CONTROL OF DIABETES

By

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Since there is growing evidence that stricter control of diabetes helps in the prevention and treatment of diabetic complications, treatment in the Armed Forces is designed to obtain, as far as possible, a physiological control of diabetes, without the treatment being irksome or unacceptable to the patient in any way, or coming in his way of retention in service and performance of duties. The patients are treated with a low-fat, high-protein diet in order of preference with —

(A) Tolbutamide, Tolbutamide+DBI-TD, and Tolbutamide+DBI-TD+Insulin,

(B) Glybenclamide, Glybenclamide+DBI-TD, and Glybenclamide+DBI-TD+Insulin.

The net results obtained in 123 adult Indian diabetics treated with regime (A) Were normal pre-prandial and post-prandial blood sugar levels under treatment in 25 cases (20.3 per cent), normal 100 g. glucose tolerace test under treatment in 74 cases (60.2 per cent), and normal cortisone glucose tolerance test under treatment in 24 cases (19.5 per cent). In comparison results obtained in 86 diabetic cases treated with regime (B) were normal pre-prandial and post-prandial blood sugar levels under treatment in 15 cases (17.5 per cent), normal 100g. glucose tolerance test under treatment in 45 cases (52.3 per cent), and normal cortisone glucose tolerance test under treatment in 26 cases (30.2 per cent). These results favour the view that glybenclamide is more powerful than tolbutamide in its antidiabetic effect.

All patients with normal cortisone glucose tolerance test under treatment qualified for medical category A, those with normal 100 g. glucose tolerance test under treatment for medical category B, and all those with normal pre-prandial and post-prandial blood sugar levels under treatment qualified for medical category C.

Introduction

The progress of diabetes from its inception to its termination in coma is as follows.

Days or years before the onset of symptoms the patient develops hyperglycaemia. Before the development of hyperglycaemia the patient is a potential or a latent diabetic and gives a positive cortisone glucose tolerance test. Since, however, diabetic complications have occurred in some cases before the cortisone glucose tolerance test is positive, there must be an abnormal stage between the absolute

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normal and the positive cortisone glucose tolerance test.

Subsequently the glucose tolerance test becomes positive. When the blood sugar rises to levels about 160-200 mg per 100 ml. the amount of glucose filtered through the glomeruli exceeds the capacity of tubules to reabsorb it, and glycosuria results. Depending on the level of blood sugar and the renal threshold, the urine sugar may vary from a trace to 10 per cent or even higher.

Large quantities of urinary glucose cause diuresis, dehydration and salt depletion.

Due to absence of usable glucose there is breakdown of depot fat and muscle protein. Owing to increased conversion of fat to acetyl coenzyme A and non-availability of glucose to facilitate the recombination of acetyl coenzyme A into fatty acid, the net formation of ketone bodies formed, are in excess of the tissues ability to consume them. The ketones consist of acetoacetic acid, beta-hydroxybutiric acid and acetone. Except for acetone they are acids, and behave as such in the blood and tissues. To begin with they are neutralised by the phosphate and bicarbonate buffers in the blood and serious fall in blood pH is prevented. This is further helped by the kidneys conserving sodium.

When ketosis becomes severe these defences break down and sodium, potassium and magnesium are lost in large amounts.

With the onset of vomiting, the loss of base, chloride and water becomes extreme.

Lactic acidosis may result from failure of the tricarboxylic or Kreb's cycle. The condition is akin to a severe hypoxic state. Normally in the presence of oxygen when the breakdown of glycogen or glucose reaches the pyruvic acid stage, the latter enters the tricarboxylic cycle to be oxidized to CO_2 and H_2O. In a hypoxic stage the tricarboxylic cycle is blocked and part of the pyruvate is converted into lactate by the diphosphopyridine nucleotide (DPN)-DPNH system. Since cell surfaces are readily permeable to both pyruvate and lactate, these two metabolites pass into the plasma. When the production of lactate exceeds the ability of the liver to reoxidize it into pyruvate for synthesis of glycogen, the blood lactate levels, which in health and at rest do not exceed 1.25 mM/L. may reach 20 to 30 mM/L. The normal levels of circulating lactate and pyruvate have a ratio of 10 : 1. In lactic acidosis the ratio is much greater than 10 : 1. Since both lactate and pyruvate are organic acids, metabolic acidosis results. The plasma bicarbonate and pH fall. The difference between the cationic and anionic concentrations, which is usually about 20mEq/L., may rise as much as twofold due to lactate.

In severe uncontrolled dehydrated diabetic, coma may result, from extremely high levels of blood glucose in the absence of ketoacidosis and lactic acidosis. The blood sugar levels vary from 400 to 2200 mg per 100 ml with an average of about 1000 mg per 100 ml. The serum osmolarity is increased. The serum sodium is often more than 150 mEq/L. The serum potassium is normal or low.

The immediate treatment of diabetes mellitus depends on the stage at which the patient is first seen, with the ultimate object of establishing as far as possible

a physiological control, if not a remission with the hope that complications will be prevented and existing ones will regress. When, potential diabetics and latent diabetics should be treated, merits considereration. Asymptomatic diabetics, symptomatic diabetics without ketosis or with compensated ketosis require routine treatment, and patients in ketoacidosis, lactic acidosis, hyperglycaemic hyperosmolar coma require the most vigourous measures to save life. Pregnant diabetics are a problem in themselves. In this paper I shall restrict myself to the routine treatment of a case of diabetes in the Armed forces.

Grades of control

Although there are differing views regarding the degres to which hyperglycaemia should be controlled, several surveys have shown that there is an undoubted correlation between the control of diabetes and the incidence of its complications. There has also been evidence of reversal of diabetic complications with stricter treatment. Although these findings do not necessarily mean a 'cause and effect' relationship, they suggest that a careful control and aggressive treatment of the disorder over the years is a most important factor in the postponement and probably in the prevention of complications. There are indications that if the normal physiologic status is restored in diabetic patients the complications may be altogether prevented. Thus, although women with abnormal cortisone glucose tolerance test, untreated with oral hypoglycaemic compounds, are prone to obstetrical complications, the incidence of these complications in treated overt diabetic women under adequate but lesser degree of control than indicated by a normal glucose tolerance test is reduced to zero. Similarly we find diabetic patients who have continued to have a normal glucose tolerance test under tolbutamide treatment have been spared diabetic complications over the past 11 to 12 years. However, it is possible that the beneficial effect in these observations was not entirely due to normoglycaemia but had also been contributed by associated normalisation of blood lipids and blood glycoproteins. Oral hypoglycaemic compounds are known to have a beneficial effect over these. It is logical therefore that the aim of treatment in diabetes should be to restore the man to absolute normal. The criteria for likely response to treatment in terms of normal physiologic status have therefore been laid down as following :

Grade IV control with abnormal preprandial and postprandial blood sugar levels.

Grade III control with normal preprandial and postprandial blood sugar levels.

Grade II control with normal glucose tolerance test.

Grade I control with normal cortisone glucose tolerance test.

The norms for blood sugar levels in these Grades of control are as follows :

Preprandial less than 100 mg. and postprandial less than 140 mg. per 100 ml. of blood.

Glucose tolerance test - fasting less than 100 mg., peak less than 160 mg., and 120 minutes less than 120 mg. per 100 ml. of blood.

Cortisone glucose tolerance test (with prednisolone 10 mg. given 8 hours and 2 hours before the glucose tolerance test) – fasting less than 140 mg., peak less than 200 mg., and 120 minutes less than 140 mg. per 100 ml. of blood.

Treatment

In planning treatment the points given attention are the patient's weight, his exercise, diet and treatment with oral hypoglycaemic compound or both hypoglycaemic compounds and insulin.

Weight

The uptake of glucose by muscles is progressively impeded as obesity increases. The reduction and shedding of obesity are associated with marked improvement in the uptake of glucose by muscles. This reduction is attributable to a reduction of the clearance of insulin into the muscles, rather than a reduction of the metabolic response of the muscles to insulin (Butterfield, 1967). It is estimated that for each insulin molecule leaving the circulation for muscle, two million glucose molecules follow. Overweight patients should be reduced to normal weight at the pre-treatment state and treated if necessary. It should be borne in mind however that when overweight patients return to normal weight, their glucose tolerance may return to normal, but in about 90 per cent of them the cortisone glucose tolerance test remains abnormal (Navarrete et al. 1966).

Exercise

Muscular exercise increases the utilisation of glucose by skeletal muscles both in the normal and the diabetic individuals. mechanism by which this is accomplished is not clear. There is no evidence that this is the result of increased insulin secretion since the serum insulin-like activity and the immuno-reactive insulin levels during exercise have been found to be either decreased or show no change at all. It seems likey that an exercise metabolite is involved which increases the clearance of insulin into the hyperaemic muscles (Devlin 1963 ; Cochran et al. 1966). Even moderate exercise increases the glucose uptake by the exercising muscles two to threefold. The increased insulin clearance into muscles during exercice may more than compensate the diminished insulin clearance in an obese individual and prevent him from becoming a diabetic.

Diet

A low-fat high-carbohydrate high protein diet is used with advantage in the treatment of diabetes mellitus. Fat depresses the insulin mechanism, where as a high carbohydrate diet promotes the development of the islets and increases the sugar tolerance. A combined low-fat high-carbohydrate diet helps in the reduction of blood triglyceride levels (Louis, 1968). It seems likely that a high protein intake favours increased insulin synthesis, as well as the synthesis of promotors of insulin secretion (Berger et al. 1964; Floyd et al. 1964 ; Berger and Vongaraya 1966).

The relationship between the carbohydrate ingested and the insulin necessary to metabolise it is approximately logarithmic. Hence the strain on the insulin mechanism resulting from high-carbohydrate intake is relatively small, and in actual practice is more than compensated by an improvement in the insulin mechanism. There is no experimental or clinical proof that prolonged use of a high carbohydrate diet will exhaust the islets of Langerhans. We have ourselves used such a diet

successfully in diabetics over the past 12 years.

The caloric value of the diet should cater for the requirements of a fighting-fit soldier. The calories for underweight patients should be initially adjusted so as to bring these patients to normal weight. A sucrose-free diet which provides 3000 – 3500 calories normally suffices for a soldier. Our practice is to make up this diet with fat 50–75 g., protein 120–140 g., and carbohydrate 520–570 g., with approximately 1/5th, 2/5th and 2/5th of the total caloric requirements provided at breakfast, lunch and dinner respectively. This distribution of calories facilities control of postprandial blood sugar after breakfast, which in many cases is more resistant to control than at any other time. The patient's cooperation is ensured by his adhering to dietetic habits within the composition and the caloric requirments of his diet.

Treatment Regimes

The pancreas normally secretes about 25 to 40 units of insulin a day. When insulin enters the liver via the portal vein part of it is trapped and the rest of it enters the general circulation. The amount of insulin trapped in the liver depends on the rate of its secretion. Thus when insulin is slowly secreted under the influence of sulphonylureas, it is almost completely trapped in the liver and little or none enters the general circulation. The action of insulin in relation to hyperglycaemia, as far as the hepatic cell is concerned, is to prevent the release of glucose into the blood. The action of insulin in relation to hyperglycaemia at the periphery, as far as the muscle is concerned, is to prevent the release of glucose into the blood. The action of insulin in relation to hyperglycaemia at the periphery, as far as the muscle is concerned, is to accelerate the transfer of glucose from plasma to the inter-cellular water.

Diabetic hyperglycaemia can be therefore treated by a drug which has an insulinogenic effect on the hepatic cell, or by a drug which will accelerate the transfer of glucose from the plasma to the intracellular water. The drug with the former action is tolbutamide or glybenclamide and the drug with the later action is phenformin. When tolbutamide/glybenclamide and phenformin, singly or in combination, are ineffective, insulin provides both effects.

The treatment regimes used in order of preference are :

A) Tolbutamide, Tolbutamide+DBI-TD, and Tolbutamide + DBI-TD+ Insulin,

B) Glybenclamide, Glybenclamide + DBI-TD, and Glybenclamide+DBI-TD+Insulin

The choice is made in 3 phases. In Phase I, all cases are treated with tolbutamide 0.5 to 1.5 g/,Glybenclamide 5 to 15 mg. given usually in a single dose with breakfast. If there is no significant improvement with tolbutamide/Glybenclamide in 6 weeks, in Phase II DBI-TD (Time-disintegration capsules of phenformin) 50 mg. is given in addition to tolbutamide/Glybenclamide with one or all meals according to requirement. If there is no improvement with the tolbutamide/Glybenclamide plus DBI-TD combination in 12 weeks, in Phase III insulin is added to the treatment. In our experience protamine zinc insulin once a day at 10 P. M. to cater for the control of fasting blood

sugar and subsequently throughout the day, on as required basis gives most satisfactory results. The duration of phase I as 6 weeks and of phase II as 12 weeks is not arbitrary, but is based on experience of treatment of a large number of cases, and represents the period in which at any time the patient may start responding to treatment. The aim of using a particular dose is, on one hand, not to precipitate hypoglycaemic reactions and, on the other, to maintain the blood sugar within normal levels as already defined. Normoglycaemia seems to beget normoglycaemia. Therefore when grade III control (normal preprandial and postprandial blood sugar levels) is obtained with any of the treatment regimes, the regime is continued and further improvement in Grades of carbohydrate tolerance is assessed. If at any time, improvement ceases short of a higher Grade of control with the tolbutamide/Glybenclamide or the tolbutamide/Glybeclamide plus phenformin regime, treatment with the next regime is instituted till a finality of response is reached. A normal fasting blood sugar favours a higher grade of control. In about 5 per cent of cases a selective adjustment of dosage and time of administration to control high fasting blood sugar may be required. Some patients may require only intermittent therapy to maintain Grade I control.

There is usually wide variance in the rate of improvement from case to case. Thus with tolbutamide/Glybenclamide Grade III control is obtained in 2-20 weeks, Grade II control in subsequent 4-36 weeks, and grade I control in 12-48 weeks; and in cases requiring treatment with Tolbutamide/Glybenclamide + DBI-TD grade I control is obtained in 1 to 47 weeks and Grade II control in 4-8 weeks.

The overall results obtained by us at the end of 12 months treatment in 123 adult Indian diabetics treated with regime (A) are: normal Pre-prandial and post-prandial blood sugar levels under treatment in 25 cases (20.3%), normal 100g. glucose tolerance test under treatment in 74 cases (60.2%) and normal cortisone glucose tolerance test under treatment in 24 cases (19.5%). In comparison, results obtained in 86 diabetic cases treated with regime (B) are: normal preprandial and post-prandial blood sugar levels under treatment in 15 cases (17.5%) normal 100 g, glucose tolerance test under treatment in 45 cases (52.3%), and normal cortisone glucose tolerance test under treatment in 26 cases (30.2%). These results favour the view that glybenclamide is more powerful than tolbutamide in its anti diabetic effect.

Grade I control caters even for stresses involved in major surgery under general anaesthesia as the following case record.

All patients with normal cortisone glucose tolerance test under treatment qualified for medical category A, those with normal 100 g. glucose tolerance test under treatment for medical category B, and all those with normal pre-prandial and postprandial blood sugar levels under treatment qualified for medical category C.

Case Record

A. S., male, 38 years old who had worked upto Grade I control with tolbutamide, 1.0 g. at breakfast between 18 Oct. 67 and 28 Feb. 68, was operated for indirect inguinal hernia on 29 Mar 68 after an overnight fast. Pre-medication of pethidine 100 mg. and atropine 0.6 mg. was given at 0845 hours. Anaesthesia was induced with thiopentone 250 mg. intrave-

nously at 0915 hours, and it was maintained with minimum quantities required of nitrous oxide, oxygen and ether. Muscle relaxation was obtained with gallamine 60 mg. The operation ended at 1030 hours. The induction, maintenance and recovery from anaesthesia were absolutely uneventful. He had a smooth post-operative phase on a normal routine without any particular management referable to diabetes mellitus. Blood sugar levels on the day of operation, in the fasting stage and just before induction of anaesthesia were 116 and 136 mg. per 100 ml. of blood respectively. Blood sugar levels which were estimated half-hourly during the operation were 140, 136 and 170 mg. per 100 ml. of blood respectively. Two, four and six hours after the operation the blood sugar levels were 150, 156 and 132 mg. per 100 ml. of blood resecctively. Next day fasting blood sugar was 112 mg. per 100 ml. of blood. A glucose tolerence test after one week and a cortisone glucose tolerance test after six weeks were normal.

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