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*Review Articles*

# Relation of Diabetic Control to Development of Microvascular Complications

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**Summary.** This review seeks to supply the arguments which support or deny the relationship between the quality of control of blood glucose levels and the course of diabetic microangiopathy. The ideal study is impossible to do in man but most prospective studies suggest that the better the control the slower the rate of progression and severity of lesions. "Scientific" but indirect arguments from biochemical, enzymatic and functional studies have shown that insulin and/or blood glucose control reverse some early diabetic changes that are probably related to the late events. Recent studies suggest that observations on animals that have shown the beneficial effect of treatment are relevant to the problem of diabetic microvascular lesions in man. Heredity influences the development of diabetic microangiopathy in diabetics but retinal and/or glomerular lesions – which are definitely not pathognomonic for diabetes – do not appear in the absence of hyperglycaemia. Muscle capillary basement membrane thickening that seems not to be a specific abnormality was not observed by several investigators in recently diagnosed diabetics. Therefore most of the arguments that have been given to support the point of view that tight control is not justified may be rejected. The opinion of the author is that strict control of diabetes is worthwile in patients with long life expectancy and no psychological, social or cultural handicaps.

**Key words:** Diabetes control, microangiopathy, blood glucose, vascular complications, treatment of diabetes.

Microvascular disorders in diabetic patients are probably of multifactorial origin (1–3) including some genetic susceptibility (4–8). However several data strongly suggest that the mechanisms responsible for diabetic microangiopathy are initiated as a result of insulin deficiency and that the development of the microvascular complications of diabetes may be inhibited and/or delayed by careful control of blood glucose concentration. Some authors have questionned, however, whether the benefits of tight control are sufficiently proven to warrant the risks of hypoglycaemia [9, 10]. They also question whether or not the microangiopathic lesions in diabetic patients could be primarily and completely determined by heredity whatever the carbohydrate tolerance [11].

This review focusses on a critique of some of these controversial points.

## Clinical studies

The definite demonstration that the microvascular complications of diabetes can be prevented by the normalisation of blood glucose concentrations in man cannot be made since normoglycaemia cannot be sustained from the beginning of the disease with our current methods of treatment. The impossibility of comparing perfectly controlled and uncontrolled diabetic patients makes it possible only to study varying degrees of imperfection. Even collecting partial evidence showing in man, that the better the control, the less the rate of progression and severity of retinopathy and nephropathy is a very difficult and frustrating task. Definite criteria are lacking for the quantification of both complications and the degree of control [12]. The ideal study is impossible to do in man for practical and ethical reasons [9, 13].

The controversies during the last 50 years were partly the result of the fact that most studies were retrospective with a great deal of bias. Numerous large reviews have discussed the relationship between the degree of diabetic control and the develop-

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ment of microangiopathy [9, 14–23]. Some were unable to show a positive effect of the quality of control [9, 14, 18, 23]. In 1964 Knowles [14], after a comprehensive analysis of more than 300 reports, concluded that "information sufficient to arrive at any conclusions is not yet at hand". Almost 10 years later, Kaplan and Feinstein [18] made an analysis of the methods that were used in 149 papers. They concluded pessimistically, that a "predominantly statistical approach to therapeutic trial cannot be expected to resolve the existing scientific controversies about treatment". Bondy and Felig wrote that ". . . this belief must be considered a manifestation of faith rather than of scientifically proven fact" [9]. Raskin's conclusions are "There has been little convincing clinical evidence for the view that rigid control of the metabolic abnormalities will prevent the vascular complications of the disease because few diabetics have ever been rigidly controlled. However, there is no overwhelming evidence to the contrary i. e. that the vascular complications are independent of the hyperglycaemia" [23]. None-the-less most reviewers concluded that good control of blood glucose in diabetic patients in beneficial [15–17, 19–22]. Their opinion resulted essentially from the analysis of prospective studies.

Yet most of the retrospective studies, even if they have never really proven that good control was beneficial, have strongly suggested that bad control was associated with more, and severer forms of complications [24–27]. It was suggested by Constam [26] and by Caird et al. [16] that the first few years of treatment are critical: diabetics whose diabetes has been well controlled in the first few years and poorly controlled later on have fewer late complications than those with the reverse sequence. Among old studies [28–31] showing inconclusive results was that by Dolger, often cited to support the lack of any beneficial effect of good control [30]. According to Pirart and Lauvaux, however, Dolger's methods do not stand up to even superficial criticism because the criteria of control were not given [21, 32].

Among the twenty or so prospective studies considered valid by recent reviewers only a few have failed to show any relationship between the incidence of retinopathy and glomerulopathy and the quality of diabetic control. That done by Knowles and his colleagues in 1965 examined very poorly controlled children and adolescents [33]. As emphasised by Pirart "not having a group of well controlled subjects the authors have compared 22 cases without retinopathy to 25 cases with retinal lesions" [32]. It could be suggested that such a study, like that of Gerritzen [34] tries mainly to answer the question whether among poorly controlled diabetic patients some develop more or fewer retinal lesions. The recent UGDP report on non-fatal events claimed that attempts to normalise blood glucose in the adult onset diabetic did not alter the incidence of renal impairment, retinal changes or the other common complications of diabetes. It stated that "of course it must be recognized that few patients were found to have renal or ocular disorders over the period covered by this report, and longer periods of follow up may yield different results with respect to these vascular changes" [35].

In the study by Malone et al. [36] on children where the retinal abnormalities did not appear related to diabetic management or control, the quality of diabetes control was estimated by the presence or absence of growth failure, a rather imprecise index for refined comparisons.

Among 14 prospective studies in patients with established retinal or glomerular lesions [21, 22, 35, 37–48] 4 drew negative conclusions. The UGDP study has just been mentioned [35]. Davis showed improvement of proliferative lesions without clear evidence of any changes in diabetic management [41]. Schlesinger et al. [39] and Burditt et al. [42] were unable to show the influence of control on the rate of deterioration of established lesions. These results were discussed by Kohner and Dollery [20] who pointed out that progression of retinopathy in those two studies, despite good control, indicates the progression of one type of retinopathy to another rather than variations in severity of a particular type of lesion.

All other studies have demonstrated that good or very good control slows down the rate of deterioration of established lesions [21, 22, 37, 40, 43–48].

Kohner et al. have shown that after an average of one year of follow up, only in the groups with good or very good control did microaneurysms, haemorrhages and new vessels not worsen [43]. Miki et al. have shown that after 6 years of follow up the patients with fair and poor control had a greater frequency of worsening proteinuria than those with good control. The difference was even more marked in the patients with the highest initial fasting blood glucose [45]. Takazakura et al. have performed serial renal biopsies in 23 patients. The average interval between the first and the second biopsy was 52.6 months. Their results, despite great heterogeneity in patients, suggest that the group of diabetics in which the lesions did not worsen tended to maintain better control of blood glucose levels than the group in which the lesions were progressive [47].

The Brussels' study by Pirart and Lauvaux that followed 4,398 subjects for 25 years has shown that "the duration and severity of hyperglycaemia seem to

be the only factors which can be definitely linked with the development, at whatever age, of diabetic triopathy and with the overall frequency of these complications. Furthermore increasing hyperglycaemia is associated with a high frequency of severe and progressive forms of diabetic retinopathy" [21, 22, 32].

Our group in Paris decided in 1968 to assign randomly insulin-dependent patients either to long-acting insulin given once a day or to a regimen consisting of 2 or 3 injections per day. The use of multiple daily insulin injections has been advocated by several authors (in 49). In our experience this technique has in short term studies been the most effective method for the control of diabetes [49–51]. The aim of the trial was to compare the increase in the number of retinal microaneurysms (by fluorescein angiogram) in the two groups. After a mean time of 3 [48] and 4 years [52] we observed that the mean yearly increase in the number of microaneurysms and the mean survey values for fasting blood glucose concentration were lower in the multiple injection group than in the single injection group. The shifting of patients from one group to another may represent an important defect in the study [10, 23]. In fact, patients were initially assigned either to the multiple (M) or the single (S) insulin injection group [48] and not "to the well controlled group scheduled to receive three injections of insulin per day" [10]. Some shifting occurred for only one fourth of the patients. In addition such a movement between groups could only diminish the significance of the results between the two groups and not improve it.

Thus clinical studies despite their difficulties and limits seem to support the hypothesis that good control of diabetes, at least in terms of blood glucose, is worthwile.

Are there any *indirect arguments* that would also justify tight control of blood sugar in some diabetic patients, at least in those with long life expectancy and no social, cultural, economical and psychological handicaps? In other words could epidemiological, pathological, biochemical and functional data help the clinician to formalise his ideas on the potential benefits of diabetes control? Dozens of abnormalities (causes or consequences of the microvasculopathy) have been described in diabetic men and animals (1–3, in 53). Among the changes that occur in the capillary wall, the perivascular tissue, the composition of blood and organ size and function, some have been proven to be reversible or preventable by conventional treatment or ideal cure of the disease.

## Epidemiological Studies in Man

In 1946 the population of Oxford, Massachussetts was screened for diabetes by post-prandial blood sugar determinations. Over the subsequent 17 years O'Sullivan et al. [54] have shown that in persons who were diabetic, hypertension, electrocardiographic abnormalities, fundoscopic changes and survival rates, were all related to high initial blood sugar levels.

Jarrett and Keen have shown [55] that the percentage of patients with retinopathy at survey and 5 years later was related to the 2-hour blood sugar levels. Katsilambros reaches the same conclusions from an investigation done in Athens on 21,410 subjects [56]. The percentage of Pima Indians with proteinuria was twice as high in those with 2-hour plasma glucose levels in the range 200–299 mg/100 ml than in those with values between 140 and 160 mg/100 ml. [57]. Above 200–299 mg/100 ml increasing glucose values were not associated with an increased frequency of proteinuria. In non-insulin dependent diabetic patients we have shown [58] that retinal changes were related to the duration of diabetes and to the degree of blood sugar intolerance analysed five years previously.

## Clinical Microangiopathy and Pathologic Changes in Animals with Experimentally Induced Diabetes

Since the specificity of pathological changes at the ultra-structural level has been questioned in the experimentally induced diabetic animal [10], it must first be emphasised that retinal lesions, including microaneuryms, obtained in alloxan-diabetic dogs were less marked in animals moderately well controlled with insulin given twice a day for 60 months than in dogs intentionally poorly controlled with a more conventional insulin regimen [59].

As stressed by Engerman et al. [59] the similarities between the microvascular disease in diabetic patients and dogs would suggest that these observations on animals are relevant to the problem of diabetic microvascular disease in man. It should be noted though that animals tend to develop background rather than proliferative retinopathy.

Studies in diabetic rats, dogs and monkeys have shown that glomerular and/or retinal capillary membrane thickening undoubtedly develops after the induction of diabetes [60–71]. This includes the streptozotocin-hyperglycaemic rats studied by Mauer [71]. In chronic hyperglycaemic eels the thickness of the basement membrane of the rete capillaries is

increased [72]. Whatever the significance [73] of such a lesion "generally held to be the sine qua non of diabetic nephropathy" (10) it should be recalled that in animals with experimentally-induced diabetes, the reduction of hyperglycaemia by conventional or "ideal" treatments of the disease prevents, reduces, reverses or minimizes the formation of diabetic-like lesions in the kidney including capillary membrane thickening [59, 66, 68–70, 74–80].

## Biochemical and Enzymatic Changes

There is more collagen-like glycoprotein in human diabetic glomeruli than in those of non-diabetics [81–83]. This is due to an increased synthesis [84, 85] and/or to a decreased degradation of glycoprotein [86, 87]. Most authors claim that the increased collagen substance is not enriched in disaccharide units and that galactosyltransferase activity is not increased as compared to lysyl and prolyl-hydroxylase activities [84, 88–90]. Whatever this controversal point, it has been shown that insulin administration normalises or reduces the lysyl-hydroxylase activity in isolated glomeruli from diabetic rats [85, 91]. Fushimi and Tarui [92] showed that in streptozotocin induced diabetic rats, beta-N-acetyl-glucose-aminidase activity was increased in the serum and decreased in the kidney after 8 weeks of diabetes. Insulin administration significantly reverses these anomalies. The authors point out that beta-N-acetyl-glucose-aminidase is implicated in glycoprotein catabolism, principally in lysosomes, and they suggest that the diabetes-induced anomalies contribute to glycoprotein accumulation in the diabetic kidney. According to Spiro and Spiro there is an increase in the proportion of disaccharide radicals linked to the polypeptide chains in renal capillary basement membrane of diabetic men and rats [93]. These authors showed that careful and early treatment with insulin normalised the increased glucosyl-transferase activity responsible for this disaccharide accumulation in rats [93].

Thus some authors have shown a beneficial effect of insulin on the diabetes-induced renal enzymatic anomalies. However Archer and Kaye [94] have shown collagen hypersecretion by fibroblasts originating from cultured skin of diabetic humans and suggested that a genetic defect could be responsible.

## Functional Microangiopathy, Organ Size and Blood Composition Changes

1) Early changes in capillary wall permeability may occur a few months or a few years after the beginning of the disease in poorly controlled diabetic subjects. Abnormal transcapillary escape rate of albumin [95], abnormal urinary albumin excretion during exercise [96] and leakage of fluorescein from the retinal vessels into the vitreous and the anterior segment of the eye have been described [97–101]. Several reports indicate that strict control of blood sugar levels reduces or abolishes these manifestations of functional microangiopathy [95–97].

Whether capillary wall thickening precedes [102], follows [103] or develops in parallel with the breakdown of the normal blood-tissue barrier is a matter of discussion. It has also been disputed whether hyperpermeability may be related to biochemical alterations in the basement membrane, such as a decrease in the cystine content of the human diabetic glomerular basement membrane [104] or an increase in disaccharide units [81, 102].

The main problem is to know whether these functional abnormalities should be regarded as "a forerunner of long-term diabetic complications or if the two should be thought of as independent entities" [105].

2) The early changes in renal size and function that have been described in animal and human diabetes have been shown to be reversible by very strict control of blood glucose. These reversible changes specifically include renal hypertrophy, glomerular enlargement, cellular hypertrophy, increased protein synthesis and increased GFR [105, 106].

3) Among the numerous changes that have been described in the blood in diabetes [1–3, 53, 107–113] some have been shown to be reversible or preventable or correlated to the degree of control [108–112]. Examples of this are glycosylated haemoglobin concentration [108, 111] and red cell deformability [110]. The fact that decrease of blood glucose may lead to a decrease in blood viscosity and to an increase in oxygen delivery to tissues [109] could be of paramount importance since hyperviscosity and/or hypoxia may act as triggering mechanisms for the development of capillary proliferation in the retina [101, 114]. It has recently been pointed out that renal and retinal diabetic-like lesions have been observed in other diseases with hypoxia and/or hyperviscosity [101, 107, 114, 115]. Strict control of blood glucose also normalises growth hormone secretion which may play a permissive role in the development of diabetic microangiopathy [116].

## Discussion

Since scientific and definitive clinical proof in human diabetics are not (yet?) available, one of the major

questions is whether indirect arguments taken from biochemical, enzymatic, ultrastructural and functional studies in diabetics and animals with experimental diabetes of rather short duration are relevant to this discussion. It has been questionned whether there is any direct or indirect causal relationship between early documented abnormalities and late clinical symptoms of diabetic microangiopathy or whether the two are independent manifestations or a primary underlying disease [87]. If the second proposition is true, the fact that insulin administration by ideal or conventional techniques prevents, delays or minimizes most of the events observed in early diabetes in men or animals cannot be retained to affirm that strict control of diabetes in man would be beneficial in the long term. For instance some reports [117, 118], but not all [6], have shown a positive relationship between muscle capillary basement membrane thickening and the presence of diabetic retinopathy and/or glomerulopathy. Capillary basement membrane thickening should not, however, be considered as a specific manifestation of diabetes [73, 119, 120] and perhaps not as a cause of the late pathological changes. It may indeed be suggested from retinal and renal studies in man and animals that there is a continuous progression from early pathological and functional changes (such as the breakdown of the blood-retinal barrier) to severe and/or life threatening lesions in the eyes and kidneys. Why unpredictable neovascularization occurs only in *some* badly controlled patients remains obscure. As was stressed previously many different mechanisms and/or a genetic suceptibility may be involved in these different evolutionary patterns.

Because of these uncertainities some prominent scientists and physicians have questionned the validity of clinical studies and findings in animals and have asked whether the benefits of tight control have been sufficiently proven to warrant the risks of hypoglycaemia [9, 10, 23, 36]. Eight groups of arguments have been given to support this point of view and these will now be discussed:

1) *"Hereditary influences may play a critical part in the pathogenesis of diabetic vascular disease"* [10].

Many studies have demonstrated genetic influences [4–8, 12]. In particular Pyke and Tattersall have shown that diabetes in concordant pairs of twins was more likely to be complicated by severe retinopathy than in discordant pairs [4]. But as stressed by these authors non-diabetic identical twins of diabetics have no diabetic retinopathy [4]. Studies of twins [122] and of triplets [123] have shown the lack of capillary changes in the non-diabetic subjects. Thus even if heredity influences the development of microangiopathy, diabetes is necessary for its appearence.

2) *"The course of clinical microangiopathy in the individual patient is often so unpredictable that it is extremely difficult to relate it to insulin deficiency alone"* [9, 10].

This only indicates that individuals are more or less prone to develop microangiopathy. Statistically microangiopathy develops with the duration of diabetes and is present in almost all subjects after three or four decades of the disease [16]. The individual evolution of retinal and/or glomerular lesions might depend on permissive or aggravating factors, of which only a very small number are known. Thus severe myopia, intra-ocular hypertension (in 101) and of growth hormone deficiency (in 116) seem to protect diabetics from the development of microangiopathy or at least from its severest forms. Conversely hypertension [96, 124] and increased glomerular blood flow [125] are accelerating factors. As recalled previously, heredity may also play a role. The argument according to which severe diabetics with severe metabolic decompensation have few lesions while benign diabetics (without great hyperglycaemia) would have serious ones cannot be retained. What do benign and serious diabetes really signify? Is it more serious to be affected with insulin-treated diabetes, unstable, oscillating from frank (but acute) hyperglycaemia to hypoglycaemia, or with obese diabetes, unknown for 20 years, characterised by moderately but constantly elevated blood glucose levels day and night? It is therefore not possible to compare the degree of retinal and/or renal lesions to the "gravity" of the diabetes in an individual.

3) *"Nodular glomerulosclerosis and retinopathy have been described in the absence of glucose intolerance"* [9, 10].

Both lesions, even if extremely characteristic of diabetes, are not specific and not pathognomonic for diabetes. Retinal lesions have been described in diseases accompanied by hypoxia and/or hyperviscosity [in 101, in 114]. Kimmelstiel-Wilson nodules have also been found in multiple myeloma and the benign monoclonal gammopathies [126, 127, in 115].

Furthermore, if one is rigorous in one's analysis of reports of so-called cases of microangiopathy without diabetes, only two [128, 129] are relevant to the discussion, i. e. those which are "characteristic" of diabetes with no present nor previous hyperglycaemia. Other reports describe either lesions that are not characteristic of diabetes or subjects who are or were previously diabetic (see 21 and 130 for reviews). Some reports deal with recently discovered

diabetes complicated by retinopathy or glomerulopathy. These can be discounted in that diabetic remissions are well known, as are the asymptomatic character of moderate chemical diabetes and the variability of glucose tolerance tests in moderate diabetes [131].

Studies on the Pima Indians where more than 40% of the subjects, 35 years old or older, are affected by the disease also carry solid arguments against the existence of diabetic nephropathy without diabetes. Kamenetzky and colleagues studied 1,848 Pima Indians. At the autopsy of 105 subjects, 43 diabetics and 62 non-diabetics, no nodular glomerulosclerosis or exudative glomerular lesion existed in the non-diabetic while the frequency in the diabetics was 55% and 44% respectively [57].

4) *"Quadriceps capillary basement membrane thickening may be present at the time of diagnosis of diabetes and in so called prediabetic subjects but not in secondary diabetes [11]". "Glomerular basement membrane width in the study by Österby was actually present at 1 1/2 years indicating that such thickening must have started even before that time [10]." "Microaneurysms and/or fluorescein leakage are demonstrated in the eyes of diabetic children at a very early stage, i. e. between one and four months"* [36].

Let us recall a) that several workers have shown that the capillary wall is normal at the onset of diabetes in kidney [132–134] as well as in muscle (see 120 for review); b) that the specificity of capillary basement membrane in quadriceps muscle has been questioned [120]; c) that the muscle capillary is probably not the best capillary for such studies [135, 136]; d) that technical problems probably explain the discrepancies between laboratories [83, 120]; e) that Ruth Österby has carried out serial renal biopsies and claimed that the capillary wall was certainly of normal width at the first biopsy [134]; f) that fluorescein leakage is a very early phenomenon in poorly-controlled diabetic rats [97] and man [99] which is reversible by careful treatment of the disease [97]; and finally, g) that microangiopathy has been described in secondary diabetes after a certain time both at the ultra-structural [137] and at the clinical level (see 138 for review).

Some studies in children have shown either normal basement membrane width, even with Siperstein's method [139], or a good correlation between basement membrane thickening and the degree of hyperglycaemia, its duration or the quality of control [140–142]. In a very recent review Raskin [23] emphasised that in the patients with secondary diabetes he studied, prolonged hyperglycaemia may play a role in the development of quadriceps capillary basement membrane thickening.

5) *"Clinical trials remain inconclusive [10] at least because we do not have reliable biochemical measurements of control"* [9].

This was discussed above.

6) *"The relevance of animal lesions to those of man remain an open question . . . Mauer et al. did not observe changes in the glomerular basement membrane material, lesions generally held to be the sine qua non of diabetic nephropathy"* [10].

As discussed previously, several authors, mainly on the eastern side of the Atlantic ocean, have shown that capillary basement thickening occurs in various species with experimentally induced diabetes. Furthermore Mauer et al. have also recently described such a lesion reversible by good control [71].

7) *"Biochemical changes (sorbitol accumulation and increased concentrations of glycosylated haemoglobin) have not be proven to be consistently associated with or causally related to the microangiopathic lesions of diabetes in man"* [10].

Proof has been obtained that sorbitol accumulation is linked to nerve changes and cataracts (see 53 and 143 for reviews) but the postulated role of sorbitol in retinal changes still has to be tested [101]. A recent review has discussed the beneficial effects of lowering red cell oxygen affinity in diabetes in order to achieve better tissue oxygen supply [109].

8) *"Frequent hypoglycaemia can be detrimental to the patient's activities. Severe hypoglycaemia has harmful effects"* [10].

Of course it is important to evaluate the risks of "rigid" treatment compared with those of a "relaxed" regimen. As was emphasised [144] little is known of the risks, in particular hypoglycaemic, run by patients who force themselves to the best possible control of their hyperglycaemia with insulin. The psychological restrictions can sometimes be difficult [145] but time has shown that children and adolescents taught and educated to control their insulin-dependent diabetes rigidly can adapt themselves perfectly to adult life [146]. Some diabetic doctors and diabetologists, or their wives, have controlled their diabetes remarkably well as illustrated by two of them [147, 148].

## Conclusions

The opinion of a great number of research workers and clinicians is that the microangiopathic and neuropathic changes observed in diabetes mellitus are secondary to insulin deficiency, hyperglycaemia and/or to their consequences. These facts call for

research into the best possible means for achieving perfect control of blood glucose levels in diabetics whose life expectancy justifies this effort and whose cultural and above all psychological conditions permit it. This effort is justified even if lesions already exist since they are, to a certain degree, still responsive to good diabetic control.

Of course if one strives to achieve the best control possible day after day, there may be immense difficulties. For such goals we must use improved techniques for teaching and education; we must persuade the patient to follow his diet strictly, to divide his daily insulin administration into two or three doses (at least for the majority of patients), to be as close to ideal body weight as possible and to include physical exercise as an important aid to his treatment. Because we also try to avoid severe hypoglycaemia this task is very difficult. Sadly, if we also try to treat his hypertension (even moderate), to give him a hypocholesterolaemic diet, to treat his eyes with laser coagulation and also to stop him smoking, he will probably ignore all our advice and merely conclude that his physicians are sadists.

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