Microcirculation in insulin resistance and diabetes: more than just a complication

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SUMMARY

The microvascular bed is an anatomical entity which is governed by specific, highly regulated mechanisms which are closely adapted to the specific function of each vascular segment. Among those, small arteriolar vasomotion and capacity of small vessels to constrict in response to physical and humoral stimuli play a major role. Other processes of importance for the adequacy of nutritive perfusion are haemorheological properties of whole blood and red cells, adhesiveness of leukocytes and capillary permeability. This review provides some description of these phenomena, how they impact on organ function and how they appear in diabetes.

Metformin, as a unique example among the drug arsenal, exerts various effects preferentially at the level of smallest vessels (arterioles, capillaries, venules). This review summarises our actual knowledge and includes several new data showing its high potential for reducing microvascular dysfunction. Most of these unique properties have also been demonstrated in non-diabetic animals or humans, suggesting they are intrinsic to the drug and not secondary to diabetic metabolic improvement. A particular focus is put on the relevance of metformin’s capacity to stimulate slow wave arteriolar vasomotion and improve functional capillary density, whereby nutritive flow can be re-established.

Finally, the implication of microcirculation in other aspects of insulin resistance and diabetes, such as macroangiopathy and metabolic control, is discussed and strengthens the concept of a broad involvement of microvascular dysfunction in these diseases as well as the potential interest of introducing adapted treatment early in the history of a patient’s diabetes.

Key-words: Microcirculation · Arteriolar vasomotion · Functional capillary density · Permeability · Metformin.

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Microcirculation: a brief description

The vascular bed can be grossly divided into three main entities: large (macro) vessels, medium (resistance) vessels and small (micro) vessels. Whereas the former are essentially conduit vessels, resistance vessels (diameter 100-500 µm) are primarily involved in the regulation of blood pressure, while the microvascular bed represents the so-called “nutritive” structure. Microcirculation comprises small arterioles, which branch in a tree-like manner into segments of decreasing diameter down to the 5 µm capillaries. These are organised into units, each unit comprising about 15-20 capillaries which depend on a same feeding terminal arteriole [1]. In view of the repetitive branching of the vascular bed, pressure in the narrow vessels is very low, which has evident consequences for blood flow, in particular for haemorheological properties of blood cells.

The microvascular bed therefore represents an entity which is completely different from the macrovascular bed, due to different physiological functions with accompanying specific regulatory mechanisms.

Microcirculation: structural and functional specificities

The main role of microcirculation is to deliver fuel and nutrients to remote cells as well as to exchange waste products with the surrounding tissues. These aspects are also interrelated since the degree of vessel permeability is not only dependent on the vessel wall structure (tight or moderate barriers vs fenestrated vessels) but also on the prevailing hydrostatic pressure across the arteriolar to venular segment. In other terms, the level of arteriolar response to venular tone (in addition to other factors) also dictates blood tissue exchange capacity.

Marked heterogeneity is found among microvascular endothelium, according to the tissue but also within an organ according to the vessel segment within the branching vessels [2, 3]. Pronounced differences in vessel wall structure are observed since smooth muscle cells tend to diminish with decreasing arteriolar diameter, whereas capillaries are only composed of one single endothelial cell layer apposed onto the capillary basement membrane. This is accompanied by adaptive changes in biochemical mechanisms: for example it has been suggested that vasodilatation becomes less dependent on nitric oxide (NO) but more on endothelium-derived hyperpolarising factor (EDHF) with decreasing arteriolar diameter [4]. The reactivity to various agonists is also varying according to the arteriolar segment under study [5]. On the other hand, physiological permeability is strictly limited to the venular end of capillaries. Such examples illustrate the heterogeneity of the microvascular bed and how structure, function and mechanisms are remarkably interrelated. Diabetic microangiopathy is the sum of multiple defects affecting blood cells, their interactions with the vessel wall, the reactivity of the vessel wall and its anatomical structure [6]. In the following sections some mechanisms which are specific of microvascular physiology will be highlighted for their importance in clinical pathology (especially in diabetes) and some unique and direct effects of metformin will be described.

Vasoconstriction is not necessarily bad!

Watching the microcirculation in situ reveals to the new investigator a picture of constant changes in blood flow within some seconds: filled capillaries coexist with “empty” ones, periodic flow (fluxmotion) is seen as well as sudden changes in flow direction. Such a pattern gives the misleading impression of a chaotic, uncontrolled situation; however this picture in fact just reflects an extremely complex but finely regulated distribution of microflow where amount, velocity and direction of flow permanently adapt to local needs. Obviously this is only made possible due to very specific crosstalk of metabolic, physical, humoural and nervous mechanisms operating in smallest dimensions. In the microvascular bed, therefore, not quantity but distribution of blood is the primary determinant.

That vasoconstriction is in the heart of these processes might at first sight sound paradoxical. Indeed most literature on vascular haemodynamics and reactivity deals with dilatation. While it is indeed of utmost importance in large vessels (amount of blood), the microvascular bed must prevent excessive blood entering the tiny vessels, thereby avoiding capillary hypertension and increased permeability. It is indeed noteworthy that, in sharp contrast to large vessels, the main physiological mechanisms governing the adaptation of flow to local factors (metabolic needs, transmural pressure) rely on constriction of the arterioles, eventually venules [7]. These are: a) the arteriolar myogenic response, whereby transmural pressure such as in exercising muscles is transmitted to the vessel wall, b) the venoarteriolar reflex, whereby signals from the venular end induce arteriolar constriction to prevent capillary hypertension and c) precapillary arteriolar vasomotion (see below).

The myogenic response adjusts the tone of the small terminal arterioles within a narrow range around normal blood pressure [8, 9]. All three mechanisms participate, at various times and to a variable extent, to the adaptive regulation of nutritive flow. The daily physiological stimuli to which microcirculation must respond are mainly local tissue metabolic needs and physical changes such as upright positioning. In the legs, the latter will induce an increase in hydrostatic pressure, to which some sensors in the veins will signal the arterioles to constrict. Thereby capillary hyperperfusion and subsequent hypertension are prevented [10]. This crucial phenomenon has been found deficient in both types of diabetes and has become famous as the “haemodynamic hypothesis” [11, 12]. It is enhanced in the presence of neuropathy [13]. The number of daily postural changes points to the potential importance of this phenomenon, which appears to be deficient.
very early in the disease [14, 15]. The capacity of the arteriole to constrict is crucial, since venous hypertension will cause increased filtration and oedema if not compensated for by a reduction at the inflow level, i.e. the arteriole [16]. Conversely, a minimal capillary venous pressure is a requisite for capillary perfusion [17]. Diabetes, in particular in its early phase, is characterised by a hyperdynamic circulation linked to insulin resistance [18] and several investigations have found abnormally elevated blood flow in early periods of diabetes. However, it must be realised that these measurements are usually performed with techniques whose accuracy does not allow to follow-up nutritive flow. Indeed it has been shown that for its main part this increase in organ flow occurs through dilated shunt pathways, whereby true capillary flow is reduced. It is thus crucial that arterioles keep their capacity to constrict to prevent maldistribution of blood flow and divert blood into the nutritive pathways. A more detailed overview on this specific concept can be found in a dedicated review [7].

**Arteriolar vasomotion**

**Physiology/pathology**

When microcirculation is observed in vivo, most tissues exhibit rhythmic changes in arteriolar diameter, the so-called vasomotion phenomenon. The typical physiological vasomotion is a slow-wave, high amplitude variation in diameter with a frequency of 1-10 Hz. Its meaning has been a matter of many debates but the fact that it is easily observed in most healthy organs and disappears in a number of pathological situations supports a physiological role for vasomotion. In particular, slow-wave vasomotion has been postulated to fill capillary units in an alternating fashion in order to economize the amount of blood flowing through. Indeed, would all capillaries be permanently blood-filled, there would be no further reserve for covering increased metabolic needs. By doing so, vasomotion therefore also induces some pressure waves which help blood flow through narrow capillaries under prevailing conditions of low pressure. Moreover these waves may well be transmitted to adjacent lymphatic vessels and stimulate the lymph pump [19]. Indeed in vivo examinations show that, at any instant in a resting skeletal muscle, neighbouring capillary units are alternatively filled with whole blood (red cells) [20], leading to an estimate of a permanent 50% perfusion of the whole capillary bed in muscle [21]. The advantages of this chaotic flow pattern over constant flow have been evaluated [22].

Most investigations have shown that slow-wave vasomotion requires the initiation of arteriolar constriction, followed by oscillations of the membrane potential [23]. The underlying mechanisms are still far from elucidated, in particular because the hypothesis of specialised pacemaker cells or pre-capillary sphincters have never been convincingly demonstrated. Recent studies have pointed towards a role for chloride channels, without precise subtype identification [24].

Arteriolar vasomotion is blunted in various pathological situations, in particular diabetes. Investigations in both experimental and clinical diabetes have shown its rapid disappearance [25-27]. Hyperinsulinaemia, possibly via its vasodilating action, also opposes vasomotion [28]. When hyperglycaemia is raised concomitantly, however, vasomotion is stimulated. However, in streptozotocin (STZ)-diabetic rats this effect, which might be of high physiological importance, is blunted [28].

In humans, 47% of diabetic patients without and 82% with neuropathy showed impaired slow-wave vasomotion, a defect appearing very early and correlated with sympathetic dysfunction [29]. This defect has also been described in the leg skin [30] and suggested to be causally involved in the diabetic foot complication [31]. The importance of preserving arteriolar vasomotion under critical perfusion has been illustrated by its influence not only in muscle itself but also for protecting adjacent tissues [32].

**Haemodynamic effects of metformin**

Metformin does not directly affect large vessel tone unless using non-pharmacological drug concentrations [33-35]. However metformin has been shown both in vitro and in vivo to improve vascular reactivity to the endothelium-dependent vasodilator acetylcholine in insulin resistant rats; this effect was independent of the accompanying metabolic improvement [33]. Similar data were obtained in uncomplicated type 2 diabetic patients when using forearm plethysmography [36]. The hypotensive effect of arginine, as an indicator of vasodilation, was potentiated by metformin in newly diagnosed type 2 diabetes free of macro- and microcomplications [37]. In contrast, metformin has the unique capacity of stimulating or restoring arteriolar slow-wave vasomotion. In line with the fundamental aspects (see above) topical application of metformin to the normal hamster cheek pouch (to eliminate possible systemic interfering effects) induced a slight constriction of arterioles, which was accompanied by enhanced vasomotion (Fig 1).

In normal animals, metformin restored vasomotion in the recovery phase from haemorrhagic shock [38] and most drug-treated animals survived. When insulin was applied topically in mildly diabetic hamsters, vasomotion was reduced as expected and restored by coadministration of metformin [39]. In experimental diabetes, metformin restored blunted vasomotion in both mild (Fig 2) and more severe diabetes [26, 39, 40]. Investigations on lymph flow have shown a stimulating effect of metformin [34] possibly explaining the reduction in albumin retention in metformin-treated type 2 diabetic patients [41] and the drastic inhibition of cyclic aedema [42].

Experiments performed either in vitro or in vivo (data not shown) failed to reveal any effect of metformin on NO production as a possible explanation for the tendency towards stimulation of vasomotion. Conceivably, inhibition of the relaxing factor EDHF in small vessels might be a possible mechanism but this can hardly be discriminated in vivo. Using microelectrodes implanted in situ into arteriolar walls
of the hamster cheek pouch, topical metformin was found to depolarise cell membranes by a mean of 5 mV, in agreement with a trend towards constriction (Bouskela, unpublished data). Many different ionic channels could be responsible for the constrictive effect but recently we could show that, in line with data in hepatocytes [43], the effect of metformin could be inhibited by chloride channel blockers (manuscript in preparation); this supports the concept that these ionic channels may indeed underlie arteriolar vasomotion [24] and that this mechanism might apply to metformin.

### Blood rheology/cell adhesion

Increase in plasma and whole blood viscosity, reduction in erythrocyte deformability and enhanced aggregation are established features in diabetes [44] albeit their causal implication in microvascular disorders remains controversial. At the least these haemorheological modifications complicate passage of blood cells through narrow capillaries and slow down blood transit. At the worst, they obstruct the capillary lumen in a manner depending on the ability of erythrocyte aggregates to disintegrate. In situations of shutting-down of capillary pressure this may become crucial, more so if the capillary lumen is reduced [45]. Although not a universal finding, capillary narrowing has indeed been described in diabetes [46]. This could be due to thickening of the capillary base-membrane, a phenomenon found early in most tissues and which rapidly follows hyperglycaemia [47]. Conceivably, thickening of the endothelial glycocalyx could reduce internal capillary diameter as well [48]. This would then further impair red cell velocity and flux and subsequently reduce oxygen delivery by up to 60% despite resting blood flow [46].

Another yet unresolved question is the importance of leucocyte adhesion as a process of capillary plugging [49]. An increased number of slowly rolling with some even adhering to the capillary walls is a common observation in the diabetic microcirculation. This could be due to an increased expression/activity of adhesion molecules such as ICAM-1 or VCAM-1, mostly as a result of prevailing glycation or inflammation. This concept is highly emerging and many recent studies have shown that insulin resistance and diabetes are characterised by elevated levels of C-reactive protein, interleukin-6 and TNF-α as a sign of inflammation [50]. The case is amplified when endothelium is glycated [51].

### Haemorheological effects of metformin

Red cell rheology has been studied both in vitro and in vivo: positive data on erythrocyte aggregation and/or deformability have been reported, although with discrepant findings according to the drug concentrations or to in vitro vs in vivo tests [37, 52-54]. Better cell deformability fits with the improvements in membrane fluidity induced by metformin [55].
In vitro, monocyte adhesion to glycated endothelium is strongly inhibited by metformin, via a reduction in the expression of the adhesion molecules (cf. Mamputu et al., this supplement). In vivo, metformin treatment of hamsters submitted to haemorrhagic shock cleared the capillary bed from adhering leukocytes and thereby maintained an almost normal capillary flow [25]. Post-ischaemic reperfusion is another situation where leukocytes stick to capillary walls; as shown in Fig 3, the degree of adhering white cells was much reduced in metformin-treated animals.

**Nutritive blood flow**

As explained above, within a large physiological range, microvascular flow is much more regulated by various components of flow distribution than by amount of flow. Variations in capillary tube hematocrit, erythrocyte velocity or countercurrent flow are just some of the very characteristic mechanisms whereby nutritive flow is tightly regulated. Capillary recruitment can serve as a first aid mechanism in the event of elevated needs and arteriolar vasodilation can serve as a second process if required. This is typically seen with insulin [56, 57]. Thus the number and degree of cell flow in the capillary bed is a prime determinant; it is termed “functional capillary density” and can be quantitated in situ by calculating the total length of whole blood-filled vessels in a given area under the intravital microscope. Finally it is a mixed quantitative and qualitative estimation of nutritive flow. It is particularly important in situations of sudden elevations in perfusion needs such as in acute exercise or during a post-ischaemic tissue reperfusion period (the no-reflow phenomenon). A good illustration is given by experiments relating functional capillary density to survival from haemorrhagic shock [58].

In basal conditions we found a 50% reduction in functional capillary density in diabetic animals (Fig 4). In human diabetics, the situation may even be worse, due to a capillary rarefaction in the presence of hypertension, which affects most patients. Such a combination would severely increase the diffusion distance of oxygen and glucose from capillaries to target cells. In post-ischaemic situations, capillary recruitment is the main determinant of early reperfusion and,
accordingly, the clinical test of post-occlusion reactive hyperemia (cuff) serves as an index to evaluate the degree of vascular impairment in man. This test has repeatedly revealed defective vascular reactivity in type 2 diabetic patients, even in the absence of vascular complications [59, 60]. Absence of normal reactivity severely limits flow reserve capacity.

**Effects of metformin**

As illustrated in Fig 4, chronic treatment with metformin partially compensates for the reduction in basal functional capillary density in diabetic animals. Obviously this beneficial effect was linked with a basal drug-induced constriction occurring simultaneously in both arteriolar and venular segments.

In post-ischaemic recovery studies, metformin remarkably restored capillary perfusion under haemorrhagic shock conditions [61], which may explain the high rate of surviving animals in the treated group [38]. In mild diabetic animals, post-ischaemic nutritive flow as estimated by functional capillary density was also improved (Fig 5). Noteworthy these effects have been also seen with very low doses of metformin (data not shown). These results support the notion that the main action of metformin must be located at the terminal arterioles and then manifested primarily by an increase in capillary perfusion. This again may likely be explained by activation of arteriolar vasomotion (see above). This hypothesis is further corroborated by experiments performed in normal as well as in diabetic rats where blood flow was measured using various tracers of different size, allowing some discrimination between arterioles and capillaries (J Rapin and N Wiernsperger, unpublished data). Although both indicators showed flow elevation, the tracer used for capillary flow was clearly more augmented than the one for arterioles. The data for the capillary flow are shown in Fig 6. This increase, which occurred similarly in normal and in diabetic rats, was confirmed in other tissues: it occurred in the rat liver (same study), intestine and pancreas [62], as well as in human adipose [63] and uterine tissue [64]. In post-occlusion tests in humans, metformin improved the peak flow in both normal [65] and arthritic, non-diabetic patients [66].

**Vascular permeability**

Permeability is another hallmark of the microcirculation: the intrinsic level of permeation of small vessels is highly variable throughout the body, ranging from very permeable in the splanchnic bed to very tight blood-tissue barriers in organs like brain or retina [67]. Again these structures are adapted to the respective functions of specific tissues and organs. Chronic hyperglycaemia, in particular when advanced glycation endproducts are formed [68] provokes permeability, i.e. extravasation of proteins. The latter may accumulate on the abluminal side and thicken the capillary basement membran-
brane. Hyperpermeability is more particularly known in diabetes in the kidney (micro/macroalbuminuria) and in the retina (proliferative retinopathy exsudates, macular aedema). Increased permeability is postulated to play a key role in initiation or aggravation of diabetic microangiopathy [69].

Effects of metformin

In diabetic hamsters basal increased permeability was reduced by metformin [70]. In diabetic patients, microalbuminuria was also reduced [71]. Albumin retention was shortened by metformin in the lymph compartment of type 2 diabetic patients [41]. However this property has also been demonstrated in non-diabetic situations: in animals, post-ischaemic cheek pouch permeability was drastically inhibited as shown by a remarkable reduction in the number of leaks (Fig 7). This corroborates earlier findings in peripheral and in brain ischaemia-induced aedema formation [54]. Finally, lower limb aedema disappeared in most women suffering cyclic aedema after 6 weeks’ treatment with metformin [42]. Although the exact mechanisms of permeability inhibition by metformin have not been examined yet, beneficial remote effects on hydrostatic pressure due to the venular constriction may be involved.

Additional considerations on metformin effects and their clinical relevance

Microcirculatory effects of metformin are only part of its pleiotropic actions on blood, vessels and related phenomena [55]. However microvascular effects of this drug make it a unique tool because they are selective for this anatomical entity, which is not known for any other drug.

Moreover, they occur independently of the metabolic actions of the drug and therefore apply in a very general way. In view of the crucial importance of microflow, its use to prevent or improve vascular disorders in prediabetes and diabetes appears particularly beneficial. The positive effects exerted by metformin on small vessel regulatory processes are also observed at concentrations equivalent or lower than those required for the metabolic actions. This means that they remain valid even when plasma concentrations fall between daily tablet intakes. They would also apply to cases where metformin is only used as a combination therapy.

On the other hand, we largely ignore what is the reversibility potential of disorders in diabetic vessels according to the severity and/or duration of the disease. Clinical research over the last decade has clearly established that most of the dysfunctions described in detail in this article can be revealed very early in the course of the disease. Especially the pioneering work of J Tooke and his group has shown that many disturbances are already present in states of normoglycaemic insulin resistance, such as IGT or acromegaly [72]. Recent studies have largely corroborated this notion, suggesting that hyperglycaemia is possibly exaggerating disorders which are largely preexisting, albeit not clinically manifest. Should this be further confirmed, as it appears today, it would mean that what is known as diabetic microangiopathy is a disturbance requiring very early intervention, ideally when most troubles are still at a functional level, before structural changes would hamper or prohibit therapeutic drug efficacy.

As an example, the beneficial effect of metformin on microangiopathy in the UKPDS [73] might have been more obvious if its introduction would have occurred earlier in the history of the disease.

Microcirculation in diabetes: its meanings

Actually, microangiopathy is considered as a typical complication of diabetes affecting mainly the eye, the kidney, the nerve and the foot for reasons that are largely unravelled. Diabetic microangiopathy in its clinical presentation is a resultant of haemodynamic defects and anatomical changes of the small vessel walls. The latter are attributable to structural modifications affecting the luminal side (glycocalyx) and the abluminal side (smooth muscle cell proliferation, protein deposi-
tion crosslinking through glycation endproducts, etc.). The respective roles played by the more haemodynamic characteristic changes of microvessels in diabetes vs the more structural ones are difficult to distinguish as they are likely intertwined. Nevertheless, when considering the fundamental role played by the microvascular bed throughout the body, some aspects of which have been detailed here, the participation of functional microvascular disorders must also be considered. Indeed, we must be aware that microcirculation is potentially involved in such a disease, at least at three levels: macroangiopathy, microangiopathy, metabolism. As such, microcirculation is an integral part of microangiopathy, which however does not totally explain the clinical development of diabetic microvascular complications. However, we will briefly analyse how functional microvessel haemodynamic defects could be linked to insulin resistance and be involved in its development towards diabetes and its complications.

**Microcirculation in diabetic micro and macroangiopathy**

Very little is known about the interrelationship between functional and structural changes in diabetic small vessels, as well as about possible pathological thresholds. Indeed, functional defects are known to occur very early in the course of diabetes. It is noteworthy that most metabolic states characterised by insulin resistance—but without fasting hyperglycaemia—also present microcirculatory disturbances (obesity, prediabetes ageing, smoking, thalassemia, low birth weight, postsurgery, etc.). These changes will not, however, translate into microangiopathy such as retinopathy or nephropathy if diabetes does not appear. On the other hand, chronicity of these disturbances may give rise to adaptive and finally deleterious constitutive changes in the microvessel walls. The latter, as for example the very early occurring thickening of capillary basement membrane, may in turn limit their vasoreactive capacity; as a consequence, opening of arterioles and recruitment of capillaries may become deficient in functional hyperaemic states. On the contrary, vasoconstriction may also be insufficient: for example in early diabetic stages, several tissues show exaggerated blood flow, which precedes retinopathy and nephropathy. Impaired vasoconstriction may favour capillary hyperperfusion and permeability.

Another argument for a partial role of haemodynamic defects in diabetic microangiopathy is the failure of even strict metabolic control to completely inhibit the small vessel complications [74-76]. These findings strengthen the need for additional therapeutic approaches, particularly in type 2 diabetes, where many factors other than hyperglycaemia are likely to be involved (hyperinsulinaemia, insulin resistance, dyslipidaemia, hypertension, etc.). Thus, in an animal model of type 2 diabetes, changes in coronary arteriolar structure and function were linked to diminished flow reserve before the appearance of fasting hyperglycaemia [77]. Blood hyperviscosity and erythrocyte rigidity are another problematic component of microcirculation which are able to impair blood passage through the capillary bed [78]. Clearly more research is needed to discriminate the respective roles of functional and structural changes in microvessels.

Large vessels have mainly a supplying role but are the site of the most dramatic, life-threatening accidents in case of atherosclerotic, haemostatic or spastic vessel occlusion. However, their consequences are found downstream of the injury, in particular when reperfusion occurs, namely in the microvascular bed [79]. Fortunately there is now a growing awareness that microcirculation is a key player in macroangiopathy, which can be causal of—or subsequent to—large vessel accidents [80, 81].

**Microcirculation in metabolic control**

Glucose homeostasis is the resultant of its production and utilisation. Insulin resistance in peripheral tissues such as skeletal muscle relies on deficient glucose uptake and glycogen storage. Despite immense efforts, the exact mechanisms of insulin resistance are still to be defined. Conceivably, hampered delivery of glucose or insulin (timely and/or quantitatively) could be another factor explaining postprandial defects underlying insulin resistance. In this period, a maximal glucose amount must reach muscle cells within a relatively short time to be stored as glycogen; a brief look at the anatomy of skeletal muscle cells reveals capillaries lying between muscle fibres, each one diffusing to several surrounding fibres and insulin-sensitive glucose transporters located in the vicinity of the capillaries. It is easy to understand that if there is a defective capillary perfusion or recruitment in this metabolic period, glucose/insulin delivery will be affected.

Conceivably, then, functional microangiopathy could be an integral part of the metabolic syndrome, as proposed by some authors [82, 83]. Usually tissue metabolism and local microflow are tightly coupled, in such a way that flow adapts to the metabolic demand of the surrounding tissue. However, this relation may be bidirectional and, although the definitive proof is still missing [83], it has been increasingly suggested that, conversely, maladapted arteriolar reactivity may impair nutrient delivery and lead to or aggravate insulin resistance [82, 84, 85]. This recent hypothesis is further supported by several observations showing microvascular dysfunctions very early in the development of insulin resistance/diabetes [72, 86, 87]. In the subsequent worsening of insulin resistance towards diabetes, this factor may even become increasingly important [88].

**Conclusion**

In conclusion, microcirculatory defects could be viewed as one factor involved at various stages in both metabolic and angiopathic aspects of diabetes (Fig 8).

Functional disorders of small vessel haemodynamics are likely involved in the worsening of metabolic disorders (in particular insulin resistance during postprandial periods) as well as of structural microvessel modifications leading to nephropathy and retinopathy when hyperglycaemia becomes superimposed.
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