Microvasculature in diabetes

John E. Tooke *

Department of Vascular Medicine (Diabetes Research), Postgraduate Medical School, University of Exeter, Barrack Road, Exeter EX2 5AX, Devon, UK

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1. Introduction

1.1. The burden of microvascular disease in diabetes

Most of the so-called long-term complications of diabetes mellitus stem from malfunction of the microvasculature. It has long been recognized that microvascular disease underlies diabetic retinopathy as well as nephropathy. More recently, damage to the microvasculature has been implicated in diabetic cardiopathy [1] as well as the pathogenesis of diabetic neuropathy [2]. The focus of this review will be on diabetic microangiopathy as it relates to the retinal renal and peripheral microvasculature.

The clinical consequences of this microangiopathic process are formidable [3]. Diabetic retinopathy remains the major cause of blindness in people aged between 30 and 60 years in the UK; diabetic nephropathy is the single major cause of commencement on renal support programmes in many western countries. Large-scale population studies have examined the lifetime risks of renal and retinal disease. In young people with diabetes 97.5% will develop evidence of some retinopathy after a disease duration of 15 years. A survey in 1983 defined a blindness prevalence of 8.5% in diabetic patients. Various studies have suggested that between 30% and 40% of patients with insulin-dependent diabetes go on to develop diabetic nephropathy. In contrast to retinopathy, this particular complication only appears to afflict a proportion of the diabetic population. However, the patient who develops nephropathy or its precursor albuminuria contends not only with the prospect of renal failure but also an increased expression of all the other complications of diabetes, as well as a mortality rate many times that of his or her counterpart who avoids this particular complication. The true prevalence of diabetic neuropathy is difficult to quantify because of variations in diagnostic criteria. It has been termed the commonest complication of diabetes and although it may be clinically silent in many patients, peripheral sensory neuropathy is a major cause of diabetic foot ulceration which results in frequent hospitalization and contributes to the fact that 40% of non-traumatic lower limb amputations occur in people with diabetes. It is not surprising that the personal impact of this clinical burden is considerable. The fear of blindness remains the major anxiety faced by people with diabetes and quality of life studies have documented the personal toll of living under the shadow of the prospect of microangiopathic complications [4]. In financial terms diabetes is a major strain on healthcare resources and the direct and indirect cost attributable to the microangiopathic complications comprise a substantial proportion of the overall cost [5].

Despite the fact that it is more than 70 years since insulin therapy was introduced to provide a means to sustain the life of people with insulin-dependent diabetes, relatively little progress has been made in the development of preventative therapy for microangiopathic complications. A variety of retrospective and short-term prospective studies pointed to a relationship between the development of microangiopathic complications and glycaemic control. The strength of this relationship was confirmed by the Diabetes Control and Complication Trial [6], a definitive prospective study confirming that long-term good glycaemic control in young people with insulin-dependent diabetes is associated with a retardation of the development of retinopathy, nephropathy and evidence of neural disease. This achievement was not without cost however; the intensively controlled group who achieved better glycaemic control experienced a three-fold risk of hypogly-
caemia and were required to conform to a rigorous surveillance programme. Furthermore, good glycaemic control is not achievable by every individual with insulin-dependent diabetes and often personal circumstances such as occupation, isolation and/or poor hypoglycaemia awareness make the pursuit of normoglycaemia a dubious strategy; in addition, it is not yet known whether the potential benefits of good glycaemic control may be extrapolated to the larger non-insulin-dependent population. There thus remains a need for alternative preventative strategies which are likely to derive from an understanding of the fundamental mechanisms linking metabolic derangement of diabetes with malfunction of the microvasculature. In recent years considerable progress has been made in understanding the physiological breakdown of the microcirculation in diabetes and the cellular and biochemical processes underlying this breakdown may now be surmised. This review summarises what is known of the microvasculature in diabetes with particular emphasis on human study, the work of the most relevance to the clinical condition.

1.2. Stages in the development of diabetic microangiopathy

Microangiopathy is not a singular process but involves various stages of development. Soon after the development of diabetes, functional changes in the microcirculation are evident which may be reversible if the metabolic abnormality is normalised. With increasing duration of diabetes structural adaptive changes occur, most marked of which is basement membrane thickening due to accumulation of extravascular matrix proteins. Basement membrane thickening is a ubiquitous finding, having been demonstrated in the microvasculature of the eye [7], kidney [8], muscle [9] and skin [10]. Although its functional significance has been debated it is sufficiently prevalent after a long duration of diabetes to be regarded as the ultrastructural hallmark of diabetes mellitus. Ultimately, in many microvascular networks complete failure of transfer function occurs perhaps precipitated by microvascular occlusion. Such a terminal event results in areas of underperfusion most well documented in the retinal microcirculation. These areas of poor tissue nutrition may trigger reparative mechanisms which in the case of retinopathy may be damaging in themselves as the new vessels may grow forward into the vitreous of the eye and run the risk of bleeding and hence obscuring the light path to the retina.

Clearly any study of the microangiopathic process must take account of the component stages of the process. In cross-sectional studies of human diabetes individual patients may be at various points along this developmental continuum depending on their individual susceptibility to the different stages. Such considerations probably account for the considerable heterogeneity in response that is observed in functional tests of the microcirculation observed in cross-sectional studies despite attempts to standardise biological variables such as age, sex and duration of diabetes.

1.3. Type of diabetes

Diabetes is conventionally divided into two major types—insulin-dependent (IDDM) and non-insulin-dependent disease (NIDDM). Although it has been customary to consider the microangiopathic complications as being of common origin in the two forms of the disease recent evidence suggests that such an assumption requires qualification [11]. Clinical observation reveals that the process resulting in blindness commonly differs in the two major forms of diabetes: proliferative retinopathy is the common cause of visual loss in IDDM, whereas maculopathy is the major problem facing those with NIDDM. Similarly, although nephropathy afflicts both types of diabetes it tends to run a slower course in NIDDM. Furthermore, it is well recognized that the prevalence of hypertension (in the absence of nephropathy) is much greater in NIDDM, as is the overall risk of arterial disease, perhaps reflecting the expression of the insulin resistance syndrome, of which NIDDM is merely one part. In any consideration of the microvasculature in diabetes therefore it is important to distinguish between these two major types of the condition. As it becomes clearer that NIDDM is a heterogeneous collection of conditions resulting from various degrees of insulin-resistance and beta cell failure, even the broad distinction between the two major types of diabetes may not be sufficient if we are to fully understand the nature of diabetic microangiopathy.

2. A pathophysiological framework

2.1. The haemodynamic hypothesis

In 1983 observations on organ and tissue blood flow in IDDM resulted in the formulation of a haemodynamic hypothesis of the pathogenesis of diabetic microangiopathy [12] (Table 1). The hypothesis argues that early in diabetes microvascular flow and pressure are increased in those organs that develop diabetic microangiopathy. These

| Table 1 |
| The haemodynamic hypothesis of the pathogenesis of diabetic microangiopathy in insulin-dependent diabetes |
| Early increased microvascular pressure and flow |
| ↓ |
| Endothelial 'injury' response |
| ↓ |
| Microvascular sclerosis |
| ↓ |
| Impaired microvascular hyperaemia |
| ± |
| Loss of autoregulation |
haemodynamic stresses result in an injury response in the microvascular wall with the production of basement membrane thickening as a consequence. This sclerotic process in turn limits the vasodilatory capacity of the microvasculature impairing maximal hyperaemia as well as interfering with the ability of the microcirculation to autoregulate.

Indirect evidence is available for each of these stages in human diabetes [13]: retinal blood flow is increased early in diabetes, yet falls in advance of the development of proliferative retinopathy; renal plasma flow is increased in recently diagnosed patients with IDDM and falls with the development of renal failure; autoregulatory impairment has been described in the renal, retinal and peripheral circulations. Particularly strong pieces of evidence in favour of the hypothesis are the facts that unilateral renal artery stenosis may retard the development of ipsilateral nephropathy, and carotid artery stenosis appears to protect against the development of retinopathy.

Changes in capillary pressure as the cause of the sclerotic process were, however, inferred from measurements of whole organ blood flow. This is a flawed assumption because increased organ flow does not necessarily imply an increase in capillary pressure which is determined by the balance of pre- to post-capillary resistance. If post-capillary resistance is reduced, organ blood flow may be high yet pressure remain within normal limits. Measurements of glomerular capillary pressure in a diabetic rat model suggested that capillary hypertension did indeed exist in diabetes [14] but measurements of human capillary pressure are confined to the nailfold capillaries. Using an electronic servonulling technique coupled with direct cannulation of individual nailfold capillaries, Sandeman et al. established that mean capillary pressure is significantly elevated in IDDM compared to age- and sex-matched control subjects [15]. Furthermore, in keeping with criteria likely to be associated with a prime moving pathogenetic mechanism, capillary pressure was positively correlated with the glycated haemoglobin concentration at the time of pressure measurement, the association being particularly strong in patients of short disease duration. Furthermore, improvement in glycaemic control through attention to blood sugar monitoring, diet and exercise over a 3-month period, resulted in a significant reduction in capillary pressure. Perhaps the most compelling piece of evidence in favour of the hypothesis was the demonstration that capillary pressure was particularly elevated in subjects with microalbuminuria who are known to be at high risk of clinical microangiopathy [16]. In contrast, mean capillary pressure in age and sex-matched patients of similar disease duration and glycaemic control without clinical evidence of microangiopathy showed values that were indistinguishable from normal (Fig. 1).

Considerable epidemiological evidence links the expression of microangiopathy to arterial pressure values. Capillary pressure has been shown to be raised in non-diabetic subjects with essential hypertension [17] and it might be assumed that the coexistence of arterial hypertension might aggravate capillary hypertension resulting from diabetes, although this remains to be confirmed. However, studies in normal subjects suggest that the peripheral microcirculation is protected from increments in arterial pressure as a result of, for example, isometric exercise [18], yet in some patients with diabetes this regulatory response appears to be deficient. It is thus likely that the overall capillary blood pressure load in IDDM exceeds that suggested from studies of subjects under resting laboratory conditions. Furthermore, the postural regulation of capillary pressure appears to be impaired in IDDM, suggesting that lower extremity capillaries are exposed to an even greater hydrostatic load on dependency [19].

The haemodynamic hypothesis argues that with increasing disease duration there is a limitation in maximal hyperaemia. Using laser Doppler flowmetry to measure cutaneous microvascular blood flow in response to a number of vasodilatory stimuli it has been possible to confirm this assertion [20]. Maximal cutaneous hyperaemia to a thermal stimulus is impaired even in children with insulin-dependent diabetes compared to age- and sex-matched control subjects. Furthermore, the impairment is related to the duration of diabetes [21].

The association between reduced maximal hyperaemia and early elevation of capillary pressure and flow is thought to be at least in part due to the physical constraints on vasodilatation resulting from basement membrane thickening and arteriolar hyalnosis. Biopsy studies have confirmed an association between maximal cutaneous hyperaemic response capillary basement membrane thickening in the area studied and autoregulatory impairment in the lower
limb has been correlated with the degree of PAS staining of arteriolar tissue obtained by biopsy [22].

2.2. Competing physiological theories: the Steno hypothesis

Increases in pressure and flow are not the only functional observations that have led to theories of the pathogenesis of diabetic microangiopathy. Various studies suggest that microvascular permeability is increased in insulin-dependent diabetes and a genetically determined increase in the leakiness of the endothelial cell barrier has been put forward as the reason why some patients with diabetes are more susceptible to nephropathy (characterized by early albumin leak) as well as the atherosclerotic process affecting large vessels [23]. This so-called Steno hypothesis (named after the Institute from which it originates) argues that inherited defects in the enzyme N-D Acetylase, an important determinant of the production of heparan sulphate proteoglycan which influences the endothelial charge barrier, is the molecular basis for the increased permeability observed. Verification of the hypothesis in human diabetes is problematic, representing the difficulties in measuring permeability. For example, it is impossible to know the surface area available for exchange, and local microvascular pressure and flow which influence the exchange process are seldom accurately known at the same time as permeability measurement. Nevertheless, using a computerized plethysmographic system it has been demonstrated that human limb capillary filtration coefficient (an estimate of capillary permeability to water) is increased in patients with incipient nephropathy (i.e. a small but excessive urinary albumin leak in the range 20–200 μg/min) compared with patients without this abnormality despite a similar disease duration and level of glycaemic control [24]. Thus it appears that patients at high risk of microangiopathy are characterized by the existence of both high capillary pressure and permeability. Whether these abnormalities are independent or in some way linked remains to be determined.

2.3. Microvascular function in non-insulin-dependent diabetes

Although there have been fewer estimates of microvascular function in NIDDM, measurements of organ blood flow under resting conditions suggest that a control-related increase in flow is also observed in this form of the disease. However, in normotensive patients with NIDDM capillary pressure [25] and capillary filtration coefficient [26] appear to be normal compared to values obtained in age- and sex-matched controls. The transcapillary escape rate of albumin is also probably normal in normotensive patients.

The most profound abnormality observably in NIDDM is a highly significant reduction in the maximum hyperaemic response which is present at diagnosis of the disease [27]. Such an abnormality could represent the impact of hyperglycaemia due to a period of subclinical diabetes before the diagnosis is made; alternatively, it could represent the impact of other components of the insulin-resistant state that commonly precedes the onset of NIDDM.

Some support for this hypothesis has been obtained by studying patients with mild impairment of glucose tolerance not amounting to the diabetic state. Maximal cutaneous hyperaemia is markedly reduced in such subjects compared to age- and sex-matched health controlled subjects [28]; furthermore, the abnormality correlates with fasting insulin levels and calculated estimates of insulin sensitivity [29], i.e. the more insulin resistant the subject is, the greater the impairment of maximum hyperaemia. There was no association between impaired hyperaemia and estimates of 24-h blood pressure load, measures of android obesity, plasma lipids or absolute glucose level.

In further support of the concept that insulin resistance may be playing an important part in the limitation of maximal hyperaemia is the observation that similar reductions are observed in other non-diabetic patient groups with insulin resistance such as acromegalic individuals with growth hormone excess [30].

It is pertinent to ask whether the observations in NIDDM negate the haemodynamic hypothesis for which there is considerable support in IDDM. It should be stressed that the observations relating to capillary pressure and filtration in NIDDM relate to normotensive patients. It is conceivable that in the presence of hypertension capillary pressure values will be elevated, as indeed is the case with subjects with essential hypertension. Furthermore, capillary pressure values thus far have only been estimated ‘at rest’ in this patient population. As it appears that the autoregulation of capillary pressure is disturbed in diabetes it is conceivable that the capillary blood pressure load is also excessive in many patients in this form of the disease.

3. Biochemical and cellular mechanisms

A physiological framework permits the generation of plausible cellular and biochemical mechanisms which fit the physiological facts. Naturally the search for biochemical mediators has centered on hyperglycaemia and its consequences, although recent evidence suggests that other metabolic and hormonal accompaniments of the diabetic state may be important in pathogenetic terms. For example, insulin-dependent patients are C-peptide as well as insulin deficient and supplementation with C-peptide improves aspects of renal function [31]. Insulin-resistant patients develop high levels of pro-insulin before the emergence of diabetes and such high levels have been correlated with the hypofibrinolysis characteristic of this metabolic state [32]. Correction of hyperlipidaemia, common in non-insulin-dependent diabetes, has been associ-
ated with preservation of renal function [33]. Nonetheless, it is likely that hyperglycaemia plays a major role and there are a number of possible metabolic pathways through which its effects may be mediated.

Hyperglycaemia results in increased flux through the sorbitol pathway facilitated by the activity of the enzyme aldose reductase [34]. Various potentially pathological consequences of increased flux through this pathway have been suggested, including increase in the cell's osmotic load due to accumulation of sorbitol, depletion of certain cofactors required for the genesis of nitric oxide and the protection against free radical damage, and an alteration in the cell's redox potential favouring vasodilatation and protection against free radical damage, and an alteration in which its effects may be mediated.

A second important mechanism through which hyperglycaemia could mediate adverse effects is the formation of advanced glycation end products, a non-enzymatic reaction with major effects on the structure and functional behaviour of proteins so modified [35]. In this manner receptor function can be disturbed, immune-mediated damage triggered and the biophysical properties of proteins altered. Accumulation of advanced glycation products within the vascular cell also increases the generation of oxygen-derived free radicals as well as quenching nitric oxide.

3.1. Co-ordinating role of the endothelium

The endothelium is no longer regarded as a passive inert membrane but a highly important tissue orchestrating many aspects of microvascular function, including pressure, flow, permeability, angiogenesis and blood fluidity. It is no wonder that this tissue has been viewed as the major culprit in the genesis of diabetic microangiopathy [36], although in the retina the pericyte which exists in equal numbers is very important and hyperglycaemia is known to have direct effects upon vascular smooth muscle structure and function. Furthermore, in vitro studies suggest that insulin pcr sc (which is present in excess due to insulin resistance and/or because of therapy) is known to cause vascular smooth muscle cell proliferation.

Nevertheless, the evidence for a co-ordinating role by the endothelium is compelling. D-glucose is known to enhance the production of nitric oxide by the endothelium as is shear force which will be enhanced in the early stages of diabetes. With increasing disease duration advanced glycation products will develop and the resultant free radical damage will inhibit the production of nitric oxide, perhaps contributing to the impaired vasodilatory responses observed. Intra-arterial infusion studies which have been used to examine the control mechanisms governing the forearm vascular bed suggest that endothelial-depen-
dent vasodilatation may be impaired in insulin-dependent patients with microalbuninuria, whereas vascular smooth muscle responses are normal [37]. In contrast, in non-insulin-dependent patients both responses are impaired [38]. Early work using iontophoresis of acetylcholine and the direct nitro donor sodium nitroprusside in the cutaneous vascular bed in non-insulin-dependent diabetes confirm these latter findings [39].

3.2. Extravascular matrix protein elaboration

A consistent feature of the microvasculature in diabetes is the re-duplication of the capillary basement membrane whereas in the kidney there is accumulation of the chemically similar mesangium. Basement membrane thickening could reflect increased production and/or reduced degradation, and there is evidence for both processes in diabetes. The stimuli to basement membrane thickening are becoming clearer but their interactions and the transduction of the stimuli into protein manufacture are less well understood. Hyperglycaemia per se will increase the mesangial mRNA expression for laminin, Type IV collagen and fibronectin by retinal endothelial cells [40], and both pressure and shear may also be capable of eliciting a similar response. Early evidence supporting the contention that hydrostatic capillary pressure is a determinant of basement membrane thickening stems from the observation that basement membrane area increases the further below the heart that a tissue sample is taken from both animals [41] and man [42]. In the renal glomerulus capsular distension stretching the mesangium has been shown to increase the production of extravascular matrix proteins in a rat model [43]. The process of basement membrane degradation has received less attention, although there is some evidence that long-term good glycaemic control reduces basement membrane thickening suggesting that the process is dependent upon glycaemic control [44]. Delayed degradation in diabetes could reflect the changed chemical composition of the membranes.

3.3. Evidence for microvascular occlusion

It is not clear what causes microvessels to occlude in diabetes or whether the process is a permanent one, although clear evidence of non-perfusion is found on retinal fluorescein angiography. Studies comparing fluorescein angiograms with retinal digest preparations have revealed that most non-perfused vessels have lost pericytes in addition to endothelium [45].

Several blood products have been implicated in the occlusive process with early attention focusing on the platelets. Despite numerous studies suggesting that platelet function is deranged in diabetes [46], attempts to inhibit platelet function have produced disappointing therapeutic results. More recently the white blood cell has been implicated as a cause of capillary occlusion in diabetic microan-
giopathy as well as many other diseases, including arterial ischaemia, reperfusion injury and physiologic shock [47]. The large volume and structural rigidity of granulocytes and monocytes makes them a natural candidate for the mediator of the occlusive process and their capacity to generate toxic free radicals as well as proteolytic damage provides further mechanisms of tissue dysfunction. In a streptozotocin rat model direct evidence of capillary occlusion by leukocytes was observed in retinal preparations [48] and the percentage of activated white cells appears to be increased in the diabetic state. Furthermore, the recent demonstration that advanced glycation end-products interact with their endothelial receptor to induce expression of the granulocyte adhesion molecule VCAM-1 may provide a mechanism for the occlusive process in diabetes [49].

More recently the role of the blood coagulation factors has received more attention with the demonstration that fibrinolysis is potentially impaired in subjects with pre-diabetes relating to pro-insulin stimulation of plasminogen activator inhibitor PAI-1 expression [50].

3.4. Angiogenesis

Angiogenesis is a significant component of the microangiopathic process in the retina for the new vessels so formed are prone to bleed but also result in the generation of fibrous tissue which can cause traction on the retina. There appears to be little doubt that the ischaemic retina can stimulate the production of new vessels by releasing angiogenic factors, numerous of which have been described. Recently it has been demonstrated that the levels of vascular endothelial growth factor (VEGF) are raised in the intra-ocular fluid of patients with active retinal and iris new vessels than in patients with quiescent or non-proliferative retinopathy [51]. Furthermore, the elevated levels decline after successful panretinal photocoagulation. The growth of endothelial cells is stimulated in vitro both by VEGF and by ocular fluids containing the growth factor. This latter effect is only partially inhibited by VEGF neutralising antibodies, suggesting that other factors are involved. Basic fibroblast growth factor levels are also elevated in ocular fluids from patients with diabetic new vessels [52] and pericyte damage/disappearance almost certainly also contributes to the genesis of proliferative diabetic retinopathy [53].

4. Conclusions and therapeutic implications

The capacity to measure human microvascular function directly is adding to our knowledge of the pathophysiology of diabetic microangiopathy. From such observations a pathophysiological framework is being derived which suggests that there are differences between the pathogenesis of vascular damage in the two major forms of diabetes [54]. As more is learned of the heterogeneous nature of non-insulin-dependent diabetes such distinctions may become more important and perhaps account for the epidemiological differences in the expression of diabetic microangiopathy observed in clinical practice. Such a pathophysiological framework or frameworks enables the genesis of plausible candidates cellular and the mechanisms which ascribe a pivotal role for the vascular endothelium. Knowledge of these mechanisms will lead to the introduction of new treatments aimed at preventing, retarding or reversing the microangiopathic process.

Thus far, tight glycaemic control is the only preventative weapon in the diabetologists' armamentarium. However, levels of glycaemic control that will significantly retard the microangiopathic process are hard to achieve without risk in clinical practice in all subjects and thus other therapies are still required. Table 2 lists the potential targets for therapeutic intervention. Of these, it has already been demonstrated that capillary hypertension can be manipulated by certain blood pressure lowering drugs [55]. As far as non-insulin-dependent diabetes is concerned, the most exciting development is the potential availability of drugs for influencing insulin resistance [56]. Alone or in combination these new therapeutic strategies provide hope for a better outlook for the diabetic patient as regards microangiopathy in the not too distant future.

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