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COMMENTARY

Vascular smooth muscle function: defining the diabetic vascular phenotype

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Abstract In this issue of *Diabetologia*, a meta-analysis performed by Montero and co-authors (*Diabetologia* doi 10.1007/s00125-013-2974-1) demonstrates a significant impairment of vascular smooth muscle (VSM) function in type 2 diabetic patients. Endothelial function and VSM function between type 2 diabetic and healthy individuals were associated, especially in the microcirculation, confirming the hypothesis that unresponsiveness of VSM cells to NO may amplify the consequences of reduced NO availability. This study suggests a novel interpretation for endothelial dysfunction in diabetic patients, indicating VSM cells as key players. Causative mechanisms of VSM dysfunction, which seems to be a feature of the vascular phenotype of type 2 diabetes mellitus, are largely unexplored in humans. Future studies should also address the crucial issue of the prognostic significance of VSM dysfunction in diabetic patients, and possibly in other conditions characterised by high cardiovascular risk.

Abbreviations

FMD	Flow-mediated dilation
PKG	cGMP-dependent protein kinase
VSM	Vascular smooth muscle

In this issue of *Diabetologia*, Montero and colleagues report the findings of a systematic review and meta-analysis of data on abnormalities in vascular smooth muscle (VSM) and comment on their contribution to vascular dysfunction in type 2 diabetes [1].

Endothelial dysfunction is widely recognised as the first step in the development of atherosclerosis and plays a key role in the pathophysiology of cardiovascular disease. Endothelial dysfunction has almost invariably been detected in the presence of any cardiovascular risk factor and is an independent predictor of cardiovascular events. Its prognostic role has been demonstrated in peripheral and central circulation, in both the microcirculation and in large arteries, and irrespective of the endothelial stimulus used [2, 3]. A recent meta-analysis of 14 prospective studies, including 5,547 patients followed for 0.5–7.9 years, demonstrated that a 1% increase in flow-mediated dilation (FMD) at baseline is associated with a 13% reduction in the incidence of cardiovascular events in an adjusted multivariable analysis, in both low risk and high risk populations [3]. Very recently, non-invasive techniques for assessing endothelial function have been standardised and demonstrate good reproducibility [4]. However, despite the increasing burden of evidence, the use of vascular reactivity tests as a clinical tool has not yet been adopted in routine medical practice [5]. Indeed, several questions in this field are still unresolved, concerning methodological, prognostic and pathophysiological aspects of the technique; among these is the extent of the influence of VSM function.

The concept of endothelial dysfunction as an expression of reduced NO availability in endothelial cells, mainly due to its inactivation by reactive oxygen species, is now widely accepted [6]. NO activates a complex cascade of events in its target cells, the VSM cells. A pivotal role is exerted by activation of soluble guanylate cyclase, leading to cGMP synthesis. cGMP exerts its biological actions mainly by activating cGMP-dependent protein kinase (PKG), thus inducing smooth muscle relaxation and vasodilation [7].

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Any defect in VSM function can reduce its capacity to respond to endogenous as well as exogenous NO. Thus, the use of exogenous nitrates is mandatory in order to determine the extent of any coexistent endothelium-independent dysfunction when studying endothelium-dependent vasodilation. Accordingly, this approach is recommended by current guidelines for invasive and non-invasive vascular reactivity tests in humans [8, 9].

Type 2 diabetes mellitus is characterised by an impairment in NO-dependent vasodilation in the micro- and macrocirculation and this can further worsen endothelial function on top of the effect of other risk factors such as hypertension [10]. Given the prognostic relevance of endothelial dysfunction, a better understanding of the mechanisms underlying its causes is warranted. The presence of VSM dysfunction in type 2 diabetes was first suggested decades ago, but its significance has not, as yet, been conclusively demonstrated because of discrepancies in reported studies, probably resulting from low sample size and the use of heterogeneous techniques.

In this context, the meta-analysis performed by Montero and co-authors [1] represents an important contribution. The authors selected 31 studies, including 1,042 patients with type 2 diabetes and 601 age- and sex-matched controls, in which VSM function was assessed, either in the micro- or macrocirculation. The meta-analysis demonstrated a significant impairment of VSM function in type 2 diabetic patients [1]. Furthermore, the standardised mean differences of endothelial function and VSM function between type 2 diabetic and healthy individuals were associated, confirming the hypothesis that unresponsiveness of VSM cells to NO may amplify the consequences of reduced NO availability.

It is also notable that meta-regression analysis showed that factors influencing VSM function are all classic components of the metabolic syndrome (blood pressure, triacylglycerol, HDL-cholesterol and obesity), which can play a causative role in determining this vascular phenotype. This hypothesis is reinforced by data obtained in experimental models of insulin resistance such as the obese Zucker rat [11]. In this model, multiple defects of the NO/cGMP/PKG pathway activation were found, including impairment of NO donor ability to increase cGMP concentrations in VSM cells and a reduced ability of both NO and cGMP to activate PKG [12].

However, other possible mechanisms cannot be excluded. Insulin, for instance, has a direct vasodilating action in the muscle microcirculation, which is markedly impaired in the presence of insulin resistance [13]. The impact of this alteration, if any, on nitrate-induced vasodilation, is unknown. Furthermore, it has been demonstrated in a human ex vivo model that the intrinsic myogenic responsiveness of small arteries from type 2 diabetic patients is impaired, leading to a failure in the efficient autoregulation of blood flow to target organs, and to downstream damage [14]. Future research should be directed at elucidating the pathophysiology of VSM dysfunction in type 2 diabetic patients.

It is also interesting to note from this study that VSM dysfunction was more compromised in the microcirculation than in the macrocirculation, even though the macrocirculatory district (e.g. the brachial artery) was studied in only a minority of the studies (12 out of 31), and this subgroup analysis, which showed inconsistent results, may have been underpowered. More studies are needed to investigate macrocirculatory VSM function in larger populations and to determine whether it is influenced by the same factors as the microcirculation. Such studies will also help to overcome limitations of this meta-analysis, such as the possibility that the dose of administered nitrates may have been a source of heterogeneity. This is important, particularly in the studies on the macrocirculation, where the doses of glyceryl trinitrate commonly used may range between 25 and 400 μg or more [8]. Indeed, while a general consensus on methodology has been reached for FMD [15, 16], similar standardisation has not yet been adopted in the study of endothelium-independent vasodilation.

In conclusion, the results of this systematic review and meta-analysis indicate that VSM dysfunction is a feature of vascular pathology characterising type 2 diabetes mellitus. Future studies should address its pathophysiology in the micro- and macrocirculation, as well as the crucial issue of the prognostic relevance of the abnormality, which at the moment is still largely unknown.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement Both authors were responsible for the conception and design of the manuscript, drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

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