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Microvascular dysfunction: Determinants and treatment, with a focus on hyperglycemia

Alfons J.H.M. Houben*, Coen D.A. Stehouwer

Department of Internal Medicine and CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, the Netherlands

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ABSTRACT

Individuals with prediabetes or type 2 diabetes have an increased risk of diseases that are partly or entirely of microvascular origin (e.g. (lacunar) stroke, depression, cognitive decline, retinopathy, heart failure, chronic kidney disease, and neuropathy). These diseases are expressions of advanced microvascular dysfunction (MVD). Yet, MVD may develop already early and contribute to impaired insulin-mediated glucose uptake and subsequent metabolic insulin resistance, characterized by hyperglycemia. However, apart from hyperglycemia being a consequence of MVD, hyperglycemia can also (further) impair microvascular function, constituting a vicious cycle. In this review we shall discuss important evidence showing that MVD may precede and predict (pre)diabetes and related co-morbidities, and discuss the important determinants of early MVD. In addition, we shall discuss hyperglycemia being both a cause and consequence of MVD. Finally, we shall focus on prevention and treatment strategies for MVD.

1. Introduction

An adverse cardiovascular risk profile (including obesity, hypertension, low grade inflammation, dyslipidemia) and/or having type 2 diabetes are associated with an increased risk of diseases that are (at least partly) of microvascular origin (e.g. (lacunar) stroke, depression, cognitive decline, retinopathy, heart failure, chronic kidney disease, and neuropathy) (Knottnerus et al., 2009; Santos et al., 2012; De Silva and Faraci, 2016; Gupta and Bhatnagar, 2015; Lee et al., 2016; Zafrani and Ince, 2015). These diseases are expressions of advanced microvascular dysfunction (MVD). However, MVD may develop already early, determined partly by factors like genetics, low birth weight, physical inactivity, and obesity. This early MVD can contribute to 1) augmented peripheral resistance, which may lead to the development of hypertension, and 2) impaired insulin-mediated glucose uptake, contributing to insulin resistance and finally the development of type 2 diabetes (Jonk et al., 2007). The latter will result in hyperglycemia as a consequence of MVD. However, hyperglycemia can also (further) impair microvascular function, constituting a positive feedback cycle.

In this review we shall discuss important evidence showing that MVD may precede and predict (pre)diabetes and related co-morbidities, and discuss the important determinants of early MVD. In addition, we shall discuss hyperglycemia being both a cause and consequence of MVD. Finally, we shall focus on prevention and treatment strategies for MVD.

2. The microcirculation: definition and function

The microcirculation can be defined, based on anatomy, as blood vessels with a diameter of less than circa 150 μm, including arterioles, capillaries, and venules. Alternatively, the definition can be based on vessel physiology, and include also larger arterioles that respond to increased pressure by a myogenic reduction in diameter (Levy et al., 2001). By approximation, the microcirculation represents 95-98% of the total circulatory system, underlining its importance in vascular physiology. The three types of vessels have different functions. Arterioles are important for blood flow regulation and distribution, as well as pressure regulation. The exchange of oxygen and nutrients and waste products within tissues takes place in the capillaries. Venules play a role in hydrostatic (capillary) pressure regulation and in tissue repair and defense, as this is the preferential site in the circulation for adhesion and extravasation of circulating stem cells and immune cells (Aird, 2007a). The main function of the microcirculation is to deliver on demand oxygen, nutrients, and metabolites to tissues (Johnson et al., 2008). In addition, the microcirculation is important in reducing systemic blood pressure to low levels in the capillary in order to balance with oncotic pressure (Levy et al., 2001). A central mechanism that efficiently accommodates these functions is vasomotion. Vasomotion is defined as rhythmic changes in (arteriolar) diameter, and results from integration of local tissue (e.g. CO2, adenosine), circulating (e.g. hormones, cytokines), and neurogenic

* Corresponding author at: Dept. of Internal Medicine, MUMC+, PO Box 5800, AZ Maastricht 6202, the Netherlands.
E-mail address: b.houben@maastrichtuniversity.nl (A.J.H.M. Houben).

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signals. Normal microvascular function (MVF) can be defined as optimal performance of the arterioles, capillaries, and venules to accommodate their respective functions. Microvascular dysfunction (MVD) can be defined as any suboptimal performance of one of the components, leading to a compromised nutrient delivery and/or vascular integrity. Notably, MVD comprises endothelial dysfunction, as the endothelium is a key player in the regulation of perfusion and exchange with tissues.

3. Assessment of microvascular function

Techniques to measure the human microcirculation (i.e. arterioles, capillaries, venules) noninvasively can be divided in direct and indirect approaches (Houben et al., 2017). Direct measurement of the microcirculation can be performed by visualization of small blood vessels using a microscopic approach in combination with (digital) photo/video recording. Using this approach one can visualize superficial capillaries in skin and arterioles, capillaries, and venules in sublingual mucosa, bulbar conjunctiva, and in the retina. The main advantage of this approach is that one can directly observe structure and function of (individual) blood vessel(s). Indirect methods to study the microcirculation allow measurement of specific characteristics of (dynamic) function of the microcirculation. Examples of such dynamic functions are blood flow/perfusion measurements using laser-Doppler flowmetry (skin) or plethysmography (skin and muscle), transcutaneous oxygen pressure measurements ($tcpO_2$; skin), blood oxygenation and hemodynamic measurements using near-infrared spectroscopy (NIRS; skin, muscle, brain), and tissue microvascular blood flow (MBF) and blood volume (MBV) measurements using contrast-enhanced ultrasound (CEUS; adipose tissue, muscle, kidney, liver, heart) (Emanuel et al., 2020), although the latter involves infusion of a contrast agent, disavowing the non-invasive character of the technique. In order to test (maximal) dynamic response capacity of the microvasculature, various stimuli may be used. For example, flicker light exposure can be used to induce reactive hyperemia in the retinal microvasculature. This response involves neurovascular coupling and is partly dependent on endothelial NO production (Dorner et al., 2003). Another example is provoking reactive hyperemia in skin following ischemia (by local arterial occlusion) or during local skin heating, which can be measured with laser-doppler-based techniques. These responses also depend on endothelial vasodilator factors (e.g. NO, EDHF, prostaglandins) (Roustit and Cracowski, 2013). Use of pharmacological approaches makes it possible to stimulate or inhibit specific parts of the microvascular wall. Systemic or local infusion of drugs, or via iontophoresis, preferentially targets microvascular endothelium (e.g. acetylcholine, endothelin-B receptor blockers) or smooth muscle cells (e.g. sodium nitroprusside). The subsequent responses (vasodilation/constriction and increased/reduced perfusion) can be monitored with both direct and indirect techniques.

Finally, the phenotype of the endothelium is heterogeneous along the vascular tree (Aird, 2007b). Hence, (re)activity of the endothelium to stimuli, including the production of vasoactive substances, differs between large and small arterioles or venules. Therefore, caution is required when comparing (the results of) the various techniques, as they measure different vessel types within the microcirculation or measure in different domains. On the other hand, combining information from different domains may be complimentary and improve for instance the diagnosis of a disease (Tan et al., 2019). Finally, the regulation of microvascular function differs among tissues, depending on their function and nutritional demand. The brain and kidney microvasculature, for example, are characterized by a low impedance as opposed to that of skin or muscle, and the retinal microcirculation lacks sympathetic innervation (Gardiner et al., 2007).

Assessment of peripheral artery endothelial function (e.g. flow-mediated dilation (FMD) of the brachial artery or finger arterial tonometry) may also partly reflect microvascular function. In these tests, the induced ischemia triggers microvascular dilation which results upstream in increased flow and shear stress in the feeding arteries. The subsequent arterial dilation is dose dependently related to the amount of shear stress on the arterial endothelium (Thijssen et al., 2011; Flammer et al., 2012; Bruyndonckx et al., 2013). In that sense, these measurements rely on both microvascular function and arterial endothelial function.

3.1. Recent developments

Advancements in both hardware and software in the past two decades have facilitated further development of techniques to measure microvascular function. This has resulted in combinations of techniques in one device, like combined LDF and $tcpO_2$ (Jonasson et al., 2020) or combined charge-coupled device (CCD) and LDF (laser speckle contrast imaging) (Roustit and Cracowski, 2013). The retinal Dynamic Vessel Analyzer is an example of advances in online computer-aided analyses of microvascular responses, which has proven its value in epidemiological research and clinical trials (Sörensen et al., 2016; Nägele et al., 2018; Günthner et al., 2019). Finally, optical coherence tomography (OCT) imaging has been introduced into the microvascular arena to visualize capillaries in the retina or microvessels in the skin (Kim et al., 2018; Men et al., 2018). Some of these developments have already proven their value, others need additional evaluations.

Obtaining and analyzing large datasets of microvascular measurements is a big challenge (Li et al., 2020a). In particular, image analyses can be very laborious. For some of the measurements (semi-)automated applications have been developed to analyse images. Apart from saving time, this approach has the advantage of improving reproducibility and being user-independent. For automatic analyses of retinal diameters, several applications have been developed (Cheung et al., 2011; Romeny ter Haar et al., 2016; Welikala et al., 2017). A promising development in this field is the use of machine / deep learning to predict for instance retinal diameters. Machine learning, and its extension deep learning, includes training computers in recognizing (predictive) patterns and refining these from a large example dataset. Using such an approach, we have recently shown that a convolutional neural network can predict retinal arteriolar and venular diameters relatively well (ICC: 0.81 and 0.89 respectively) (Heslinga et al., 2019). Finally, results of deep learning approaches may also teach us new associations between (retinal) microvascular and other anatomical features and cardiovascular risk factors. Poplin et al. (2018) used fundus photos and clinical data of almost 285,000 people to develop a deep learning model. The model could accurately predict several cardiovascular risk factors like age, sex, and SBP from a fundus photo. Interestingly, the deep learning models also produced heat maps indicating which anatomical features in the image were used to predict a specific risk factor. Thus, certain microvascular features proved highly predictive of age, smoking, and SBP. In contrast, for the prediction of DBP or BMI other anatomical features were used. Such findings may help in understanding how specific characteristics or risk factors may affect the microvasculature.

4. Important drivers of MVD

Dysfunctioning of the microcirculation can occur already early in life (Touwslager et al., 2012; Lona et al., 2020) and may have various determinants (Sörensen et al., 2017b). Non-modifiable determinants of MVD are amongst others genetics, low birth weight, and aging; (potentially) modifiable determinants are physical inactivity and overweight/obesity. (Fig. 1). Here we discuss a few examples.

4.1. Genetics

Hypertension is (partly) an inherited disorder. Thus, the presence of MVD in offspring of hypertensive parents suggests that genetic factors are involved. Indeed, offspring (both normotensive and hypertensive) of hypertensive parents have a lower number of capillaries and impaired capillary recruitment and microvascular reactivity (Noon et al., 1997; Antonios et al., 2003). In addition, a blunted

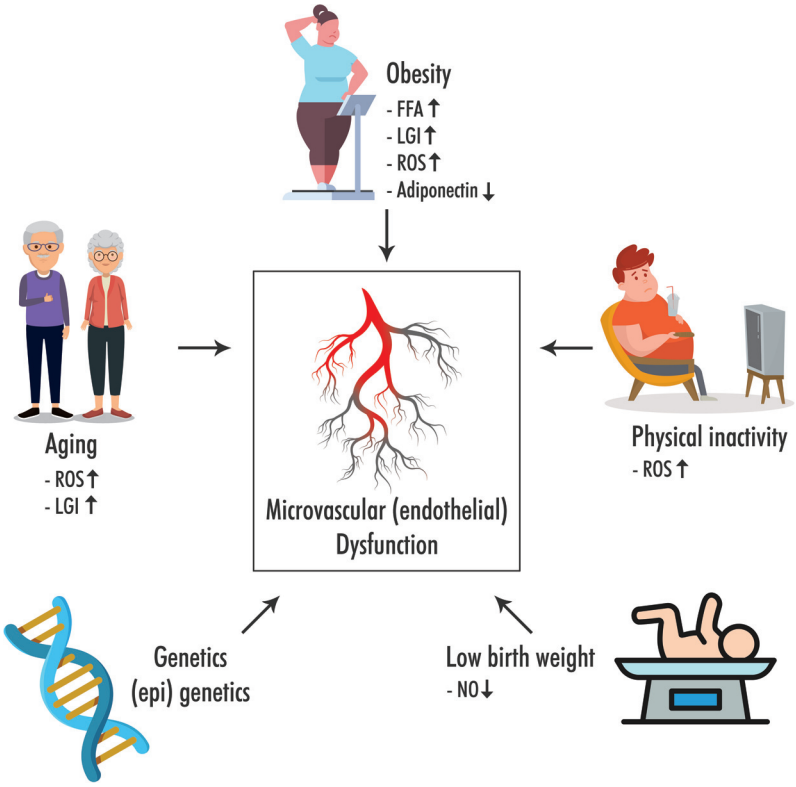

Fig. 1. Drivers of microvascular dysfunction (MVD). Both modifiable (obesity and physical inactivity) and non-modifiable (genetics, low birth weight, and aging) determinants contribute to the development of early microvascular/endothelial dysfunction. Important underlying mechanisms include oxidative stress and low grade inflammation. FFA: free fatty acids; LGI: low grade inflammation; ROS: reactive oxygen species; NO: nitric oxide.

glomerular filtration reserve in response to amino acids infusion was observed in normotensive offspring of hypertensive parents, being indicative of renal MVD (O'Connor et al., 2001). Epigenetic influences on microvascular function, which may be considered a modifiable determinant, were recently demonstrated by Streese et al (2020). In elderly subjects with increased cardiovascular risk, they studied the effect of high intensity interval training on promotor DNA methylation of a mitochondrial protein ($p66^{Shc}$) that contributes to reactive oxygen species (ROS) production and on retinal microvascular diameters. The training programme reduced oxidative stress by methylation of the promotor DNA of $p66^{Shc}$ and improved retinal microvascular diameters.

4.2. Low birth weight

The developmental origins of adult disease hypothesis, introduced by Barker (1995), proposes that cardiometabolic diseases in adult life are associated with low birth weight as a result of fetal malnutrition. In a study sample of 102 healthy term newborns we demonstrated that (endothelium-dependent) skin microvascular responses to acetylcholine were associated with body size (represented by head circumference) (Touwslager et al., 2012). A similar association was found with body weight (Martin et al., 2000). This may be explained by reduced NO synthesis. Interestingly, it was shown that accelerated infant growth was inversely associated with endothelial function at later age for both children born after natural conception and born after IVF/ICSI treatment (Touwslager et al., 2015; Zandstra et al., 2020). In prepubertal children it was shown that capillary recruitment was inversely associated with birth weight (Ijzerman et al., 2002; Bonamy et al., 2007). Finally, in pre-term born adults a reduced skin capillary number (Lewandowski et al., 2015) and narrower retinal arterioles (Hellström et al., 2004) were demonstrated.

4.3. Aging

Aging is characterized by a progressive loss of functional reserve capacity in the (micro)vasculature, in which inflammation and oxidative stress are important drivers (El Assar et al., 2013). Interestingly, the capacity to adapt to mechanisms of aging differs among vascular territories, as demonstrated in a rat model (El Assar et al., 2018). Endothelial-mediated vasorelaxation showed a progressive decline with increasing age, with an earlier onset in aorta and coronary arteries as opposed to mesenteric arteries and corpus cavernosum (El Assar et al., 2018). In a population-based cohort study, we have shown that age is independently associated with both retinal and skin microvascular function (Muris et al., 2014; Sörensen et al., 2017b). In addition, follow up data from another population-based study showed a decline in retinal microvascular diameters with increasing age (Myers et al., 2012).

4.4. Physical inactivity

Several population-based cohort studies have shown that low levels of physical activity are associated with wider retinal venules (Tikellis et al., 2010; Anuradha et al., 2011a, 2011b). In addition, low levels of physical activity have been associated with skin microvascular dysfunction in individuals with type 2 diabetes (Sörensen et al., 2020). Such associations can already be seen at a young age, as was demonstrated in a cohort of 6-year old children (Gopinath et al., 2011). The effect of physical inactivity on MVD is almost instantenuous, as MVD was demonstrated in healthy volunteers already after 5 days of bedrest (Hamburg et al., 2007). In contrast, several weeks of exercise training can improve skin microvascular function, as was demonstrated in a meta-analyses of studies in older previously untrained subjects (Lanting et al., 2016). Similar results were found in a group of elderly sedentary subjects, who showed improved retinal diameters after a 12 week high intensity interval training program (Streese et al., 2020). In parallel to the microvascular improvements, a reduction in oxidative stress levels was observed, supporting the concept that exercise reduces oxidative stress levels with consequently higher bioavailability of NO (Gielen et al., 2010).

4.5. Overweight and obesity

The presence of MVD, characterized as reduced retinal arteriolar or increased venular diameters, in overweight and obesity can already be demonstrated at a young age (Siegrist et al., 2014; Rijks et al., 2018)

and has been shown to be reversible by a healthy lifestyle (Siegrist et al., 2014). In obese adult individuals MVD has been demonstrated in the retina as well (Boillot et al., 2013) and additionally as reduced skin capillary recruitment (de Jongh et al., 2004) and impaired skin and muscle endothelium-dependent vasodilation (Jonk et al., 2011a; Steinberg et al., 1996). In some of these studies the amount of adipose tissue appears to be correlated with the level of MVD (Muris et al., 2014; Rijks et al., 2018). Enlarged and dysfunctional adipose depots can contribute via several mechanisms to MVD: higher levels of circulating free fatty acids, increased inflammatory signaling, and changes in adipokine profile (e.g. more angiotensinogen, leptin, and resistin; and less adiponectin and omentin) (Saxton et al., 2019). MVD in obesity contributes to relevant clinical consequences such as impaired insulin-induced glucose uptake and raised blood pressure (Jonk et al., 2007). Similar to children, as previously mentioned, MVD in obesity can be (partly) reversed by changes in lifestyle. In a recent trial we have shown that the adverse effects of MVD on insulin-induced glucose uptake could be reversed following weight loss (Kusters et al., 2017).

5. Interplay between hyperglycemia and MVD

Diabetic microangiopathy, leading to clinical complications as retinopathy, nephropathy, and neuropathy, is an advanced stage of MVD and structural microvascular damage. Hyperglycemia plays an important role in the development and progression of diabetic microangiopathy. Studies have shown that reducing the levels of hyperglycemia results in delayed development and progression of these diabetic microvascular complications (Zoungas et al., 2017). The damaging effects of hyperglycemia on microvascular function start already early in the course of diabetes, even before its clinical establishment (prediabetes). We have shown that early MVD, in retina, skin, and brain, is present in prediabetes, is augmented in diabetes, and is associated with measures of hyperglycemia (Sörensen et al., 2016; van Agtmaal et al., 2018; Li et al., 2020b). Using mediation analyses, we demonstrated that hyperglycemia is the main contributor to (pre)diabetes-associated MVD in skin and retina (Sörensen et al., 2017a). These data indicate that subtle levels of hyperglycemia may already contribute to MVD and subsequent development of complications before the onset of clinical diabetes. This ticking clock parallels that of increased coronary heart disease risk in prediabetes, as described three decades ago (Haffner et al., 1990). Furthermore, these data indicate that hyperglycemia-induced MVD seems to be generalized. Besides damage to the retina and the kidney, other organs may suffer from MVD. Indeed, markers of MVD have been shown to be associated with cognitive decline and with prevalent and incident depressive symptoms (Rensma et al., 2020; Geraets et al., 2020).

The mechanisms responsible for hyperglycemia-induced MVD have been described extensively (Brownlee, 2001; Schalkwijk and Stehouwer, 2020). In short, the endothelium is the first tissue to be exposed to hyperglycemia. Being equipped with GLUT1 transporters, endothelial cells will freely take up glucose independently of insulin. The increase in intracellular glucose will not only upregulate the glycolytic pathway with overproduction of superoxide by the mitochondrial electron-transport chain, but also upregulate parallel pathways: the glycation, the protein kinase c, the hexosamine, and the sorbitol pathways. This leads to augmented intracellular levels of reactive oxygen species, reactive dicarbonyls (e.g. methylglyoxal), glucosamine, and activation of protein kinase C. Finally, these products will result in decreased bioavailability of NO and increased production of endothelin-1, representing MVD and increasing risk of atherosclerosis.

In contrast to hyperglycemia causing MVD, there is also proof of the reverse. MVD leads to attenuated insulin-mediated glucose disposal (Muris et al., 2013). Following a meal, the microcirculation is instrumental in distributing the absorbed nutrients to specific tissue for use or storage. Glucose is primarily stored in skeletal muscle (±85%) for which insulin is required (Defronzo et al., 1981). As a first step, insulin binds to microvascular endothelium, stimulates the PI3-kinase Akt eNOS pathway in order to produce NO and induce arteriolar dilation and augmented vasomotion, finally resulting in functional capillary recruitment. As a result, exchange surface capacity is increased and glucose together with insulin can cross the capillary wall into the tissue. Disturbance of this insulin-mediated capillary recruitment pathway, as observed in obesity (Clerk et al., 2006; Kusters et al., 2017), contributes to disturbed insulin-mediated glucose disposal, insulin resistance, and finally type 2 diabetes. The latter has been supported by a meta-analysis of longitudinal studies, in which it was demonstrated that individuals with MVD at baseline had a 25% higher risk of developing type 2 diabetes within a mean of seven years. (Muris et al., 2012).

In summary, the relation between MVD and hyperglycemia is bidirectional (Fig. 2). MVD contributes to the development of hyperglycemia and vice versa hyperglycemia contributes to the development of MVD. In this way both mechanisms reinforce each other leading to a vicious cycle (Stehouwer, 2018). Notably, a similar cycle appears to exist between blood pressure and MVD (Lona et al., 2020).

6. Treatment of MVD

Lifestyle may contribute to two determinants of MVD, physical inactivity and overweight/obesity. Hence, changes in lifestyle, albeit not simple, are a good target to improve normal microvascular function and consequent glucose metabolism.

6.1. Weight loss

Examples of studies that applied lifestyle changes in individuals with type 2 diabetes are the DiRECT and the Look AHEAD trial. In the DiRECT (Diabetes Remission Clinical Trial), a (diet based) weight loss intervention programme in the primary care setting, resulted in a remission to a non-diabetic state in 50% of the participants after one year and in 36% after two years (Lean et al., 2018, 2019). In the Look AHEAD (Action for Health in Diabetes) trial, a weight loss and exercise intervention study, persons with a reduction in weight loss of >10% in the first year had a 21% lower risk of CVD in 10 years follow up (Look AHEAD Research Group, 2016). In addition, the weight loss and exercise intervention was associated with improvements in, amongst others, renal outcome and depression (Rubin et al., 2014; Look AHEAD Research Group, 2014). These data underline the importance of lifestyle interventions to improve cardiometabolic health. Whether these improvements in both trials are linked to improvements of MVD, remains to be studied. However, as mentioned previously, we have shown in abdominally obese men that a ~10% reduction in body weight, induced by a low caloric diet for 8 weeks, improves insulin-mediated capillary recruitment in muscle and retinal diameters together with a reduction in insulin resistance (Kusters et al., 2017; Joris et al., 2017). Finally, bariatric surgery-induced weight loss is also accompagnied by sustained improvement of retinal arteriolar diameters (Streese et al., 2019; Martín-Rodríguez et al., 2014). In one study, the improvement of skin microvascular function was indepently associated with improvement in HDLc and reduction in oxLDL levels (Martín-Rodríguez et al., 2014).

6.2. Physical activity

Observational studies have shown that high levels of sedentary time and low levels of high-intensity physical activity are independently associated with higher risk for the metabolic syndrome and type 2 diabetes (van der Velde et al., 2018), and with wider retinal venules (Tikellis et al., 2010). Vice versa, higher levels of physical activity are associated with better skin microvascular reactivity in individuals with but not in those without type 2 diabetes (Sörensen et al., 2020). In a recent randomized controlled trial the effects of exercise on MVD were studied. Eighty-four elderly sedentary subjects were randomized to either a 12-week high intensity interval training program or standard physical activity advices. The exercise program improved retinal arteriolar

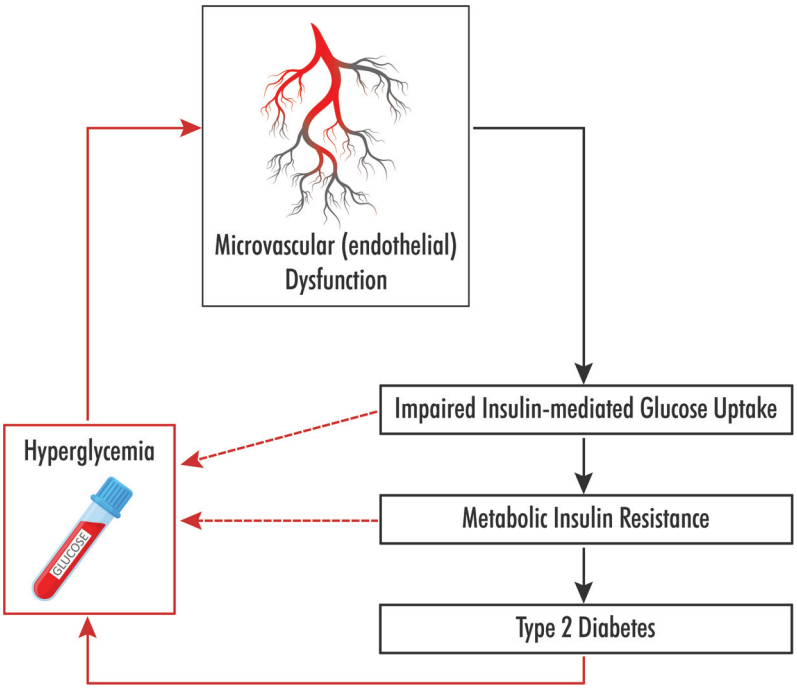

Fig. 2. Interplay between hyperglycemia and microvascular dysfunction (MVD). MVD contributes to impaired insulin-mediated glucose uptake, predominantly in skeletal muscle. In addition, MVD contributes to subsequent metabolic insulin resistance and the development of type 2 diabetes. All these stages of disturbed glucose metabolism result in hyperglycemia which leads to MVD. Both mechanisms reinforce each other leading to a vicious cycle.

and venular diameters independent of changes in BMI and blood pressure; fasting glucose levels were unchanged (Streese et al., 2020). These data support the concept that physical activity improves both MVD and glucose metabolism independent of concomitant weight loss and blood pressure lowering. The contraction of muscle not only increases blood flow but also recruits capillaries, thereby increasing the exchange surface area. In addition, muscle contraction stimulates the translocation of GLUT4 to the plasma membrane of muscle cells, thereby increasing glucose uptake. (Clark et al., 2003). Exercise-stimulated glucose uptake and insulin-mediated glucose uptake are additive, which may be related to different signaling cascades. In case of exercise via AMPK, and in case of insulin via PI3-kinase Akt pathways (Richter et al., 2001).

6.3. Drugs

6.3.1. Antihyperglycemic drugs

Since hyperglycemia is a major driver of MVD and MVD is strongly associated with (pre)diabetes, drugs that lower blood glucose levels are expected to attenuate MVD. As mentioned above, it has been shown that reducing hyperglycemia leads to a reduction of diabetic microvascular complications (Zoungas et al., 2017). However, independent of their glucose lowering effect, some of these drugs directly affect the microvasculature (Triggle et al., 2020). For example, long-term metformin treatment was shown to reduce plasma endothelial biomarkers (de Jager et al., 2014) and a 12 week treatment with metformin significantly improved endothelium-dependent microvascular dilation in type 2 diabetic patients (Mather et al., 2001) and large artery endothelial function in type 1 diabetic patients (Pitocco et al., 2013). These effects may be related to a reduction in ROS levels by metformin (Apostolova et al., 2020).

Thiazolidinediones, which are PPAR- γ agonists and insulin sensitizers have been shown to exert anti-inflammatory and anti-oxidative stress effects at the endothelial level (Wang et al., 2016). PPAR- γ overexpression in endothelial cells results in elevated NO levels (via de PI3-kinase pathway) and decreased ET1 levels (via the MAPK pathway) (Marx et al., 2004; Kong et al., 2019). Similar beneficial effects of thiazolidinediones treatment on arterial endothelial function were demonstrated in a placebo-controlled trial in patients with coronary artery disease and newly detected type 2 diabetes (Sourij et al., 2006).

Sulphonylureas bind to the sulfonylurea receptor and close the ATP-sensitive potassium channels. These receptors are also present in vascular smooth muscle cells and stimulation leads to vasoconstriction. Indeed this has been shown in an animal model (Cyrino et al., 2003), but the effect was only seen with glibenclamide and glimepiride, and not with gliclazide. In two trials the effects were studied of sulfonylurea treatment on arterial stiffnes and endothelial function, and on microvascular function (Cosenso-Martin et al., 2018; Jax et al., 2017). Both trials showed that sulfonylurea treatment did not affect macro- or microvascular function.

Alpha-glucosidase inhibitors act predominantly in the bowel, where they attenuate the break down of complex carbohydrates into glucose. Although direct vascular effects of these drugs are not obvious, some studies reported protective effects of alpha-glucosidase inhibitors on endothelial cells via reduction of oxidative stress (Aoki et al., 2012; Li et al., 2019). A twelve-week treatment of type 2 diabetic individuals with acarbose resulted in increased postprandial arterial endothelial function (Kato et al., 2010). However, this effect was suggested to be secondary to reduced hyperglycemia.

In healthy volunteers, infusion of glucagon-like peptide 1 induces capillary recruitment in both skeletal and cardiac muscle and concomittant glucose disposal, similar to insulin (Tan et al., 2018). These GLP-1 effects are preserved in insulin resistant obese subjects (Wang et al., 2020), which may be related to the fact that GLP-1 stimulates endothelial function via the AMPK pathway. Besides the microvascular effects of GLP-1 in skeletal and cardiac muscle, treatment with GLP-1 receptor agonists can reduce the incidence and progression of nephropathy (mainly albuminuria) in diabetes, but not that of retinopathy (Dicembrini et al., 2017).

Exposure of endothelial cells in a hyperglycemic milieu to dipeptidyl peptidase-4 (DPP-4) inhibitors shows a reduction in oxidative stress levels (Gao et al., 2020; Pujadas et al, 2017). In addition, endothelium-dependent relaxation of aortic rings from diabetic mice treated with DPP-4 inhibitors was normalized as compared to untreated mice (Gao et al., 2020). This effect was independent of any GLP-1 effects on the vasculature. Individuals with uncomplicated type 2 diabetes treated with DPP-4 inhibitors also show improved skin microvascular vasodilation, which seems to be independent of glucose control (Jax et al., 2017). The effects of DPP-4 inhibitors on large artery endothelial function, however,

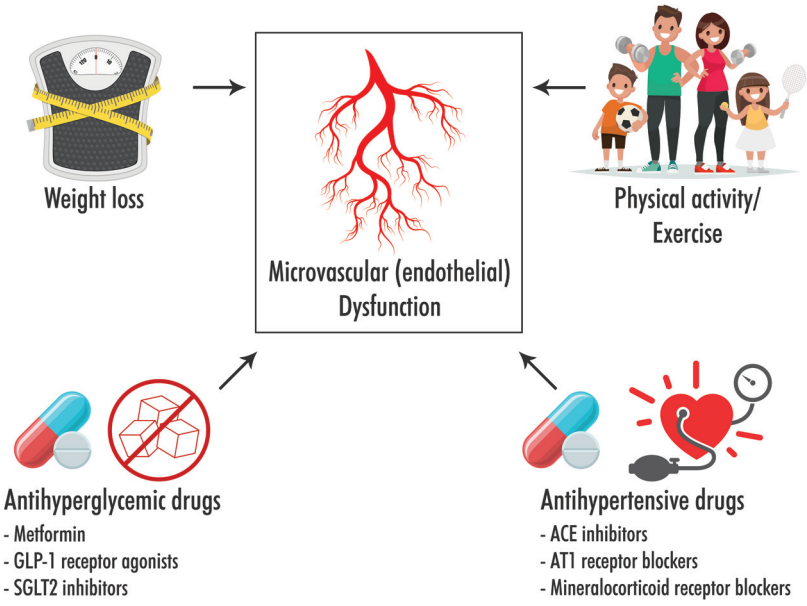

Fig. 3. Treatment of microvascular dysfunction. Both lifestyle (weight reduction and increased levels of physical activity/exercise) and pharmacological interventions (antihyperglycemic and antihypertensive drugs) are effective in reducing microvascular/endothelial dysfunction. Notably, the effects of the drugs mentioned on MVD appear to be independent of their antihyperglycemic or antihypertensive effects.

is unclear as unchanged, attenuated, and increased endothelial function has been reported (Jax et al., 2017; Ayaori et al., 2013; Leung et al., 2016).

Sodium glucose cotransporters type 2 (SGLT2) are present in mouse aorta and inhibition of SGLT2 results in reduced ROS levels and improved endothelium-dependent dilation via blockade of endothelial glucose entry (El-Daly et al., 2018). Adding SGLT2 inhibitors to the treatment regimen of diabetic patients also improved endothelial function, determined as flow-mediated dilation of the brachial artery (Shigiyama et al., 2017), although similar effects could not be demonstrated in a trial using peripheral arterial tonometry to estimate endothelial function (Tanaka et al., 2019).

6.3.2. *Renin angiotensin aldosterone system drugs*

Angiotensin II has been shown to have detrimental effects on endothelial function. An important effect of angiotensin II is stimulation of ROS production. In addition, angiotensin II stimulates endothelin-1 production, release of inflammatory cytokines, and phosphorylation of IRS-1. All these processes interfere with insulin-dependent activation of the PI3-kinase pathway, resulting in inhibited NO synthase and glucose uptake (Jonk et al., 2007). Blocking the angiotensin II receptor in hypertensive subjects indeed improves insulin-mediated microvascular function (Jonk et al., 2011b). Blocking the conversion of angiotensin I to angiotensin II by an ACE inhibitor or blocking the angiotensin II receptor both have been shown to decrease the risk for new-onset diabetes mellitus in hypertensive patients (Elliott and Meyer, 2007). Similar to angiotensin II, aldosterone attenuates endothelial function via stimulation of oxidative stress, and endothelin-1 and TNFa production (Schütten et al., 2017). Indeed, in animal models of obesity it has been shown that mineralocorticoid receptor blockade improves endothelial function (Bender et al., 2015). In individuals with type 2 diabetes mineralocorticoid receptor blockade was shown to improve coronary microvascular function (Garg et al., 2015). However, in mild abdominally obese men plasma aldosterone levels were not associated with MVD and levels of insulin resistance (Schütten et al., 2018). Possibly the negative effects of aldosterone on microvascular function and related glucose disposal become more prominent in more severe obesity.

In summary, both lifestyle and pharmacological interventions are effective in reducing MVD (Fig. 3) and contribute to restoring normal glucose metabolism. Whether the combination of lifestyle intervention and glucose lowering therapy will have a multiplier effect on MVD is currently being addressed in a randomized clinical trial: ePREDICE (Gabriel et al., 2020).

7. Conclusions and future directions

Early microvascular dysfunction contributes to disturbed glucose disposal and augmented blood pressure, and in the long run to the development of cardiometabolic diseases. Important drivers of MVD are obesity and physical inactivity, in addition to genetic factors and low birth weight. The interaction between MVD and hyperglycemia operates in two directions. MVD contributes to hyperglycemia and hyperglycemia induces MVD, culminating in a vicious cycle. Hyperglycemia-related MVD is widespread and results in dysfunction of various organs. Lifestyle changes, e.g. weight loss and exercise, are effective strategies to reverse MVD in metabolic disease, and can also reverse diabetes. In addition, using antihyperglycemic medication not only breaks the aforementioned vicious cycle, but directly leads to improved microvascular function. Finally, drugs blocking the production or action of angiotensin II are effective in improving MVD. Technical developments in the past decades have advanced the measurements of MVD in clinical trials and on an epidemiological level. Finally, the presence of isolated diabetic microvascular disease (retinopathy, nephropathy, or neuropathy) has been shown to increase the risk of future cardiovascular events, which is even higher in individuals with disease in multiple microvascular beds (Brownrigg et al., 2016). Similarly, early MVD increases the risk of (pre)diabetes and hypertension (Muris et al., 2012; Ding et al., 2014), both being important risk factors for cardiovascular disease. A future challenge is the development of a personalized microvascular fingerprint for risk stratification and preventive strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Alfons J.H.M. Houben: Conceptualization, Writing - original draft. **Coen D.A. Stehouwer:** Conceptualization, Writing - review & editing.

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Peer Review Summary

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