Diabetes in Children and Adolescents; Observations on Diabetic Microangiopathy

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You may well wonder why I have combined a talk on diabetes in children and adolescents with one on diabetic microangiopathy when as pediatricians we rarely, if ever, see clinical evidence of the sequelae of vascular disease in our patients. If we see proteinuria in a child, we seek another cause. We may see young teen-agers with a microaneurysm or a trace of protein, but we soon refer them to our internist friends who fall heir to the care of problems that doubtless have their beginning in childhood years. Pediatricians are, therefore, concerned about these problems and the adequacy of treatment they are prescribing for their young diabetic patients.

There is a recent movement to place considerable emphasis again on strict control of blood glucose as a means of reducing complications of diabetes. In an effort to achieve better control many physicians are placing their patients on two injections a day.

I believe we can say that there are few, if any physicians today who could duplicate Dr. Elliott P. Joslin's success in obtaining patient cooperation in his efforts to control their diabetes. Yet data from his clinic show that only a small percentage achieved what he considered excellent control. Nor did we see a striking difference in the incidence of complications in his patients when compared with that in the general diabetic population.

I do not minimize the need for achieving as nearly optimal control as one can with insulin, but I believe a return to the old emphasis on strict control does a disservice to our diabetic children and adolescents. It misleads them into thinking that controlling the blood sugar adequately is possible with present day methods of insulin administration; that if this is achieved, it will prevent or slow down complications; and that if this is not achieved, even with the most conscientious efforts, it is the patient's fault. I believe there is evidence that none of the above is true. Also, this re-emphasis on control and what it does or does not do to the basement membrane, diverts our attention from pursuing other productive avenues of research that may uncover clues and therapeutic approaches. It is with some of these avenues that I would like to acquaint you and stir your interest.

I would like first to address myself to important considerations in the care of the child or adolescent who has diabetes.

It is, of course, fundamental that the patient and the parents be properly educated about diabetes and its control at the very beginning if one is to expect acceptance and participation in a program of good management. We feel this should always be initiated on a hospital ward even if the child is not acidotic. Here the patient and parents can work with a teaching team in a relaxed setting where questions can readily be answered before the family is left on its own. The focus of instruction for the very young child and infant is both parents; by 7 to 10 years of age the child can help with urine testing; the 11-year-old can learn to give his or her own injections. In the teens the patient becomes the focus of instruction with parents also learning the facts and techniques. Do not be misled on this point: teen-agers very much need and want the support of their parents in these circumstances.

As soon as the patient has intravenous feedings
Our goal is to allow a trace or 1+ glycosuria in urines tested prior to meals and at bedtime. The Lente® is increased daily by 2 to 4 units until control is achieved.

We teach the patient to monitor his or her diabetic control through daily urine tests: that is, a double-voided specimen before breakfast, before supper, and at bedtime. After discharge from the hospital we allow time for a pattern to develop in response to the child's home and school routine. If the glycosuria falls to negative levels after discharge as so frequently happens, the patient reduces the Lente® Insulin by 2 units after a day of negative tests, or by 4 units if there are symptoms as well. If glycosuria increases uniformly before breakfast and before supper, the patient increases it by 2 units every three to four days until control is again achieved. If a pattern of glycosuria develops in which all the morning urines are 3+ to 4+ and the pre-supper urines are 0 to 1+, the patient increases the Ultralente® or long-acting portion of the Lente® mixture. Conversely, if late afternoon urines are high in sugar, the patient increases the short-acting or Semilente® portion. In this way we achieve as good control over the 24-hour period as with those who use NPH® twice a day and avoid the use of two injections. For this reason we have abandoned the use of NPH® in favor of the Lentes®. As those of you who follow young children know very well, there frequently is no pattern to the glycosuria, and levels will go from negative to 4+. One may be guided in such circumstances by daily urine volumes and adjust the insulin to keep urine volumes in the normal range.

If acetone appears, the patient is to take regular insulin at that time. He or she is asked to take 1/5 of his or her daily dose of Lente® for moderate or large and 1/10 for small amounts of acetone. This is repeated at subsequent testings if acetone persists.

If the child becomes ill and is unable to eat or is vomiting, the Lente® is omitted and small amounts of regular insulin are given. Depending on the nature of the problem, the child will be seen in the Emergency Room, admitted, or followed at home by phone instructions.

The diet we propose for the diabetic is no different from one we propose for the non-diabetic. It consists of a good source of protein as the cornerstone of the diet, carbohydrate obtained mainly from starches, a drastic reduction in refined sweets, a mixture of predominantly unsaturated and saturated fats, and, finally, foods containing adequate rough-
The term "brittle" diabetic is frequently used to describe the majority of juvenile diabetics. I believe this is too broad a use of the term and often reflects only a poor understanding of how to manage youngsters whose exercise pattern is unpredictable and whose increased needs with growth are not properly met. I would reserve the term for the juvenile diabetic who is truly difficult to manage; in hypoglycemia, but it can also result in a curious unexplained phenomenon called the Somogyi reaction, which usually appears after sudden and excessive increases in insulin. The reaction is characterized by polydipsia and polyuria, sometimes to an overwhelming degree. Unlike the patient in acidosis, however, the CO2 is not elevated though the glucose values may be very high. The explanation given by Somogyi is that the intense hypoglycemia generated by excessive insulin, usually occurring between 2 AM and 4 AM, causes a discharge of adrenalin and a swift rise in blood glucose to excessive levels. The increased glycosuria in the morning and the excessive polyuria suggest the need for more insulin, and a vicious circle ensues. The patient needs to be hospitalized, taken off long-acting insulin, and regulated on regular insulin before returning to Lente®.

Over-treatment with insulin can of course result in hypoglycemia, but it can also result in a curious and unexplained phenomenon called the Somogyi reaction, which usually appears after sudden and excessive increases in insulin. The reaction is characterized by polydipsia and polyuria, sometimes to an overwhelming degree. Unlike the patient in acidosis, however, the CO2 is not elevated though the glucose values may be very high. The explanation given by Somogyi is that the intense hypoglycemia generated by excessive insulin, usually occurring between 2 AM and 4 AM, causes a discharge of adrenalin and a swift rise in blood glucose to excessive levels. The increased glycosuria in the morning and the excessive polyuria suggest the need for more insulin, and a vicious circle ensues. The patient needs to be hospitalized, taken off long-acting insulin, and regulated on regular insulin before returning to Lente®.

One final problem we encounter, especially in
teen-agers, is noncompliance. This must be dealt with in a sympathetic yet firm manner. One can only have deep feelings of empathy for youths who are struggling to establish their own identity in a world generally hostile to teen-agers, and who are aware that in the not-too-distant future they will be on their own.

Our approach, therefore, is to keep the demands on the patient simple but to work closely with him to follow these simple rules:

1) Double void urine twice a day, test for glucose and acetone, and record results so they can be reviewed with the patient.

2) Take insulin without fail each morning.

3) Eat a sound diet at regular time intervals and in amounts that satisfy appetite and maintain normal weight.

4) Keep regular medical appointments at 3-month intervals. This provides an opportunity to review the patient's understanding of diabetes and its control.

I would now like to turn to a discussion of abnormalities in serum proteins, platelets, and red blood cells of diabetic subjects discussed at a conference on Diabetic Microangiopathy held by the Kroc Foundation in April, 1976. The conference was arranged by Dr. Donald McMillan of the Sansum Medical Research Foundation and Dr. John Ditzel of Aalborg, Denmark, and the papers have appeared in the November, 1976 supplement of Diabetes.

The abnormalities I wish to describe may play a role in the genesis of diabetic angiopathy or are factors that reduce tissue delivery of oxygen by hemoglobin. These mechanisms can lead to tissue hypoxia and subsequent tissue damage.

First, Dr. McMillan, as well as others, describes significant increases in serum proteins in diabetics. No system of proteins is spared. Studies of newly diagnosed diabetics show increases as great as those in established diabetics. Abnormalities are independent of the presence of sequelae of microangiopathy.

The majority of the proteins elevated in diabetics are acute phase reactants: α₁ acid glycoproteins, α₁ antitrypsin, haptoglobin, ceruloplasmin, C-reactive protein, C3C, C4 and C3 activator, and fibrinogen. Albumin levels are lower than normal. By direct measurement Dr. McMillan has shown that diabetic serum has a greatly increased viscosity which is due to the elevation of these proteins. The abnormal viscosity bears no relation to age, sex, body weight or duration or type of treatment of the diabetes.

Erythrocyte aggregation is markedly increased due to the increased fibrinogen level as well as to increases in other elongated proteins. Increased erythrocyte aggregation has the added effect of enhancing the coagulation of blood.

Platelet aggregation is also increased in diabetics in the early stages of the disease as well as later. There is a greater sensitivity than normal to aggregating agents such as adenosine diphosphate (ADP), epinephrine, and collagen.

At the same time that intravascular factors are leading to the occlusion of small blood vessels, the fibrinolytic system, the body's defense against vascular occlusion, is decreased. This abnormality is more pronounced in patients with signs of microangiopathy.

We have recently made observations on red cell membranes in diabetics and have noted an abnormal adherence of hemoglobin to the red cell membranes.

Red cell ghosts prepared by the method of Dodge were solubilized in 1% sodium dodecyl sulfate (SDS), separated by gel electrophoresis and stained with Coomassie Blue (Figure). Increased amounts of hemoglobin were noted in the membranes of diabetics, B, C, and D, compared to those of a non-diabetic child, A. Dislodging the hemoglobin from red cell ghosts with Tris (hydroxymethyl aminomethane), a nonionic buffer, simultaneously

Figure-Membrane proteins of erythrocyte ghosts in 1% SDS separated by polyacrylamide gel electrophoresis and stained with Coomassie Blue. A to D (untreated ghosts): A, normal 12-year-old; B, 8-year-old on insulin one month; C, top layer of ghosts, pale yellow; D, bottom layer, pink, 15-year-old on insulin five years. E and F (ghosts extracted with 0.01 M Tris, pH 8.2): E ~ A; F ~ B. G to J (Tris eluates): G ~ A, H ~ C, I ~ D, and J ~ B. In D note the doublet of band 6 and the heavy band of hemoglobin, and the appearance of those components in the Tris eluate. The proteins are eluted roughly in proportion to the amount of hemoglobin adhering to the membrane.
removed both peripheral and integral membrane proteins. E and F represent the ghosts after membrane bands 4.1 to 4.5, 5, 6, and 7, as well as the hemoglobin. It is suggested that the tightly adhering and increased amounts of hemoglobin on diabetic membranes interfere with normal erythrocyte deformability because deformability is influenced by the peripheral proteins of the inner aspect of the red cell membrane. Normal deformability is essential for normal blood flow since the diameter of erythrocytes is greater than the diameter of the smallest blood vessels through which they must pass.

Finally there is evidence of disturbance in oxygen transport in diabetics. Rahbar originally described the abnormal increases of the minor hemoglobin components \text{Al\textsubscript{a}}, \text{b}, and \text{c} in diabetic adults. We have made a similar report in children. In spite of acceptable control of their diabetes, young children, and adults as well, have levels that are twice normal. The important fact about hemoglobin \text{Alc} is that it does not react with 2, 3 diphosphoglycerate (2,3 DPG), thus reducing the ability of hemoglobin \text{Alc} to yield oxygen to the tissues. Opposing this impairment of oxygen release due to increased levels of \text{Alc}, Ditzel has found elevated levels of 2,3 DPG but a lower than normal \text{P}\textsubscript{50}. Phosphate administration to these diabetic children brought their \text{P}\textsubscript{50} to the level of the normal control group. This may be a therapeutic approach toward improving oxygenation of diabetic tissue that warrants further study.

The possibility thus arises that glucagon excess in a setting of insulin deficiency is the initiating factor of the sequence of events leading to microvascular occlusion. We have begun a prospective study in our young diabetics of the degree of abnormality of glucagon secretion and its progression, and the levels of acute phase proteins, to determine if a correlation exists between them.

I conclude by paraphrasing a well-known slogan, "We want to find a cure for diabetic microangiopathy before our diabetic children leave adolescence," because success of treatment undoubtedly lies in applying it in the trouble-free childhood years.

The figure is reproduced with permission from Diabetes (25: 805-930, 1976).

REFERENCES