**DIETARY REVERSAL OF THE CARBOHYDRATE INTOLERANCE IN URAEMIA**

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The first description of an acquired abnormality in carbohydrate metabolism associated with renal insufficiency was made by Neubauer in 1910. Since these initial observations and despite the efforts of many investigators (Wetervelt and Schreiner, 1962; Cohen, 1962; Horton et al., 1968), we still lack a clear understanding of the pathophysiology linking uraemia and carbohydrate intolerance. The decreasing insulin requirements in diabetics when renal failure supervenes, in contrast to the non-diabetic patient who develops carbohydrate intolerance when renal failure occurs, remain an interesting unanswered dilemma (Zubrod et al., 1951).

It is well known that glucose tolerance decreases with age, starvation and obesity. It is therefore essential that these factors be considered in studying this problem in patients with renal insufficiency. In addition patients with a family history of diabetes mellitus should be eliminated from such a study.

Chronic uraemia can be successfully managed by intermittent haemodialysis. Frequent haemodialysis in addition has shown to correct the carbohydrate intolerance (Hampers et al., 1966). Based on these observations it is possible that a dialyzable, small molecular weight substance or substances which accumulate(s) in uraemia has a detrimental effect on carbohydrate tolerance. This substance or substances is eliminated by frequent haemodialyses effecting a normalization of carbohydrate metabolism. We and others (Giordano, 1963; Snyder and Merrill, 1966) have been successfully managing chronic uraemic patients with a diet deficient in non-essential amino acids. Our diet and the results of a nitrogen balance have been described in a detailed study in another publication (Snyder and Merrill, 1966). The present report details our investigation into the effects of this diet, the selected protein diet (S.P.D.) (similar to the Giordano-Giovannetti diet), on carbohydrate metabolism and plasma insulin levels in uraemic patients with carbohydrate intolerance.

**PATIENTS AND METHODS**

Twenty patients with symptomatic chronic renal failure from various causes were selected from a group of 28 patients being managed with the S.P.D. at the Maimonides Medical Center. Patient selection was based on the absence of obesity, a negative family history of diabetes mellitus, adherence to the diet and willingness to cooperate. All but three patients tested had an abnormal intravenous glucose tolerance test. The results of the intravenous glucose tolerance tests were expressed by the K value, i.e. the diminution rate of the blood sugar in percent per minute. Following an intravenous load of glucose the decrease in blood sugar is exponential. Therefore, the value for blood sugar constitutes a straight line function when drawn on semilogarithmic paper, from which the K value is easily calculated. A K value less than 1.0 is indicative of carbohydrate intolerance similar to that seen in patients with diabetes mellitus (Lundbaek, 1962).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Creatinine clearance ml/min.</th>
<th>K value</th>
<th>BUN mg%</th>
<th>FBS mg%</th>
<th>Serum creatinine mg%</th>
<th>Serum K mEq/l</th>
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<tr>
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<td></td>
<td>*Pre</td>
<td>Post</td>
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<td>1.41</td>
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<td>184</td>
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<td>5.7</td>
<td>3.2</td>
<td>1.02</td>
<td>1.32</td>
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<td>2.2</td>
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<td>.140</td>
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<td>1.8</td>
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<td>3.7</td>
<td>1.05</td>
<td>1.44</td>
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<td>1.37</td>
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</table>

Mean = 46

± S.E. 8

* Pre: After at least two weeks of the control diet.
Post: After two weeks of the selected protein diet.

D. Snyder, L. B. Pulido, and A. Kagan
DIETARY REVERSAL OF THE CARBOHYDRATE INTOLERANCE IN URAEMIA

The patients were all hospitalized at the Maimonides Medical Center. Remaining renal function was estimated by endogenous creatinine clearance. All patients had chronic renal failure with relatively stable renal function. None of the patients selected had previously any form of dialysis, or drug therapy which would influence carbohydrate metabolism.

After selection for the study but prior to initiation of the S.P.D. all patients were maintained on a 20 g unselected protein diet containing 4 calories per kg body weight. The S.P.D. contains 20 g of protein devoid of non-essential amino acids and was made isocaloric with the control diet. Vitamin supplementation was provided throughout the study in a constant dosage. Intravenous glucose tolerance tests and sampling of venous blood for the determination of immuno-reactive insulin were performed after an overnight fast during the control period and again two weeks after beginning the S.P.D. The intravenous glucose tolerance tests were all performed by injecting 0.5 g of glucose per kg body weight over a three minute period and sampling the venous blood at 0, 3, 6, 10, 20, 30, 40, 50 and 60 minutes.

Because of variable degrees of nausea and vomiting during the control period optimum caloric intake could not be ensured. To obviate the complication of starvation causing the abnormality in carbohydrate metabolism, five patients were restarted on their control diet after two weeks on the S.P.D. The studies of intravenous glucose tolerance and measurements of immuno-reactive insulin levels were repeated in these 5 patients one week later.

Glucose concentration was determined by the method of Somogyi (1945). Measurements of plasma immuno-reactive insulin were obtained by the method of Yalow and Berson (1964). Other determinations were made by standard laboratory techniques.

RESULTS

Twenty patients (12 females and 8 males), ranging in age from 26 to 62 years, were studied (Table 1). The mean endogenous creatinine clearance was only 5.7 ml per minute. The BUNs and serum creatinines were commensurately elevated, ranging from 81 to 204 mg per 100 ml and 7.1 to 23.7 mg per 100 ml respectively. Seventeen of the 20 patients studied had abnormal responses to intravenous glucose loads during the control diet. The mean K value for the entire group while consuming the diet was .70 ± .23. Excluding the three patients with normal K value (i.e. 1.0) during the control period, the mean K value was .69. The carbohydrate intolerance was not reflected, however, in their fasting blood sugar values which were normal in all patients with a mean of 93 ± 11.0 mg%.

In all but two patients (C.L. and G.M.) initiation of the S.P.D. was associated with a remarkable amelioration of the gastrointestinal symptomatology usually associated with uraemia. As demonstrated in a previous study (Snyder and Merrill, 1966) and later confirmed by others the disappearance of nausea, vomiting, dyspepsia, etc. occurred long before any significant fall in BUN values.

In Figure 1 the individual K values during ingestion of the control diet are compared with the K values after two weeks of the S.P.D. There was a significant improvement from control values (P < 0.01). The K values increased from a mean of .70 ± .23 to 1.21 ± .24. Only two patients did not follow this pattern. G.M. showed no improvement and G.D.’s K value actually deteriorated. These two patients did not tolerate the diet and admitted to cheating. It is interesting to note that their gastrointestinal symptoms did not improve.

In Figure 2 the K values are plotted against the blood urea nitrogen levels. The increase in the decay constant and thus an improvement in carbohydrate tolerance was unrelated to BUN levels. The mean BUN for the group increased from 130 to 140 mg%, In addition there appeared to be no correlation with serum creatinine or serum potassium levels as seen in Table I. Because starvation is a well-known cause of carbohydrate intolerance and it is conceivable that untreated uraemic patients with variable degrees of nausea, anorexia and vomiting are starved individuals, we restarted the control diet in 5 of our patients after the two week course on the S.P.D. These patients were all tolerating the diet well and had had a

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substantial improvement in their gastrointestinal symptoms. After one week on the re-instituted control diet, carbohydrate tolerance was again evaluated. K values fell from a mean of 1.24 to .82 (Fig. 3), indicating that starvation per se was not the cause of the carbohydrate intolerance, but rather that the composition of the diet was of paramount importance.

The plasma insulin levels during the intravenous glucose tolerance tests are shown in Figure 4. During the control period there is a greater than normal release of insulin in response to the glucose load and a marked delay in the rate of fall compared to normals. This pattern is similar to that observed in adult-onset diabetes mellitus. After therapy with the S.P.D. there

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**Fig. 1.** Decay constants for blood glucose after an intravenous glucose load.

**Fig. 2.** The relationship of the blood urea nitrogen to the K value.
Fig. 3. The K value response to reinstating the control diet. Mean K values were 1.24 during the S.P.D. and 0.82 during the second control diet.

Fig. 4. Plasma immuno-reactive insulin response to an intravenous glucose load.

occurs a normalization of insulin responsiveness. The mean peak insulin response fell from control values of 142 to 105 mU/ml; insulin disappeared from the plasma much more rapidly after the two week course of the S.P.D. than during the control period and it reached a much lower plateau after one hour.

DISCUSSION

The evidence in favour of insulin antagonism as the cause of the carbohydrate intolerance in uraemic patients has become quite substantial, albeit indirect. The marked delay in the fall of blood sugar levels following exogenously administered insulin points specifically
to some form of ‘peripheral’ antagonism unrelated to plasma insulin levels (Cerletty and Engbring, 1967; Horton et al., 1968). This lack of response is similar in many ways to that seen in ‘maturity-onset’ diabetes mellitus. This obviously argues against the thesis of inadequate pancreatic stores of insulin or a delay in insulin release. More to the point, we have demonstrated directly that the pancreatic insulin response to an intravenous glucose load is actually greater than normal. This correlates well with the greater than normal levels of plasma insulin induced by tolbutamide administration in uraemic patients (Cerletty and Engbring, 1967). The delay in the fall of blood glucose after tolbutamide administration is most likely the result of antagonism acting in the periphery. This response to tolbutamide may reflect an abnormal effect on hepatic glycogen mechanism; however, the repeatedly documented normal response of uraemic patients to glucagon tends to refute this (Tchobroutsky et al., 1965).

Inadequate caloric intake for a prolonged period of time will cause a degree of carbohydrate intolerance. It is conceivable that uraemic patients with anorexia, nausea and vomiting may well be starved. However, the studies on the effects of haemodialysis on this problem (Hampers et al., 1966; Alfrey et al., 1967) implicate at least another mechanism for the carbohydrate intolerance. This possibility was considered in our study and caused us to restart the control diet in five patients who had been successfully treated with the S.P.D. At a time when their gastrointestinal symptoms had disappeared and they were eating well, one week of the unselected protein control diet was sufficient to reproduce the abnormal glucose tolerance results seen during the control period. Thus, inadequate caloric intake does not appear to be the major mechanism in the production of uraemic carbohydrate intolerance.

Similarly, total body potassium depletion which has been reported in uraemic patients (Spergel et al., 1967) and thought to be a cause of the abnormal carbohydrate metabolism has been shown not to be directly related. Our patients were restricted to 1500 mg of potassium in both the control diet and the S.P.D. Thus, if total exchangeable body potassium was low in our patients, no effort was made to supplement their potassium intake. Serum potassium values, which cannot be correlated with total exchangeable potassium, remained unchanged for the group.

The role of amino acid selection in the diet in the correction of the carbohydrate intolerance of uraemia is not clear. The possible factors of ‘peripheral’ insulin antagonism include disturbances such as impaired intracellular utilization of glucose, circulating antibodies to insulin and interference with insulin-dependent transfer of glucose. It is possible that promotion of protein anabolism with S.P.D. therapy would improve carbohydrate utilization by the liver, the liver being the major site of glucose utilization during the hour following the intravenous load. This does not correlate well with the improvement in glucose utilization following frequent haemodialysis nor the deterioration of glucose tolerance in the 5 patients we restarted on the control diet. Data published in a previous paper (Snyder and Merrill, 1966) does reveal a marked improvement in nitrogen balance with the S.P.D. This occurs, however, at about three weeks following the initiation of the diet and nitrogen balance and carbohydrate tolerance cannot be directly equated.

The general effect of the S.P.D. on protein metabolism may of itself be an important factor. All the data available do not completely fit this hypothesis. The fact that carbohydrate intolerance of uraemia does not require therapy and that no clinical effects can be detected does not detract from the lesson that this particular area of deranged metabolism can teach us regarding the metabolic defects induced by chronic renal failure. In addition the ability of the S.P.D. to turn on and off carbohydrate intolerance in these people provides us with a very useful tool for the investigation of this and related problems.

REFERENCES

Dietary Reversal of the Carbohydrate Intolerance in Uraemia


