BLOOD GLUCOSE CONTROL AND DIABETIC MICROANGIOPATHY

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SUMMARY

There is overwhelming evidence that the microangiopathic complications (retinopathy, nephropathy and neuropathy) of diabetes can be minimised, prevented or improved by optimal blood glucose control. There is little evidence to show otherwise. This paper reviews evidences to demonstrate that poor diabetic control predisposes to diabetic microangiopathy. The only way to minimise diabetic microangiopathy is to avoid hyperglycaemia and achieve euglycaemia for most part of the day. In doing so the dangers of hypoglycaemia must be clearly recognized and avoided.

INTRODUCTION

Since the introduction of insulin in 1922, patients with diabetes mellitus rarely perish from acute diabetic ketosis. Diabetics now survive longer and with longer survival the longterm complications of diabetes such as retinopathy, nephropathy and neuropathy are now becoming increasingly more common. These complications are due to involvement of the small blood vessels and are commonly referred to as diabetic microangiopathy (abbreviated to DMA in the rest of the text).

In Singapore, like in other countries, DMA is common; in a recent survey, nephropathy is found in 9.8%, retinopathy in 8.5% and neuropathy in 3.3% (Cheah *et al*, 1978).

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The controversy as to whether good blood glucose control will prevent or minimise DMA is as yet not answered conclusively. Most practising diabetologists believe that current knowledge does indicate that good blood glucose control in diabetes does prevent or minimise DMA (Cahill *et al.*, 1976; Tchobroutsky, 1978) but a few are skeptical (Siperstein *et al*, 1977: Raskin, 1978). The controversy was brought into focus in 1970 when the University Group Diabetes Program (UGDP) reported that the development of vascular complications or mortality is not reduced by improving control of blood glucose in maturity-onset diabetics not prone to ketosis (University Group Diabetes Program, 1970). An answer or balanced perspective to the controversy seems more urgent than even today in view of the fact that good blood glucose control in a diabetic is now feasible with multiple daily insulin injections or with the many types of insulin delivery devices available today (Eaton, 1980) and monitoring of blood glucose is not only possible in the hospital or clinic but also in the patient's home (Tattersall, 1979); needless to say, such attempts to establish good blood glucose control is not without cost, inconvenience and even hazard to the patient and such an attempt seems to be justified if there is a positive relationship between good blood glucose control and the development of DMA.

This paper reviews the evidence for and against the belief that good blood glucose control does improve, minimise or prevent the development of DMA.

CLINICAL STUDIES

Dr Glen R. Shepherd, a 50 year old physician, suffers from diabetes with age of onset at 5½ years

and after 40 diabetic years he has had no diabetic complications except for 5 peripheral microaneurysms (Shepherd, 1971). He attributed his freedom from diabetic complications after 27-28 diabetic years to good diabetic control with diet and 2 or 3 daily injections of unmodified insulin. Dr. Shepherd's case is somewhat similar to that of Dr Petes Forsham, another physician who has suffered from diabetes since childhood (Krall, 1977). These 2 examples of physicians with long history of diabetes since childhood show that DMA can be minimised with good blood glucose control.

Dollery and Oakley (1965) reported that in a 14 year old girl with long-standing and poorly controlled diabetes the retina showed masses of hairpin capillary loops; these changes were reversed after 8 months of strict diabetic control. Improvement and arrest of proliferative retinopathy following a few months of good blood glucose control using continuous subcutaneous insulin infusion have been reported (Pickup *et al,* 1980).

In 1952, Keiding, *et al,* reported that in 451 patients (onset under 30 years) with duration of diabetes from 10 to 36 years, control of diabetes materially decreased the incidence of complications. Among 32 patients with excellent or good control for 20 years or more, none had grade 4 retinopathy; on the other hand among 157 patients with diabetes of the same duration who had only fair or poor control, 16 percent had grade 4 retinopathy. Among the total group of 451 patients, 101 (22 percent) had nephropathy; none of the 11 with excellent control and only one of the 50 with good control showed this complication while 17 percent of 12 patients with fair control and 28 percent of 298 patients with poor control had this condition (Keiding *et al.* 1952). In a group of 140 juvenile diabetics (range of their disease was 10 to 29 years), highly significant correlations between the degree of control and severity of retinopathy were demonstrated (Harding *et al,* 1956).

Many other series can be cited to show the beneficial results of good diabetic control (Tchobroutsky, 1978) with few exceptions (Dolger, 1947; Knowles *et al,* 1965). Dolger (1947) reported that in 200 cases, the vascular complications were not correlated with the level of control. Knowles *et al* (1965) found that in 108 juvenile-onset diabetics, most of whom had poor control, the prevalence of vascular complications was similar to other groups of diabetics with more rigid control.

Most of the above studies were retrospective with some bias and the level of control was variable. While in some studies such as that of Keiding, *et al,* (1952) the criteria of control was spelt out in detail in others such as that of Dolger (1947) the criteria of control was not given.

Johnsson (1960) reviewed all diabetic patients in Malmo, Sweden, diagnosed between 1922 and 1945 who were less than 40 years of age at the onset of disease. Series I consisted of 54 patients diagnosed from 1922 to 1935; all these patients were treated with strict diet and multiple injections of insulin to keep the urine as free of glucose as possible while Series II consisted of 105 patients (diagnosed between 1935 to 1945) and these cases were treated with a single injection of long-acting insulin and less strict diet. The patients in Series II had a much higher incidence of vascular complications than did those in Series I; thus 32 percent in Series I had nephropathy compared to 56 percent in Series II in spite of the fact that the mean duration of diabetes in Series I was 10 years longer than that in Series II (Johnsson, 1960).

Among the 20 or so prospective studies considered valid by recent reviewers only a few have failed to show any relationship between the incidence of DMA and the quality of control (Tchobroutsky, 1978). In the Brussel's study by Pirart and Lauvaux (1977) in which 4398 diabetics were followed for 25 years, they concluded that the duration and severity of hyperglycaemia serum to be the only feature that 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 (Pirart and Lauvaux, 1977).

Eschwege *et al* (1979) in a prospective study assigned insulin-dependent patients either to long-acting insulin given once a day (S group) or to a regimen consisting of 2 or 3 injections per day (M group). The group that received multiple daily insulin injections had better diabetic control than that with a single daily injection (Tchobroutsky *et al,* 1980). The aim of the trial was to compare the increase in the number of retinal microaneurysms. There were 21 patients in each group; the mean duration of follow-up in the S group was 49.1 $\pm$ 3.4

months while in the M group it was 51.1 ± 2.6 months. The mean yearly increase in the number of microaneurysm in the S group was 9 ± 1 while in the M group it was 3 ± 1 and the difference is highly significant.

The UGDP has been referred to earlier (The University Group Diabetes Program, 1970). In a later report on non-fatal events it claimed that attempts to normalise blood glucose in the adult-onset diabetic did not alter the incidence of renal impairment, retinal changes or other common complications of diabetes (UGDP, 1976). It further added 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". The UGDP study has been charged as having discrepancies, omissions and errors (Horwitz, 1978). In a restudy of the patient data released by the UGDP coordinating center, Kilo and Williamson (1979) concluded that "the variable insulin regimen was highly efficacious in reducing cardiovascular mortality. The data support the thesis that control of blood glucose helps prevent vascular disease in diabetes".

Most physician would agree with the conclusion of Tchobroutsky (1978) that "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 worthwhile".

THE BASEMENT MEMBRANE CONTROVERSY

In 1965 Osterby published a quantitative electron microscopic study of glomerular capillaries showing that at the onset of juvenile diabetes the basement membrane thickness is normal. Three years later, in 1968, Siperstein *et al* reported on a study of quadriceps muscle capillary. They found that there was a 27% thickening of the quadriceps muscle capillary basement membrane in 30 patients with prediabetes and a more pronounced thickening in 51 diabetics. No increase was found in the basement membrane thickness in the course of life of diabetic patients or of normal subjects.

The results of Siperstein *et al* were confirmed by the findings of Kilo *et al* (1972); they reported that there was a clearcut correlation between the thickening of the quadriceps muscle capillary basement membrane and the duration of diabetes. The findings of the Williamson group was confirmed by other studies on muscle and glomerular capillaries (Gundersen *et al,* 1978).

In 1976, Aronoff *et al* reported that there was a clearcut correlation between basement membrane thickness and duration of diabetes and there was no significant difference between the mean basement membrane thickness of normal and prediabetic Pimas. They concluded that "data from this laboratory and from the National Institutes of Health cooperative study would support the conclusion that DMA does not result from the hyperglycaemia or the hypoinsulinaemia of diabetes".

Raskin (1978) in a restudy of 8 patients with pancreatic diabetes, 4 of whom were original patients of Siperstein, found that there was a significant increase in capillary basement membrane width over the years. It was concluded that "prolonged hyperglycaemia may play a role in the development of quadriceps capillary basement membrane thickening".

The basement membrane controversy continues unabated; eloquent arguments for and against the view that capillary basement membrane thickening is affected by hyperglycaemia have been put forward by Gundersen *et al* (1978) and by Siperstein *et al* (1978). Most reviewers are of the view that hyperglycaemia does affect basement membrane thickness (Tchobroutsky, 1978).

EPIDEMIOLOGICAL STUDIES

In the population diabetic survey of Oxford, Massachusetts, it was found that in diabetics; hypertension, fundoscopic changes and survival rates were related to high initial blood sugar levels after a 17 year follow up (O'Sullivan *et al.,* 1968). Jarret and Keen (1976) reported that the percentage of patients with retinopathy at survey and 5 years later were related to the 2-hour blood sugar levels. Similar conclusions were found by Katsilambros (1976) in Athens in a survey on 21,410 subjects. In Pima Indians it was found that proteinuria was twice as high in those with 2-hour plasma glucose in the range 200-299 mg% than in those in the range of 140-160 mg% (Kamenetzky *et al,* 1974).

Epidemiological studies show that raised blood glucose level is associated with raised incidence of DMA.

PATHOLOGICAL DATA

Recent studies using immunochemical methods have added considerable information about the renal lesions in diabetes. Miller and Michael (1976) found that the most specific reaction was the presence of IgG and Albumin lining the tubular basement membrane. The findings are consistent with the observation that in basement membrane observed from human diabetics the decrease on the cystine content may reflect an alteration on the disulfide cross-linkage and thus make diabetic basement membrane more permeable to large macromolecules (Westberg, 1974).

For at least 2 years, Mauer *et al* (1976) studied renal transplant tissues from 12 diabetic and 28 non diabetic patients who had a renal graft. Of the 12 kidneys from diabetics, 10 showed arterior hyalinosis and one developed nodular glomerulosclerosis 35 months after transplantation. Of the 28 non diabetic renal transplants, only 3 had hyaline vascular changes in rare blood vessels.

Many studies on animals have shown that capillary basement membrane of the retina and glomeruli occur after induction of experimental diabetes and that ideal treatment prevents, reduces, reverses or minimises the capillary basement membrane thickening (Tchobroutsky, 1978).

Raskin (1978) states that "the pathologic data are perhaps the most convincing that control of hyperglycaemia in diabetes might alter the course of the vascular complications. The development of typical diabetic immunofluorescent and pathologic changes in previously normal kidneys transplanted into diabetic subjects and reversal of similar lesions when experimental diabetes is reversed by islet-cell transplantation strongly supports this conclusion".

OTHER STUDIES

Rahbar (1968) reported that Haemoglobin A_{1c} (Hb A_{1c}) is increased in diabetes. Since then the measurement of HB A_{1c} or glycosylated Hb has been increasingly used as an index of blood glucose control in diabetes. The degree of diabetic control, assessed by a combination of both pre and postprandial blood glucose levels, give the best correlation with Hb A_{1c} levels (Koenig *et al,* 1976).

The potential use of HB A_{1c} measurements in studies designed to determine whether long-term diabetic complications are a consequence of less than optimal control is of great importance; to date there are no prospective studies that answer this question (Gonen and Rubenstein, 1978). Peterson *et al* (1977) measured Hb A_{1c} and platelet functions in a group of poorly controlled diabetics over 2 months; as metabolic control improved, Hb A_{1c} decreased and platelet aggregation improved. Increased platelet aggregation has been implicated in the pathogenesis of diabetic retinopathy (Dobbie *et al,* 1974).

Strict control of blood glucose also normalises growth hormone secretion which may play a role in the development of DMA (Lundbaek, 1976; Larkins *et al,* 1978).

In rats made diabetic by the administration of streptozotocin, sciatic motor nerve conduction was impaired; this impairment was corrected when insulin was given twice daily in doses adjusted on basis of blood glucose determination (Winegrad and Greene, 1976). There was a reduction of free myoinositol concentration in nerves which correlated with motor nerve conduction velocity. Supplementation of the diet with 1% myoinositol prevented the impairment on nerve conduction velocity in diabetic rats. In glycosuric patients 40 percent of the dietary intake of myoinositol is excreted in the urine as compared to only a small fraction in non diabetics (Clements *et al,* 1974).

DISCUSSION

At present there is no definite and conclusive proof based on clinical and scientific studies that diabetic microangiopathy (DMA) in man can be prevented or minimised by good blood glucose control; most reviewers are of the view that the bulk of evidence favour a positive correlation (Cahill *et al,* 1976; Tchobroutsky, 1978). A few workers are not convinced that there is significant evidence (Siperstein *et al,* 1977; Raskin, 1978).

A major difficulty in clinical study is that there is no uniform method for assessment of metabolic control; attempts are being made to remedy this difficulty (Pyke and Tattersall, 1973). A precise method of assessment would among other data state such values as MAGE (mean amplitude of glycemic excursion) and MODD (mean of daily differences).

Another difficulty is that with conventional injections of insulin it is relatively easy to eliminate glycosuria and restore fasting euglycaemia but postprandial hyperglycaemia persists; this is being overcome with more and more sophisticated insulin delivery devices, which are compact enough to allow frequent intermittent, continual or continuous delivery of insulin requirements in the ambulant patient (Eaton, 1980). Hopefully future clinical studies would produce more conclusive results.

It is true that other factors such as heredity influences the pathogenesis of DMA. Pyke and Tattersall reported that diabetes in concordant pairs of twins were more likely to be complicated by severe retinopathy than in discordant pairs (Pyke and Tattersall, 1973). In Singapore we have shown that HLA B17 strongly influences complication rates in juvenile onset diabetes on insulin therapy in the 10 years after diagnosis (Yeo *et al,* 1981). Cigarette smoking has been implicated in diabetic retinopathy (Paetkau *et al,* 1977) but this has been denied by others (West *et al,* 1980).

The relevance of animal studies in the human situation has been questioned (Siperstein *et al,* 1978). No one would deny that extreme care has to be exercised in extrapolating results in diabetic animals to that in man. As stressed by Engerman *et al* (1977) the similarities between the microvascular disease in diabetic humans and dogs would suggest that these observations are relevant to the problems of diabetic microvascular disease in man.

Nodular glomerulosclerosis and retinopathy, although highly characteristic of diabetes, are not specific for diabetes. Similar retinal lesions have been described in diseases accompanied by hypoxia and/or hyperviscosity. Kimmelsteil-Wilson nodules have been found in multiple myeloma and benign monoclonal gammopathies (Tchobroutsky, 1978). These are very rare exceptions. Studies on the Pima Indians (where 40% of those 35 years or older are diabetic) also carry solid arguments against the existence of diabetic nephropathy without diabetes. Kamenetzky *et al* (1974) studied 1,848 Pima Indians. At the autopsy of 105 cases, 43 diabetics and 62 non diabetics, no nodular glomerulosclerosis or exudative glomerular lesion was found in the non diabetics while in the diabetics the frequency was 55 percent and 44 percent respectively.

Every diabetologist would endorse the view of Siperstein *et al* (1978) that "the effects of frequent hypoglycemia can be very detrimental to the patient's normal activities (employment or driving an automobile), ... and if carried to extremes, can lead to serious neurologic complicatons". It is important to evaluate the risks of rigid treatment compared with those of a relaxed regimen. 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 be difficult 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 (Guthrie, 1977). Two physicians, Drs Shepherd (Shepherd, 1971) and Forsham (Krall, 1977) have shown that it is possible to control their juvenile-onset diabetes with multiple insulin injections daily to achieve good blood glucose control for many years without serious side effects from hypoglycaemia; both have practised their professions very successfully. Surely what is good for the physician is good for the patient!

Even those who believe that current data have not shown that good blood glucose control can prevent or minimise DMA readily state the uncontrolled hyperglycaemia is not good for the diabetic. Raskin (1978) states; "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". Siperstein *et al* (1977) writes "It is only prudent to strive for reasonable control of the blood glucose in the diabetic patient ..... At no time have we said that good control might not have value. We will continue to recommend the best possible control of blood glucose in the diabetic patient under our care, but never at the price of hypoglycaemic attacks". Those who are skeptical of the direct correlation of blood glucose control and DMA have produced no evidences to the contrary. As Cahill *et al* (1976) put it "These data therefore place the burden of proof upon those who maintain that diabetes control is without effect".

The majority of physicians who treat diabetics would accept the policy statement of the American Diabetes Association in 1976 that the weight of evidence strongly supports the concept that microvascular complications of diabetes are decreased by reduction of blood glucose concentration. "In summary current clinical and experimental data clearly demonstrate that optimal regulation of glucose levels should be achieved in the treatment of diabetes particularly in young and middle-aged individuals who are at greatest risk of developing the microvascular complications ..... Finally, good diabetic management necessitates education and training of both patients and healthy professionals in the technics involved, in close coordination and cooperation in patient management. Most important is a commitment to the view that better control, when achievable, is beneficial" (Cahill *et al,* 1976).

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