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Diabetes, cardiovascular disease and the microcirculation

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Abstract
Cardiovascular disease (CVD) is the leading cause of mortality in type 2 diabetes mellitus (T2DM), yet a significant proportion of the disease burden cannot be accounted for by conventional cardiovascular (CV) risk factors(1). Hypertension occurs in approximately 80% of people with diabetes, substantially more frequently than would be anticipated based on general population samples. Further, the impact of hypertension is substantially higher within those with diabetes than it is within the general population, suggesting either increased sensitivity to its effect or a confounding underlying aetiopathogenic mechanism of hypertension associated with CVD within diabetes. This mini-review aims to describe the changes in the vascular tree seen within people with diabetes compared to the general population and explore the hypotheses to account for the common causality of the increased prevalence of CVD and hypertension in those with diabetes.

Key words: diabetes – cardiovascular disease – microcirculation

The vascular anatomy in cardiovascular disease

Although there is increasing evidence that the venous tree regulates cardiac output and total body circulating fluid, the majority of the pathology occurs within the arterial circulation. Broadly the vascular tree is divided into four components, the elastic (conduit) arteries, the muscular conduit arteries, the muscular resistance arterioles and the capillaries (Figure). This, however, suggests a clear distinction within the vessels. In reality, the basic architecture displays a progressive change from predominantly elastin and vascular smooth cells at the aortic arch, which gradually gives way to a collagen rich media by the distal aorta. Over the last 5 cm of the thoracic aorta, and aortic branches, there is a rapid transition to a predominantly collagen and vascular smooth cell muscular artery. In the resistance arterioles and capillaries, vascular smooth muscle cells become increasingly sparse, until they are no more than one cell layer in the terminal branches. Further, the vascular smooth muscle cells have differing embryonic origins in the vessel beds, with the proximal elastic and muscular vessels being derived from ectodermal tissue, whereas the small muscle beds and arterioles having mesodermal origin. The formation of microcirculation is a result of the complex process of angiogenesis from these mesodermal tissues stimulated predominantly by hypoxia. These differences in embryology are thought to trigger the differential effects of certain classes of vasodilators such as, for instance, calcium channel blockers or α-adrenoceptor antagonists, on the proximal vs distal vessels.

Hypertensive target organ damage in those with diabetes

One of the hallmarks of hypertensive vascular damage is increased arterial stiffness in the large elastic arteries. This precedes evidence of atherosclerosis but independently predicts CV death, after adjustment for hypertension, age and sex, in end stage renal failure [1], essential hypertension [2] and in T2DM [3]. Concomitant diabetes and hypertension, however, is associated with a greater degree of arterial stiffness than either alone, independent of conventional CV risk factors or ethnicity [4].

Several mechanisms have been proposed to account for this interaction. Glycaemia is a major determinant

Figure. The 4 component artery types that make up the vascular tree

	elastic arteries	muscular conduit arteries	muscular resistance arterioles	capillaries
diameter	> 2 mm	150 µm–2 mm	15 µm–150 µm	< 15 µm
regulation	media structure > endothelium	media structure & endothelium	endothelium > media structure	endothelium only
function	conduit: elastic recoil (diastolic BP)	conduit: minor resistance	resistance	nutrient and waste exchange

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of arterial stiffness, and carotid intimal medial thickness (IMT), another well-established measure of blood pressure related damage which independently predicts CV events. This is felt to be a result of the adverse effect of glycaemia on endothelial function. The exact mechanisms remain elusive, although among proposed mechanisms is non-enzymatic glycaetion of proteins with covalent cross-linking of collagen (AGEs) altering the mechanical properties of interstitial tissue of the arterial wall [5]. This is supported by evidence that drugs interfering with the formation of these glycosylated vessel wall molecules attenuate, but not reverse, the progression of the arterial stiffness seen in diabetes.

An alternative, or possibly complementary mechanism of vascular damage, is the inactivation of nitric oxide by oxygen-derived free radicals. Interestingly this has been associated with glycaemic variability rather than glycaemia per se *[6]*. This observation is supported by the association between glycaemic variability, as measured by mean amplitude of glycaemic excursion (MAGE) and clinically relevant outcomes. MAGE has been shown to predict re-hospitalisation with CV events in type 2 diabetes, supplanting other measures of glycaemia including HbA_1c, fasting plasma glucose or post prandial glucose [7]. Further, the use of DPP-4 inhibitors to blunt daily glucose fluctuations has also been associated with reduction in oxidative stress and inflammation [8]. Within a three month period, when glycaemic variability was reduced, there was also commensurate and proportionate reduction in carotid IMT [9], suggesting glycaemic variability is a potentially reversible therapeutic target to address at least part of the increased CVD risk in those with diabetes.

The role of the microcirculation

The emphasis on large vessel disease, such as increased arterial stiffness and carotid IMT, ignores the contribution of the microcirculation to CVD. Whilst the association between disease of the conduit or resistance arteries and CVD has been explored and well-characterised much of the variance in the increased frequency of CVD in diabetes remains unexplained. Further, the exact mechanisms associating, for example, hypertension and atherosclerosis in those with diabetes are unclear.

The microcirculation provides an attractive target for further investigation as it represents the location of the principle role of the vascular tree, namely the delivery of oxygen and other essential substrates into cells and removing their metabolic waste products. There are significant differences in the way small arteries remodel in response to hypertension in people with or without diabetes. In patients with essential hypertension alone, small arteries show a greater media thickness and a reduced lumen and external diameter (with an increased media-to-lumen ratio), without any significant change in the total amount of wall tissue [10]. Therefore, the major part of the structural changes observed in these patients is the consequence of inward eutrophic remodeling without net cell growth. In patients with diabetes, however, a clear increase in the media cross-sectional area in small vessels has been observed, suggesting the presence of hypertrophic remodeling [11]. It has been proposed that increased wall stress resulting from impaired myogenic response of the small arteries in diabetes is a possible stimulus for hypertrophic remodeling [12]. Simultaneously, microvascular permeability to large molecules, such as albumin, is increased in diabetes, a process that is linked to hyperglycaemia and oxidative stress [13]. Linking these observations, impaired microvascular auto-regulatory myogenic responses in populations with diabetes predicts urinary albumin excretion rate (UAER), and accounts for its association with adverse cardiac remodeling [14,15]. Finally, people with diabetes show alterations of the vascular extracellular matrix, as demonstrated by an increased collagen-to-elastin ratio in their small arteries. The increased collagen deposition in the vessel wall is thought to be due to inflammatory and pro-fibrotic changes.

A final vascular site of damage in hypertension and diabetes are the small arterioles and capillaries. Vascular resistance is not only determined by the arteriolar diameter, but also by the number of perfused vessels. Microvascular rarefaction may be the result of closure of the small arterioles (functional rarefaction) or structural rarefaction, where the vessels are actually missing. Microvascular rarefaction has been a consistent observation over many years in hypertensive patients and animal models [16]. In most vascular beds, not all microvessels are perfused at any one time; the fraction of non-perfused vessels constitutes a reserve that may be called upon under conditions of high metabolic demand. Progressive non-perfusion can lead to structural loss of vessels. Microvascular rarefaction has been consistently reported in the myocardium of individuals with hypertension and/or diabetes. The functional consequence of it is a reduced coronary flow reserve. Reduced maximal blood flow is probably related to structural abnormalities in the coronary microcirculation, although functional factors, including endothelial dysfunction, may also contribute. Although not associated with atherosclerosis, this predicts cardiac symptoms, and may explain the high prevalence of refractory angina in people with diabetes, despite normal or only mildly diseased coronary arteries.

Microcirculatory dysfunction: cause or effect?

Diabetic retinopathy is the biggest cause of premature blindness in Western society as well as being a strong risk marker for CV mortality. The presence of retinopathy, however, may predate the occurrence of T2DM, suggesting the diabetic phenotype may have a microvascular aetiology.

The nature of the association between microvascular and macrovascular disease is often questioned. There is an established co-linearity in the development and progression of microvascular and macrovascu-

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lar disease [17]. However, it remains to be established whether there is a causal effect in either direction or the association simply represents shared risk factors, although it is most likely to be a complex combination of bi-directional interactions. A typical example of this would be the interplay between diabetic nephropathy, metabolic syndrome and atherosclerosis.

Microalbuminuria: from epidemiology to clinical practice and back again

An UAER was first described as a feature of glomerulosclerosis with a poor prognosis in 1936 by Clifford Wilson and Paul Kimmelstiel. Consequently many textbooks still refer to diabetic nephropathy as "Kimmelstiel-Wilson" syndrome. At that time it was thought to represent local pathology within the renal microcirculation, while it has subsequently been recognised as a predictor of future CV events and mortality in diabetes, renal failure, hypertension and the general population at large. Further, it predicts survival after myocardial infarction and stroke [18]. As such, UAER or its proxy, albumin : creatinine ratio (ACR), has become an accepted surrogate for microcirculatory target organ damage in T2DM. Currently there remains little debate as to the importance of albuminuria as a prognostic indicator, although consensus has not been reached regarding the threshold of "abnormality" given that the association persists down into levels that are currently considered normal and below the sensitivity of commercially available assays.

The lack of a clear mechanistic pathway to explain the association between microalbuminuria and adverse CV outcomes has led many clinicians to believe it is solely a marker of blood pressure exposure. Nevertheless recent mechanistic studies suggest the systemic microvascular disturbances that account for the association between microalbuminuria and cardiac target organ damage are independent of either acute or long term blood pressure effects [14,15].

Microvascular function as an aetiopathogenic step in those with diabetes and CVD

T2DM alone is an important CV risk factor which has been demonstrated to have a similar impact on morbidity and mortality as a history of a CV event [19]. Microvascular damage has been recognised in patients with diabetes for at least four decades and it appears to precede the development of CV events in those with diabetes while changes in microvascular function appear to precede microangiopathy. Whereas in type 1 diabetes these abnormalities take several years to develop and appear to be proportional to glycaemic control, in T2DM, however, the impairment is evident at diagnosis, in normoglycaemic women with a history of gestational diabetes [20] and in those at risk of developing T2DM.

The epidemiological link has been strengthened by interventional work demonstrating improvement in skin microvascular hyperaemic responsiveness with good glycaemic control over a 12-month period [21]. This association was very strongly associated with degree of improvement of glycaemic control ($R^2 = 0.53$ between one percentage increase in HbA_{1c} and increase in maximum hyperaemia). However, the support for this being a mechanism for improvement in CV event rate with good glycaemic control has been challenged by the observation that the peroxisome proliferator-activated receptor gamma antagonist, rosiglitazone, improves nitric oxide dependent skin microvascular responsiveness, independent of changes in glycaemic control, whilst at the same time apparently increasing the CV event rate [22]. Interestingly, whilst the risk of myocardial infarction was increased with rosiglitazone therapy in the latter work, there was a trend towards fewer strokes that has subsequently been confirmed in alternative studies.

Skin microcirculatory reactivity has been shown to correlate with coronary heart risk scores as there is a strong association between endothelium dependent and independent microvascular function and 10-year coronary heart disease risk scores calculated from the Framingham risk scores. As this association is independent of sex and body mass index it suggests that the skin microvascular function is a valid model for studying the association between CV risk and microvascular function. Recent work elucidating potential links between CVD and skin microvascular function has clearly supported the association between those with arterial disease and impaired systemic microcirculation [23]. However, despite the clear attenuation in microvascular function in those with angiographically confirmed coronary artery disease compared to healthy controls, there was no direct association between atherosclerotic burden suggesting the association may be more complex than previously thought.

This complexity is highlighted by inter-ethnic comparisons between those of European and African Caribbean descent. African Caribbeans are known to be relatively protected from atherosclerotic disease despite the increased prevalence of salt sensitive hypertension, diabetes and insulin resistance. Given what is known about the relationship between microvascular function and coronary artery disease, it may be anticipated that African Caribbeans have better microvascular function. Paradoxically, however, the opposite is observed: African Caribbeans in the general population have attenuated microvascular function compared to Europeans [24]. Microvascular function is further attenuated in those with diabetes and, unlike their European counterparts, this impairment is not accounted for by measures of insulin resistance [25]. This impaired microvascular function is in keeping with the previously observed increased risk of retinopathy and renal disease in African Caribbeans. The contrasting relative protection from large vessel atherosclerotic disease in African Caribbean patients and yet higher prevalence of stroke and heart failure than their European counterparts, challenges the axiom that stroke and ischaemic heart disease have the same mechanisms just affecting different vascular beds. It also supports the role of microcirculatory dysfunction in the aetiopatho-

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genesis of stroke. This is further supported by the observation that two measures of microvascular damage assessed in the Atherosclerosis Risk In Communities (ARIC), namely retinopathy and cerebral white matter lesions as detected on magnetic resonance imaging (MRI) predict future stroke [26]. Additionally, elevated UAER, as a marker of systemic microcirculatory dysfunction, predicts both incident stroke and survival after stroke.

The microcirculation and clinical practice

Most CVD occurs in the proportionately larger number of individuals with low to moderate absolute risk. Clinical intervention decisions are often based on the likelihood that an individual will have a CV event over a given period of time; however, these decisions are often made on an incomplete assessment of risk. Investigating the retinal microvasculature is relatively simple and can be employed on a large-scale. As such, it has been translated into clinical practice for those with diabetes. Similarly UAER translates easily into clinical practice as assessment of ACR which can be measured on a single urine specimen. Changes in urinary albumin excretion have been shown to be very useful for estimating risk of future CV events [27]. Therefore progression of urinary albumin excretion should be prevented and regression thereof regarded as a primary treatment goal when reducing the risk for CVD. However, there is limited data on the long-term cost-effectiveness of systematic screening for urinary albumin excretion and more importantly, targeting it as a therapeutic outcome in those at high risk either by virtue of their hypertension or their past disease such as stroke, transient ischaemic attack or myocardial infarction. This clearly requires further investigation.

Conclusions

The role of the microcirculation in the aetiopathogenesis of CVD in those with diabetes has been highlighted in a series of epidemiological studies over the last century. We currently recognise the independent morbidity of microvascular disease and the prognostic role this carries for future disease. Current epidemiological studies are focusing on attempting to untangle the inter-relationship between risk factors and pathological mechanisms in order to attempt to determine whether these represent therapeutic targets or simple markers of unmeasured risk. These studies have produced a paradigm shift in the understanding of vascular disease especially in diabetes, have triggered many mechanistic studies and provide evidence to support clinical monitoring of microvascular function in the future.

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vyskytne KV udalosť počas určitého obdobia, avšak tieto rozhodnutia sú robené po neúplnom zhodnotení rizika. Vyšetrovanie mikrocirkulácie sietnice je relatívne jednoduché a môže byť uskutočnené na veľkej skupine pacientov. Vyšetrenie sa uplatnilo najmä u diabetikov. Hodnotenie UEAR a ACR je široko uplatnené v klinickej praxi, keď je potrebný odber len jednej vzorky moču. Zmeny vylučovania albumínu sa osvedčili ako veľmi užitočné pri hodnotení budúceho KV rizika [27]. Predchádzanie progresie a nastolenie regresie vylučovania albumínu do moču by malo byť cieľom pri redukcii rizika KVCH. Na druhej strane ale chýbajú dôkazy o dlhodobej efektívnosti skríningu vylučovania albumínu do moču ako aj pri cielenej liečbe u pacientov s hypertenziou s predchádzajúcou mozgovou príhodou, tranzientným ischemickým atakom alebo infarktom myokardu. Toto sa musí podrobiť ďalšiemu výskumu.

Záver

Úloha mikrocirkulácie v etiopatogenéze KVCH bola skúmaná v niekoľkých epidemiologických štúdiách u pacientov s diabetom v priebehu minulého storočia. Aktuálne je nezávislý vplyv mikovaskulárnych ochorení na morbiditu a ich prognostická úloha pre rozvoj budúcich ochorení. Súčasné epidemiologické štúdie sa zameriavajú na identifikovanie asociácií medzi rizikovými faktormi a patologickými mechanizmami v zmysle, či jednotlivé rizikové faktory predstavujú liečebné ciele alebo len jednoduché markery nemerateľného rizika. Tieto štúdie posunuli chápanie vaskulárneho ochorenia, najmä pri diabete. Taktiež dopomohli k uskutočneniu mnohých štúdií, ktoré podporujú klinické monitorovanie funkcií mikrocirkulácie v budúcnosti.

Doc. Strain absolvoval na Liverpoolskej univerzite a zahájil svoju pracovnú dráhu v oblasti kardiológie. V rocku 2000 sa presťahoval do Londýna a začal pracovať v Medzinárodnom centre pre kardiovaskulárne zdravie (International Centre for Cardiovascular Health), kde získal titul doktora medicíny (MD) na základe svojej výskumnej práce Etnické rozdiely v účinkoch inzulínovej rezistencie na vaskulatúru, v rámci ktorej popísal marker mikrocirkulačnej dysfunkcie autoregulácie. Toto meradlo, dnes nazývane „Strainův index", podáva štatistické vysvetlenie súvislostí medzi hypertrofiou ľavej komory, vylučovaním albumínu močom a – minimálne u Európanov – aterosklerotickou záťažou koronárnych tepien.

Po dokončení klinickej praxe nastúpil na Lekársku fakultu Exeterskej univerzity, kde získal postgraduálne štipendium pre docenta v oblasti klinického výskumu. V súčasnosti pracuje vo výskumnom tíme, ktorý skúma etiopatogenetické mechanizmy rôznorodých typov vaskulárneho ochorenia, počínajúc infarktom až po diabetickú kardiomyopatiu. Bol hlavným výskumníkom Spojeného kráľovstva v štúdii Diabetes u starších ľudí, ktorá skúmala uskutočniteľnosť nastavenia cieľov individualizované liečby pre diabetikov vo vyššom veku.

Doc. Strain je tiež predsedom riadiaceho výboru, členom ktorého je tiež Sir Michael Hirst, súčasný prezident Medzinárodnej diabetologickej federácie, ktorá pracuje na projektu Time 2 Do More (Prišiel čas urobiť viac). Tento projekt sa usiluje o riešenie fenoménu „klinickej zotrvačnosti" cestou motivácie pacientov a lekárov k efektívnejšej vzájomnej komunikácii, ktorá povedie k správnej reakcii na zmeny v stave pacienta.

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