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MONOSACCHARIDES IN HEALTH AND DISEASE

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It is difficult to conceive that a normal, important, everyday nutrient such as glucose could be the cause of chronic functional changes and permanent structural damage in many bodily tissues of man and animals. We have, over the years, accepted the atherogenic consequences of high levels of plasma cholesterol and triglycerides, particularly when they are carried as LDL. We have taken note of the damage done to nephrons by very high protein intakes. Yet, somehow, many of us have resisted the notion that an abnormally high blood glucose level could be responsible, in whole or in part, for the severe and often fatal complications of diabetes: loss of vision (retinopathy); painful damage to peripheral nerves (neuropathy); irreversible renal failure (nephropathy); and to a certain degree the increased frequency and severity of cardiac and peripheral atherosclerosis (2, 5, 51, 68, 71, 96, 115).

Experimental and clinical observations over the past 20–30 years, supported by plausible biochemical data, have brought convincing evidence that those

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who advocated "strict" control of the blood sugar in the treatment of diabetes will be shown to have been right in this long controversy.

GLUCOSE HOMEOSTASIS

In man and other homeothermic animals, the level of fasting blood glucose (as well as the range of its excursions when perturbed by meals, by fasting, by exercise, etc) are kept well controlled by a variety of enzymatic and hormonal factors. The diurnal curve of blood glucose in man lies between a low of about 70–80 mg% and a high of 120–130 mg% attained for a short period after a sizeable meal. These lower values of the range serve, of course, to maintain the supply of the obligatory fuel for the central nervous system. Hypoglycemia (<40 mg%) inflicts severe functional and anatomical damage on brain tissue.

But are there any damaging functional and morphological consequences of hyperglycemia? Above a level of 200 mg% in the blood, glucosuria supervenes with the consequent loss of fuel from the body. But that does not wholly explain the biological origin and survival value of all the mechanisms operating to keep the circulating glucose below 120–130 mg% at all times.

Diabetes mellitus in all of its clinical and experimental forms, whatever be the etiology of a particular case, is characterized by a persistent chronic state of hyperglycemia. This is, of course, rather easily influenced by the quantity and kinds of foods ingested. Dietary and hormonal treatments that markedly reduce or abolish the urinary excretion of sugar completely relieve the classical metabolic symptomatology of diabetes. How important is it then to reduce the patient's blood sugar to within the normal ranges? The older clinicians advocated "strict" blood sugar control because (*a*) the ideal was to change any abnormal values to "normal" and (*b*) in their experience adherence to strict criteria of control seemed to decrease the incidence and extent of the "complications" of the disease: retinopathy, neuropathy, nephropathy, and atherosclerosis.

For years this viewpoint was challenged mainly on the basis that in many instances there was no consistent correlation between blood sugar "control" and severity of complications; and also because it was difficult to believe that glucose (as a substance), could be involved in damaging small and large blood vessels throughout the body and in peripheral nerve degeneration.

INSULIN-INDEPENDENT PATHWAYS OF GLUCOSE METABOLISM

During the past 20–25 years, however, a growing body of evidence has been developed implicating certain metabolic pathways of glucose and galactose in the production of changes in various tissues that may lead to many of the

diabetic complications (14, 31–34, 44, 66, 77, 80, 102, 108). Hence, the nutritional details of the diet for diabetics have become very important for the patient and the physician. The goal is to structure caloric and carbohydrate intake together with appropriate medication and muscular exercise, so as to approach as closely as possible to the diurnal blood sugar curves of the nondiabetic individual.

We review here our present state of knowledge of two chemical pathways glucose may take in the body that are thought to have chronic injurious effects. One is the so-called polyol pathway; and the other is the nonenzymatic glycosylation of proteins.

The Polyol Pathway

Muscle tissue, the fat cells, and the cells of connective tissue all require insulin for the transmembrane entry of glucose. Insulin is also necessary for the efficient autoregulation of liver sugar output by the blood glucose level. Neurons, as well as all epithelial and endothelial cells, do not depend upon insulin for glucose entry. Their carbohydrate metabolism depends primarily upon the level of circulating glucose. The overwhelming bulk of glucose is processed by initial phosphorylation to G-6-phosphate for storage and/or oxidative breakdown. At high blood sugar levels in those tissues that possess the particular enzyme (aldose reductase), glucose and other aldoses are reduced to the corresponding sugar alcohols; glucose forms glucitol (better known as sorbitol) (14, 31, 33, 34, 44, 66, 72, 80, 102, 108), and galactose gives rise to galactitol or dulcitol. A second enzyme, iditol dehydrogenase, catalyzes the transformation of sorbitol to fructose. In states of hyperglycemia the polyols (sugar alcohols) tend to accumulate within those cells and tissues that are not insulin sensitive (1).

It was thought at first that the polyols are retained within cells and then damage tissues by the osmotic imbibition of water. This osmotic damage theory could not be wholly substantiated (44). Yet, in some way the activity of the polyol pathway is involved because substances that inhibit the action of aldose reductase may prevent or reverse the functional and/or morphologic changes (1, 6, 7, 24, 39, 43, 71, 72, 87, 95, 104, 111).

Coincident with the rise of tissue levels of sorbitol there generally occurs a fall in another of the normal sugar alcohols, myoinositol (14, 15, 41, 44, 45, 79). The full role of inositol in cellular functions is not yet clear, but it is most probably related to the functions of the membrane-bound phosphoinositides, which are involved in signal transmission for the regulation of ion fluxes, propagation of the nerve impulse, and synaptic transmission.

When the first enzyme of the polyol pathway (aldose reductase) is inhibited, myoinositol levels return toward normal values. The relationship between the polyol pathway and myoinositol levels may be indirect in that hyperglycemia

may enhance polyol formation and also inhibit myoinositol uptake (41, 42, 44, 119).

Until very recently the aldose reductase system had been implicated to some degree in cataract formation and in the neuropathic changes of diabetes. Now, however, work has appeared linking diabetic vascular disease to the aldose reductase pathway. Induction of diabetes in rats increases capillary permeability to albumin in newly formed vessels. This phenomenon is increased markedly by galactose feeding (79) and is prevented by the use of an orally active aldose reductase inhibitor (39, 65, 87, 95, 111).

Of interest is the recent finding that castration of the diabetic animal has the same ameliorative effect on the increased vascular permeability as does the use of the aldose reductase inhibitor. This seems to be due to the fact that reductase is a sex-steroid-dependent enzyme.

The obvious therapeutic deduction from all of these studies is the need for regimens of treatment, nutritional and hormonal, that result in nearly normal levels of blood glucose. When needed, this could be supplemented by safe, orally effective aldose reductase inhibitors.

GLYCOSYLATION In 1968 Rahbar, a hematologist then working in Iran, screened a large number of patients and found that diabetics had an increased concentration of an "abnormal" Hb component, previously described by Allen & Schroeder (see 49). This was designated as $HbA1_c$ (91). Further studies by Holmquist & Schroeder (49), Bookchin & Gallop (9), and H. F. Bunn and colleagues (10–12) established that this form of Hb was created by the attachment of a molecule of glucose to the *N* terminus of the β-chain. This occurs chemically without the intervention of an enzyme by the formation of a Schiff base that is converted to a ketoamine linkage by an Amadori rearrangement.

The content of $HbA1_c$ in terms of percentage of total Hb seems to depend on the mean blood glucose level and the survival time of the red blood cells. In the nondiabetic population the hemolysate contains, on the average, 4–5% of the $A1_c$ variant; among diabetics the percentage varies between 8 and 15% depending upon the degree of chronic hyperglycemia (8, 29, 38, 40, 67, 74, 75, 106).

These findings have led to the use of $HbA1_c$ determinations to assess the average degree of metabolic control in individuals and groups during several weeks preceding the assay. This has, of course, the advantage of not depending upon the peaks and valleys of the diurnal curve of blood glucose, nor upon the acute administration of insulin or an oral hypoglycemic agent. These assays are used widely in outpatient diabetes clinics for routine follow-up and for evaluating the chronic effects of dietetic and drug therapy (20, 21, 28, 35, 86).

Interest in protein glycosylation goes beyond using the $HbA1_c$ test. It has been established that most proteins will condense with sugars even at the

physiological concentrations of glucose found in the body. Those known to form glucose adducts include collagen, the crystallins of the lens (98, 103), serum proteins (25, 62, 118), nerve myelin, all membrane proteins (70, 93), transferrin (83), fibronectin (105), etc. Those diabetics tested incorporate more glucose in albumin (70, 93), red cell membrane proteins, collagen, and basement membranes (16, 19, 69, 73, 82).

In the case of lens crystallin, it has been argued that glycosylation may predispose to cataract formation by rendering the proteins more susceptible to formation of aggregates of high molecular weight. Glycosylated circulating plasma proteins may be transported across capillary walls at rates different from the non-sugar-containing molecules. It is tempting to speculate that glycosylation of certain degree may change some functional properties of certain circulating and cellular proteins, and thus induce those structural changes in the tissues that form the basis for the vascular and renal complications.

While the evidence for the role of the polyol pathway in the genesis of diabetic complications is stronger than that for protein glycosylation, neither one has as yet been clearly defined as to mechanism. In the practice of medicine, however, ethical considerations demand that we adopt a therapeutic regime fashioned by pragmatism even if, as yet, the demands of scientific proof have not been wholly met.

The conditions of the polyol pathway and of glycosylation dictate that a desirable treatment of a diabetic be based upon maintaining a diurnal blood sugar curve oscillating between about 80 and 130 mg%. This therapeutic need is the basis for (*a*) administering insulin by multiple small injections per day, or by means of computer-driven pumps; (*b*) glucose level monitoring by patients; and (*c*) other devices aiming at strict control. Among these other devices are the purely nutritional methods of slowing the rate of appearance, and the subsequent rise of blood glucose related to food intake. Hence, the search for techniques to slow the rates of digestion and absorption of carbohydrates.

EFFECTS OF COMPLEX CARBOHYDRATES ON GLUCOSE TOLERANCE

Plant "fiber," which is a mixture of many polysaccharides and lectins (e.g. guar, tragaranth, pectins, and the celluloses), has been ingested for ages as a preventative of chronic constipation. It seems to lower postprandial glycemia, perhaps by inhibiting the rate of polysaccharide digestion and/or sugar absorption in the small intestine. Hence, it is being advocated as an important adjuvant in the dietary regimen for diabetics in general (both Types I and II) (3, 30, 52, 58, 64, 76, 78, 92, 94).

Acarbose, an oligosaccharide obtained from certain strains of actinomycetes, is a competitive inhibitor of the brush-border glucosidases, especially sucrase, and it also inhibits glucoamylase and pancreatic α-amylase. It is therefore able to lower the postprandial blood glucose rise (27, 53, 89, 90, 104, 107). The combination of acarbose with the guar fiber is especially favorable since it seems to decrease markedly any side reactions.

Until very recently the dietary formulae devised for diabetics concerned themselves only with the total amount per meal and per day, and with the ratio of simple sugars to complex carbohydrates present in foods. The concept of carbohydrate "exchange" was based on quantitative chemical analysis of foods rather than on actual testing in vivo (59–61) since it was assumed that these parameters predicted more or less the extent of the postprandial rise in blood glucose. However, it seems that the degree of rise in blood sugar and the shape of the rise in the blood sugar curve after ingestion of test meals containing equal amounts and ratios of simple and complex carbohydrates differ over a wide range. The glycemic response after meals compared to the pure glucose test meal is about 30% for legumes, 35% for dairy products, 50% for fruit, and 60% for cereals (55, 56, 113). The judicious choice of foods with small glycemic responses and the addition of fiber to the meals, can significantly affect the blood sugar excursions of diabetics whether of the Type I or Type II variety. These dietary maneuvers aid in achieving diurnal glucose curves approaching the normal range (55, 56, 113).

Factors responsible for the variation in the glycemic indices of various meals are not precisely understood. It has been speculated that a variety of conditions might be responsible, such as (*a*) differential susceptibility of particular starches to hydrolytic enzymes (61, 84); (*b*) chain length of the amyloses (113); (*c*) amount and kind of proteins in the foods being tested; and (*d*) the amount and nature of the nondigestible polysaccharides or "fiber" in the food mixture (4, 58, 78, 100).

Jenkins, who with his colleagues has contributed greatly to this field (52, 54, 60), argues that the use of purified fiber preparations and enzyme inhibitors (of amylases and glucosidases) is creating a new and useful nutritional pharmacology by modifying the rates of gastrointestinal events. This allows the achievement of "carbohydrate lente," i.e. meals that consist of sustained-release carbohydrate, which in turn facilitates a dietary management of diabetes aimed at achieving a normal diurnal blood sugar curve (3, 37, 57, 100).

The special nutritional features and properties exhibited by sugars other than glucose have been reviewed in the biochemical and clinical literature quite frequently and need not be explained here (63, 85, 101, 114). However, particular aspects of some importance that have been recently observed deserve mention.

METABOLIC EFFECTS OF SPECIFIC SUGARS AND SUGAR ALCOHOLS

Sucrose

Diabetogenic effects of a high sucrose intake have been asserted and denied over the years. Sucrose consumption seems to cause a degree of insulin resistance as shown by elevations of both glucose and insulin levels. Fructose is the responsible component of sucrose for these effects, both in rodents (13, 46, 47, 85, 110) and in normal and diabetic humans (18, 22, 23, 117, 120). Fructose does not elicit an *acute* insulin response, but the chronic feeding of fructose or sucrose leads to hyperinsulinemia and high triglyceride levels in rodents (47) as well as to a very significant loss of insulin sensitivity (110, 112, 116). These findings are reminiscent of the observations made years earlier that a high sucrose intake could be diabetogenic in certain selected populations in man and among rodents (18, 99, 109).

Fructose appears attractive in constructing diets for diabetics since it is sweeter to the taste than glucose, and because in normal humans and mild diabetics fructose ingestion produces a milder excursion in the blood sugar curve than does glucose (50). However, the situation changes under chronic conditions and also depends upon the metabolic severity present in the tested patient. Over time, moderate insulin resistance develops and the mean blood sugar rises, as does the blood insulin and the blood fats—a situation resembling mild Type II diabetes.

While the development of obesity is related chiefly to high caloric intake, there is increasing evidence that under certain conditions foods may be oxidized with less or more efficiency of production of useful metabolic energy. Thus, it has been argued that the degree of thermogenesis after meals may vary widely. This may depend on many factors, including the type of carbohydrate ingested (48, 81, 97).

High sucrose diets tend to induce obesity in rats as compared to the equicaloric intake of glucose. A glucose meal is followed by significant rises in oxidation rates of brown adipose tissue, while fructose is not. Fructose is used more "efficiently". Hence, it can, over time, result in greater deposition of fat than glucose (17).

We have previously referred to the diabetogenic potential of high sucrose and/or fructose intakes, as seen in certain ethnic groups and selected rodent strains. Among other observations it was noted that sucrose and fructose induced retinal vascular damage resembling diabetic retinopathy or renal glomerulosclerosis. The precise mechanisms responsible for such lesions have not been demonstrated. Speculation and indirect evidence have centered on a secondary vitamin A deficiency, increased lactate production, selenium and/or

chromium deficiencies. The latter suggestion is of great interest, since chromium deficiency leads to the loss of glucose tolerance factor and increasing glucose intolerance (88).

Xylitol

For over 100 years attempts have been made to influence the metabolic state of diabetes by providing carbohydrates of equal sweetness and caloric value that would not raise the patient's blood glucose levels significantly, and that would not require insulin for their entry and prompt metabolism by cells. More recently nonglucose monosaccharides, especially fructose and the sugar alcohols sorbitol and xylitol, have been advocated for use by parenteral infusion for the nutritional support of patients after the trauma of surgery, during severe infections, etc (36). (The paper by Georgieff et al is a thorough review of the literature on this sugar alcohol in relation to its nutritional use.) Since under such conditions of physical stress the hormonal setting favors insulin resistance, it was thought advantageous to supply the carbohydrate calories in a form not requiring the extra secretion of insulin in the process of utilization.

In actual practice, the use of fructose and some of the sugar alcohols did not meet with more than temporary success or acceptability for a variety of reasons, as described in many reviews. As our knowledge of intermediary metabolism developed, it became obvious what the difficulties were that gave rise to years of controversy.

In the first place, fructose and the sugar alcohols are not utilized significantly by extrahepatic tissues. In the liver they are fairly rapidly metabolized to trioses, which are then catabolized further to CO_2 or synthesized into the hexosephosphates and glycogen. Thus, any portion not immediately "oxidized" ultimately becomes blood glucose by the gluconeogenetic pathway. This is immediately evident when such sugars or polyols are given to a severe diabetic; hyperglycemia and glucosuria follow rapidly. This undoubted fact has deterred many from using these "substitute" carbohydrates, since it seemed to be a waste of effort of providing "glucose" in a circuitous manner.

It would be of advantage, however, if one could provide fructose or xylitol in amounts that would inhibit proteolysis and lipolysis yet would not raise blood glucose values significantly. At infusion levels of about 0.2 g/kg/hr, xylitol apparently produces no rise in blood glucose. The oxidative rates of its metabolism are raised independently of glucose and of insulin. There is also no tendency to deposit liver fat when xylitol is infused compared to lipogenesis stimulated by glucose and insulin.

Felber has shown that when insulin secretion is suppressed by pharmacologic means, carbohydrate utilization from the infusion of fructose, sorbitol, and xylitol is significantly increased. The rise in carbohydrate oxidation rates and the decrease in lipid oxidation when using the nonglucose sugar alcohols or

fructose were the same whether or not insulin secretion was kept suppressed. This was true when the infusion rates were kept at about 20–25 g of substrate per hour (26).

SUMMARY

In healthy persons, glucose homeostasis maintains blood glucose levels between 70 and 130 mg/dl despite perturbations by meals, fasting, and exercise. Long-term follow-up of diabetic patients has suggested that "good control" of blood sugar levels minimizes the long-term complications of diabetes, such as retinopathy, nephropathy, and atherosclerosis.

It now seems likely the products of insulin-independent metabolic pathways in epithelial and endothelial cells leading to polyol formation and protein glycosylation may be factors in the genesis of retinopathy, neuropathy, nephropathy, and premature atherosclerosis of diabetic patients.

Dietary complex carbohydrates of various type, including those rich in dietary fiber, which are the cell walls of fruits, vegetables, and cereals, may slow the rate of absorption of glucose from those diets and contribute to a lowering of the postprandial glucose peak. Glycemic responses to various foods compared to glucose have been studied and show a large variation, which is dependent upon gastric emptying, overall effects on rate of hydrolysis and absorption of glucose from food mixtures.

Dietary sucrose seems to cause a degree of insulin resistance. The active part of the disaccharide is fructose, which does not elicit an acute insulin response, but appears indirectly to increase insulin levels in both animals and man. Sucrose in animals appears to promote obesity more than glucose because of its lack of stimulation of thermogenesis. Xylitol has been used as a sweetener and as a sugar substitute in total parenteral nutrition.

It is a paradox that the most physiological of sugars (glucose) can be a menace at high concentrations. The use of nonphysiological sugars or their derivatives in diabetics and patients with special needs, such as TPN, requires much more investigation to develop a sound rationale in nutrition management.

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