Small artery remodelling in diabetes

Enrico Agabiti Rosei, Damiano Rizzoni *

Clinica Medica, Department of Medical and Surgical Sciences, University of Brescia, Italy

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Abstract

The aim of this article is to briefly review available data regarding changes in the structure of microvessels observed in patients with diabetes mellitus, and possible correction by effective treatment. The development of structural changes in the systemic vasculature is the end result of established hypertension. In essential hypertension, small arteries of smooth muscle cells are restructured around a smaller lumen and there is no net growth of the vascular wall, although in some secondary forms of hypertension, a hypertrophic remodelling may be detected. Moreover, in non-insulin-dependent diabetes mellitus a hypertrophic remodelling of subcutaneous small arteries is present. Indices of small resistance artery structure, such as the tunica media to internal lumen ratio, may have a strong prognostic significance in hypertensive and diabetic patients, over and above all other known cardiovascular risk factors. Therefore, regression of vascular alterations is an appealing goal of antihypertensive treatment. Different antihypertensive drugs seem to have different effect on vascular structure. In diabetic hypertensive patients, a significant regression of structural alterations of small resistance arteries with drugs blocking the renin–angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) was demonstrated. Alterations in the microcirculation represent a common pathological finding, and microangiopathy is one of the most important mechanisms involved in the development of organ damage as well as of clinical events in patients with diabetes mellitus. Renin–angiotensin system blockade seems to be effective in preventing/regressing alterations in microvascular structure.

Keywords: remodelling • hypertension • diabetes mellitus • microcirculation • small arteries

Introduction

Microvascular complications are major contributors to morbidity, mortality and costs of both non-insulin-dependent (NIDDM) and insulin-dependent diabetes mellitus (IDDM) [1]. Damage of the small vessels in the kidney can lead to end-stage renal disease, structural alterations of the smaller vessels that supply nutrients and oxygen to peripheral nerves contribute to neuropathy and damage of the microvasculature of the eye is the leading cause of loss of vision in working-age adults. The clinical manifestations of microvascular disease are so characteristic of the disease that diabetes itself is defined primarily by the level of hyperglycaemia which causes microvascular complications.

Alterations in the microcirculation involve small resistance arteries, arterioles, capillaries and post capillary venules. Mechanisms possibly involved in the development of microvascular alterations

are summarized in Table 1. A relevant role in the impairment of vascular distensibility may be played by advanced glycosylation end-products, which may be involved in the formation of collagen cross-links [2]. Changes in the mechanics of small vessels may also induce changes in the structure. Although there is a huge amount of data about microangiopathy (capillary and arterioles), very few data about morphology of small resistance arteries (diameter ranging from 100 to 350 μm) in diabetes mellitus are presently available. In one study [3], no difference in subcutaneous small artery structure was observed between control patients and patients with IDDM. On the contrary, it has been demonstrated that, in both hypertensive and normotensive patients with NIDDM, marked alterations in small artery structure are present [4], and that these alterations are more pronounced in

*Correspondence to: Professor Daminno RIZZONI,
Chair of Internal Medicine,
Department of Medical and Surgical Sciences, University of Brescia,
c/o 2^a Medicina Spedali Civili di Brescia,

Piazza Spedali Civili 1 25100 Brescia, Italy.
Tel.: +030-3905251
Fax: +030-3384348
E-mail: rizzoni@med.unibs.it

Table 1 Mechanisms possibly involved in the genesis of micro-angiopathy

Direct effect of growth factors, such as insulin or insulin-like growth factor-1 on vascular smooth muscle cells.

Glycosylation of collagen fibres with alterations of extracellular matrix, production of advanced glycosylation end-products, involved in vascular damage (stimulation of cytokines, complement activation, up-regulation of growth factor synthesis, induction of collagen cross-links), depletion of basement membrane glycosaminoglycanes.

Metabolic effects such as activation of polyol pathway, with consequent production of sorbitol and fructose which are unable to diffuse outside cells, thus inducing osmotic endothelial cell injury and protein kinase C activation.

Glycosylation of proteins, including haemoglobin, with reduction of its affinity to oxygen and thus induction of micro-ischemia and endothelial damage.

Formation of reactive oxygen species (hydrogen peroxide, superoxide).

hypertensive patients with NIDDM than in patients with essential hypertension or in normotensive diabetics (Fig. 1) [4]. In addition, in diabetic patients a clear increase in the media cross-sectional area of the vessels was observed, thus suggesting the presence of hypertrophic remodelling (vascular smooth muscle cells hypertrophy or hyperplasia) [4, 5] (Fig. 2). This was not the case of patients with essential hypertension, in which a eutrophic remodelling (re-arrangement of the same amount of wall material around a narrowed lumen) is usually observed [4, 5].

A weak, but significant correlation between circulating levels of insulin and media to lumen ratio of subcutaneous small arteries was observed in diabetic patients, thus suggesting a possible role of insulin or insulin-like growth factor-1 in the genesis of hypertrophic remodelling in these patients [4]. However, an alternative explanation for the presence of hypertrophic remodelling in these vessels has been proposed [5]. In fact, a possible stimulus for hypertrophic remodelling could be the increased wall stress, as a consequence of the impaired myogenic response. Myogenic response is a pressure-induced vasoconstriction, which is the key component of blood flow autoregulation and stabilization of capillary pressure. The observation by Schofield *et al.* [5] of the lack of such a myogenic response in diabetic patients may therefore be responsible for the development of hypertrophic remodelling of small arteries (Fig. 3) [5]. Diabetic patients with NIDDM also show particularly evident alterations of the vascular extracellular matrix, as suggested by the observation of increased collagen to elastin ratio in their small arteries [4] (Fig. 1).

Although small resistance arteries and arterioles may undergo a remodelling process and fibrosis in patholological conditions, capillaries may undergo a functional or structural rarefaction, with consequent reduction in the density per area units of tissue. This process of vascular rarefaction was previously observed in patients with hypertension [6] and also in patients with NIDDM, at least in the skeletal muscle [7].
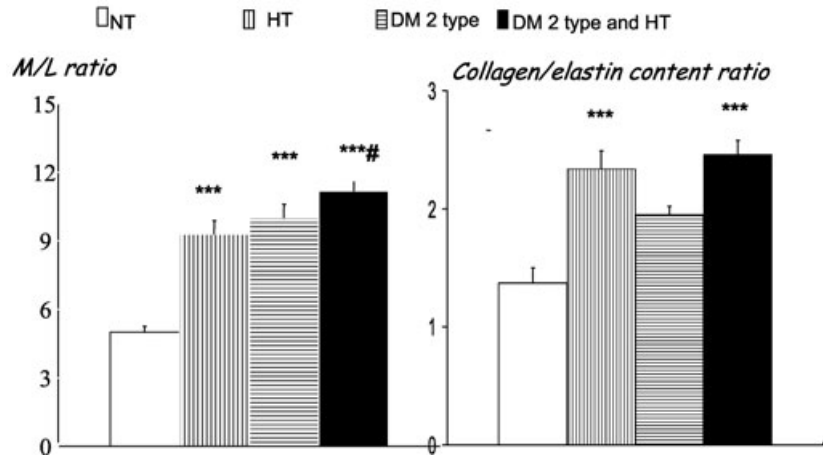
On the contrary, in other vascular districts such as the retina, microvascular proliferation may be observed. In fact, diabetic retinopathy results either from capillary leakage or from new vessel formation (neovascularization, angiogenesis), caused by capillary closure and retinal ischemia. The capillaries leak lipid products and fluid in the area around the fovea and thicken the retina, which may lead to macular oedema. Angiogenesis is the result of retinal ischemia, and retinal haemorrhages are the consequence of the fragility of neovessels. The haemorrhage can enter the vitreous and cause sudden loss of vision. Several mechanisms and metabolic abnormalities, acting alone or in concert with each other, may lead to capillary death, leakage and occlusion and to the release of growth factors, finally resulting in new vessel formation and increased vascular permeability. A relevant role is played by vascular endothelial growth factor. Whereas vascular endothelial growth factor is involved in vascular leakage and angiogenesis, growth hormones and the insulin-like growth factor-1 are involved, as mediators, in angiogenesis. At present, inhibitors of these growth factors are under investigation in clinical trials in patients with diabetic retinopathy.

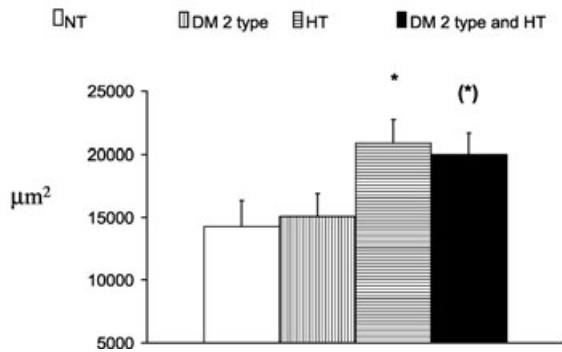# Vascular structural alterations, end organ damage and cardiovascular events

As previously mentioned, the extent of structural alterations in small resistance vessels is more pronounced in patients with both diabetes mellitus and hypertension, thus suggesting that clustering of risk factors may have synergistic deleterious effects on the vasculature [4, 5]. An important pathophysiological and clinical consequence of the presence of structural alterations in small resistance arteries and arterioles may be an impairment of vasodilator reserve [8]. In fact, as mentioned in the previous section, remodelling of small resistance arteries is characterized by a narrowing of the lumen, which leads to an increase of flow resistance even at full dilatation, *i.e.* in the absence of vascular tone. A significant correlation between coronary flow reserve and subcutaneous small resistance artery remodelling has been observed in hypertensive patients, suggesting that structural alterations in small resistance arteries may be present at the same time in different vascular districts, including those of paramount clinical importance, such as coronary circulation [9]. An impaired microvascular hyperaemic response (which may reflect an altered flow reserve) has been observed in children with diabetes mellitus [10] as well as in adult patients with NIDDM [11]. Thus, alterations in the microcirculation may play an important role in the development of organ damage not only in hypertension but also in diabetes mellitus. In fact, a relevant prognostic role of an increased media to lumen ratio of subcutaneous small resistance arteries in

## Structural alterations of small resistance arteries in the presence of diabetes and/or hypertension

Fig. 1 Left: Media to lumen ratio in subcutaneous small resistance arteries from normotensive patients (NT), essential hypertensive patients (HT), normotensive patients with NIDDM (DM 2 type) and hypertensive patients with NIDDM (DM 2 type and HT). A clear increase may be observed in all three pathologic groups, which is more evident in hypertensive patients with NIDDM. Right: collagen to elastin ratio (measured with electronic microscope) in the different groups. An increase was observed in essential hypertensive patients and in hypertensive patients with NIDDM. ***$P < 0.001$ *versus* normotensive patients; #$P < 0.05$ *versus* essential hypertensive patients. Mean ± S.E.M. (from [4]).

Fig. 2 Medial cross-sectional area in subcutaneous small resistance arteries from normotensive patients (NT), essential hypertensive patients (HT), normotensive patients with NIDDM (DM 2 type) and hypertensive patients with NIDDM (DM 2 type and HT). An increase may be observed in the diabetic patients, which is more evident in normotensive patients with NIDDM. (*)$P = 0.06$, *$P < 0.05$ *versus* normotensives. Mean ± S.E.M. (from [4]).
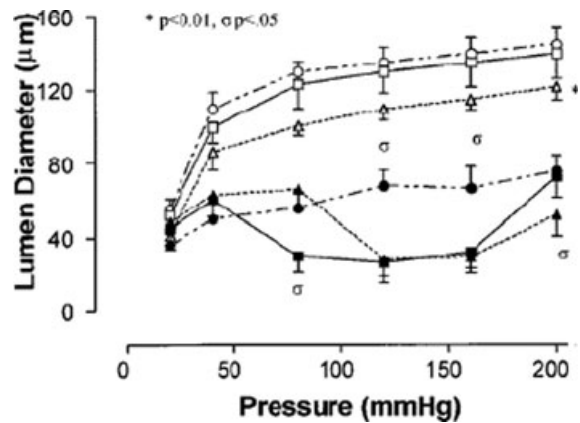
Fig. 3 Myogenic response in subcutaneous small resistance arteries in patients with NIDDM. Passive pressure–lumen diameter relations for arteries from control patients (€), patients with EH (Δ) and hypertensive patients with NIDDM (°). * = $P < 0.05$, ANOVA, *versus* control. Active pressure–lumen diameter relations for arteries from control patients (■), patients with essential hypertension (▲) and hypertensive patients with NIDDM (•). σ = $P < 0.05$ *versus* control vessels (from [5]).

a high-risk population (including normotensive and hypertensive diabetic patients) has been previously demonstrated [12]. More recently, these data have been re-evaluated, taking into account also the characteristics of the vascular remodelling. As previously mentioned, an increased media to lumen ratio in small arteries may be ascribed either to eutrophic or to hypertophic remodelling. For the same values of internal diameter, those patients who suffered cardiovascular events had a greater media cross-sectional area, in comparison with those without cardiovascular events [13], thus suggesting the presence of vascular smooth muscle cell growth. Therefore, it seems that, for the same size of the vessels

explored, a greater amount of vascular wall material, suggesting the presence of hypertrophic remodelling, such as that observed in diabetic patients, could mean an even worse prognosis. It may be postulated that hypertrophic remodelling might be a 'less physiological' adaptation to increased blood pressure levels, thus playing a role in the development of target organ damage, both in hypertension and in diabetes mellitus. It has been also suggested, as previously reported, that an impairment of myogenic response may have a relevant role in the development of hypertrophic remodelling in patients at high cardiovascular risk. In addition, an impaired myogenic response in small vessels may also induce an

increase of high blood pressure flow to target organs and down-stream increase in capillary pressure, with consequent increased permeability and capillary leakage. Fluid extravasation may induce organ damage. Some data support the presence of an increased capillary pressure in patients with diabetes mellitus [14], especially if they have increased blood pressure values [15], although presently there is no general agreement about this issue. The increase in capillary pressure seems to be related to the extent of clinical complications as well as to metabolic control [16]. Also vascular rarefaction may have important consequences in terms of tissue perfusion. In fact, it has been demonstrated that in patients with NIDDM, the mechanisms through which insulin is able to increase total limb flow or achieve optimal microvascular perfusion is impaired [7].

Endothelial dysfunction

An impairment of the endothelial function, as evaluated by the vasodilator response to acetylcholine, has been detected in large and small arteries of patients with IDDM [17–21] as well as of those with NIDDM [4, 5, 22–24]. Endothelial cells are known to have important regulatory effects on the cardiovascular system through the release of vasodilator and vasoconstrictor factors. In addition, platelet aggregation as well as leucocyte extravasation through endothelium may be influenced by locally produced compounds. Therefore, endothelial dysfunction and damage may contribute to the inflammatory and thrombotic vascular lesions. We and others have previously demonstrated the presence of an impaired dilatation to acetylcholine and bradykinin in subcutaneous small resistance arteries of hypertensive and normotensive patients with NIDDM [4, 5, 24]. However, the concomitant presence of the two cardiovascular risk factors does not seem to induce a further worsening of endothelial function [4, 24]. A possible explanation is that, both in hypertension and in diabetes mellitus, oxidative stress, resulting from the vascular production of free radicals and/or cyclooxygenase-dependent substances, may reduce nitric oxide bioavailability. If the pathogenetic mechanism of endothelial dysfunction is similar in the two conditions, no additive effect should be expected.

A second important point relates to the mechanisms of endothelial dysfunction in small resistance arteries of hypertensive and diabetic patients. In essential hypertensive patients, the relatively small vasodilator responses to acetylcholine and bradykinin infused into the brachial artery are not usually blocked by inhibitors of nitric oxide synthase (*i.e.* L-NMMA), whereas in normotensive patients the inhibitory effect of L-NMMA is preserved. In subcutaneous small arteries of patients with essential hypertension, and also in those with NIDDM, inhibitors of nitric oxide synthase are able to block about 50% of the vasodilator effect of acetylcholine or bradykinin, whereas the remaining vasodilatation is blocked by ouabain, thus suggesting that production of both nitric oxide and endothelium-derived hyperpolarizing

factor may be involved [4, 24]. No effect has been observed when indomethacin was added to the organ bath; therefore, the production of cyclooxygenase-dependent substances seems to be of minor importance [4, 24].

It has been also proposed that insulin and insulin resistance may be involved in the genesis of endothelial, and in general, microvascular dysfunction in diabetes mellitus. Insulin is able to induce a vasodilating effect in the microcirculation (which is, at least in part, endothelium dependent) in normal patients [25, 26]. In addition, insulin may recruit skeletal muscle capillaries *in vivo* by a nitric oxide dependent action, and this increased capillary recruitment may contribute to the subsequent glucose uptake [27]. However, part of these effects is lost in diabetes mellitus [25]. Hyperinsulinaemia, as a result of insulin resistance may have detrimental effects on microvascular function also in the pre-diabetic state [28]. On the other hand microvascular structural alterations may contribute to an impaired delivery of insulin to skeletal muscles [29]. Therefore, a complex interplay of structural and functional alterations of the microcirculation may, at least in part, explain the detrimental consequences of diabetes mellitus in terms of organ perfusion [30], and, ultimately, in terms of increased incidence of cardiovascular events.

Effect of treatment

There are relatively few data about the effect of treatment on structural and functional alterations in the microcirculation of patients with diabetes mellitus. In the United Kingdom Prospective Diabetes Study, a large randomized controlled trial that included almost 5000 patients, it has been demonstrated that a tight haemodynamic and metabolic control is associated with a lower incidence of microvascular disease [31], and, in general, of clinical end-points related to microvascular disease [32].

Even fewer data are presently available about the effects of antihypertensive drugs on small artery structure in hypertensive diabetic patients. Despite effective antihypertensive treatment, resistance arteries from hypertensive diabetic patients showed marked remodelling, greater than that of vessels from untreated, non-diabetic, hypertensive patients, in agreement with the high cardiovascular risk of patients suffering from both diabetes and hypertension [33]. Recently, a study has compared the effects of 1-year treatment with the angiotensin-converting enzyme (ACE) inhibitor (enalapril) or the angiotensin II receptor blocker (candesartan), on subcutaneous small artery structure in hypertensive patients with NIDDM [34]. The two drugs were equally effective in reducing media to lumen ratio of small arteries (Fig. 4); however, candesartan was more effective than enalapril in normalizing vascular collagen content, probably through a more pronounced stimulation of the local production of metalloproteinase 9 (a collagen-degrading enzyme). At variance to what observed in the majority of studies in normoglycaemic hypertensive patients, media to lumen ratio of small arteries in treated diabetic patients

EFFECTS OF 1 YEAR TREATMENT WITH CANDESARTAN OR ENALAPRIL ON SUBCUTANEOUS SMALL RESISTANCE ARTERY STRUCTURE IN DIABETIC HYPERTENSIVES

Fig. 4 Media to lumen ratio in subcutaneous small resistance arteries from hypertensive patients with NIDDM, before and after 1-year treatment with the ACE inhibitor enalapril or the angiotensin II receptor blocker candesartan. A significant and similar reduction was observed with both drugs. BP = blood pressure ** = $P <$ 0.01 *versus* Basal (from [34]).
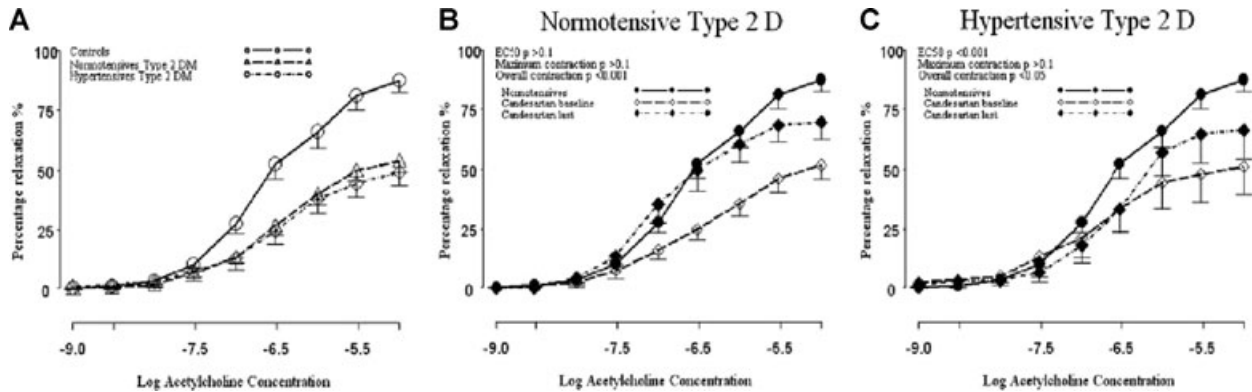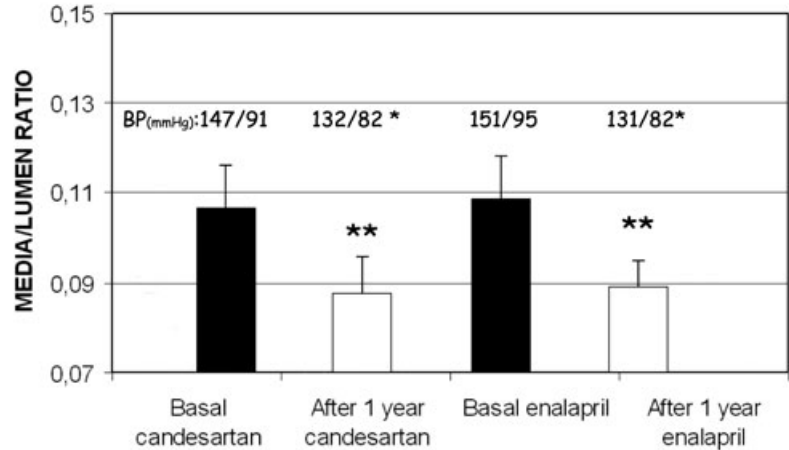
Fig. 5 Dilatation of vessels comparing control patients with normotensive and hypertensive type 2DM (**A**) and response assessed by change in EC50, maximal relaxation and overall relaxation to candesartan in normotensive (**B**) and hypertensive (**C**) type 2 DM exposed to increasing concentrations of acetylcholine after pre-constriction with norepinephrine (from [36]).

did not reach the values observed in normotensive controls, therefore suggesting that a complete regression of vascular hypertrophic remodelling is probably more difficult to obtain [34]. Angiotensin II receptor blockers seem to be effective in diabetic hypertensive patients also when given on top of an ACE inhibitor treatment [35]. In addition, angiotensin II receptor blockers seem to be also particularly effective in terms of improvement of endothelial function in small resistance arteries [36] (Fig. 5). It has been recently proposed that drugs that may stimulate PPAR-α or PPAR-γ receptors (such as fibrates of glitazones) may be useful in terms of vascular protection and regression of structural alterations in the microcirculation. However, no data are presently available in human beings. In addition we do not know whether a regression of vascular structural or functional alterations in diabetic patients may be prognostically rele-

vant, *i.e.* whether it is associated to a real protection from cardiovascular events [37].

Few data about patients with type 1 diabetes mellitus are presently available. Recently, it was observed that small arteries from patients with type 1 diabetes mellitus show hypertrophic growth in response to elevated blood pressure, similar to that seen in type 2 diabetes mellitus [38]. However, metabolic improvements enable eutrophic remodelling to occur in response to an increase in blood pressure [38].

Development in the topic in the next years

The relative invasiveness of the fat tissue biopsy, the limited availability of the technique (performed in few laboratories) and the

lack of prognostic data about regression of microvascular alterations, 'makes this approach unsuitable for general use' [39]. We are presently waiting for non-invasive approaches, which may provide us with further important insight about the effect of anti-hypertensive drugs, and, more importantly, about the possible prognostic impact of the regression of vascular structural alterations in hypertension and diabetes. The recently proposed evaluation of the media to lumen ratio of retinal arteries seems to represent a promising approach in this regard [40].

Conclusions

Alterations in the microcirculation represent a common finding, and microangiopathy is one of the most important mechanisms involved in the development of organ damage as well as of clinical events in patients with diabetes mellitus. Both patients with essential hypertension and those with NIDDM are characterized by alterations in the resistance vasculature, *i.e.* an increased media to lumen ratio, which in diabetics is the consequence of the

so-called hypertrophic remodelling. Structural alterations of small arteries are associated with an increased cardiovascular risk in hypertensive and diabetic patients, perhaps as a consequence of an impaired organ flow reserve in several vascular districts, including the coronary vascular bed. In fact, it has been observed that the presence of an increased wall to lumen ratio in the subcutaneous resistance arteries is associated with a worse prognosis in high-risk patients. Hypertrophic remodelling, such as that observed in diabetic patients, seems to be associated with an even worse prognosis. Data about the effect of therapy on microvascular structure in diabetic patients are scarce; however, renin–angiotensin system blockade seems to be effective in regressing, at least in part, the microvascular structure, although we do not know whether this improvement is associated with a better clinical prognosis.

Conflict of interest

The authors confirm that there are no conflicts of interests.

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