong stimuli are needed to disrupt this barrier. Currently it is not known whether small vessel disease in the brain is organ specific or part of a generalized microangiopathy and thus could also be measured in the skin.

Can red wine polyphenols improve the component criteria of the metabolic syndrome by improving microvascular function?
Wine has a long history in human culture and medicine. Recently, scientific interest in wine was sparked by epidemiological studies suggesting beneficial relationships between moderate use of alcoholic beverages, red wine in particular, and cardiovascular disease (15). This
hypothesis has been proposed as an explanation for the "French Paradox", the observation of low cardiovascular mortality of French despite a high consumption of saturated fat and high prevalence of other risk factors (16). Later on it has been proposed that the polyphenol fraction of red wine (RWPs) represents the beneficial component of red wine. Polyphenols are found in plants, especially grapes and berries, and can be defined as macromolecules generally containing >12 phenolic hydroxyl groups with five to six aromatic rings per 1,000 daltons. Red wine does not only contain high concentrations (approximately 100 mg per glass of wine versus about 40 mg in a glass of white wine) but also a wide variety of polyphenolic substances. In pre-clinical studies, auspicious effects of (red-wine) polyphenols on insulin sensitivity (17), blood pressure (18) and lipid levels (19) have been described. Furthermore, in ex-vivo models it has been shown that RWPs improve endothelial NO-mediated relaxation using the same PI3-kinase/Akt pathway as does insulin (20) and another study suggested that RWPs may also reduce endothelin-1 expression (21). Hence, RWPs might provide a more favorable balance of insulin's vascular effects by relative amplification of insulin's activation of nitric oxide. Studies in humans are however limited.

Aims and scope of this thesis:
1. To study the role of microvascular dysfunction in the development of hypertension and end-organ damage.
2. To study whether RWPs, by improving microvascular function, could be beneficial to obesity-associated insulin resistance, hypertension and/or dyslipidemia.

In Chapter 2 we report on an association between systemic vascular resistance and metabolic insulin resistance. Systemic vascular resistance is an important factor in determining blood pressure. We measured systemic vascular resistance both during pharmacology induced hyperinsulinemia and physiologically hyperinsulinemia (after a meal).

Chapter 3 describes associations between proliferative retinopathy, microvascular dysfunction in skin and microbleeds in the brain in patients with type 1 diabetes. In this manuscript we hypothesize that vascular dysfunction as measurable in the peripheral circulation (i.e. the skin) reflects generalized microangiopathy throughout the body.

Chapter 4 is a systematic review of the effects of grape polyphenols on components of the metabolic syndrome. This study gives an overview of all previously published clinical trials in which grape polyphenols are used and measured glycemia, insulin sensitivity, blood pressure and/or lipid levels.

Chapter 5 & 6 describe the results of a randomized, placebo-controlled, double-blind clinical trial in which we studied the effects of red wine polyphenols. In chapter 5 we focused on the metabolic outcomes, in particular insulin sensitivity as this was the primary outcome of our study. In chapter 6 we described the vascular effects including (insulin stimulated) endothelial function and blood pressure.

Chapter 7 is the general discussion of this thesis.
Reference


