The Blood Sugar and Serum Insulin Response to Intravenous Glucagon in Chronic Renal Failure[1] (34746)

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(Introduced by A. M. Lawrence)

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Although fasting hyperglycemia and impaired glucose tolerance in azotemia have been recognized for many years, the pathogenesis of these abnormalities is still unclear (1). We have shown that the uremic state is characterized by insulin antagonism. Evidence supporting this concept is based upon decreased sensitivity to exogenous insulin, elevated endogenous fasting insulin levels, and an exaggerated insulin response to oral gulcose (2). On the other hand, the results of Cohen (3) contrast with these findings, for he described normal peripheral utilization of glucose in uremic patients and postulated that the carbohydrate intolerance was due to impaired uptake of glucose by the liver. In addition, hepatic stores of glycogen were depleted in many of these subjects.

The degree of hyperglycemia following glucagon administration is related to the hepatic content of glycogen (4). In addition, glucagon directly stimulates the secretion of insulin from the beta cells (5,6). In an attempt to throw further light on the role of the liver and the reactivity of the pancreas in renal failure, we have evaluated the blood sugar and serum insulin responses of uremic subjects to the administration of glucagon and compared the results with a control group. Although the rise in blood sugar stimulated by glucagon has previously been measured in a few patients with renal disease (7–10), the findings are difficult to interpret because of the absence of a control group (7, 8, 10), the small number of patients (8, 9, 10) and the variable sampling times (9, 10).

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Materials and Methods. Five male and 3 female subjects with chronic renal failure were selected for study. They did not give a history of diabetes, liver disease, or infection. Five subjects had chronic glomerulonephritis, two had chronic pyelonephritis, and the remaining subject had analgesic nephropathy. Because electrolyte disturbances alter glucose tolerance, tests were only performed after the renal function and electrolyte pattern had stabilized. Six male subjects with normal renal function served as controls. They included nonprofessional hospital employees and patients who had been admitted to hospital with a variety of minor illnesses, but who had fully recovered before testing. Both the control subjects and the patients with chronic renal failure were given oral glucose tolerance tests 4 to 7 days prior to administration of glucagon (2).

All subjects were kept on a high carbohydrate diet for at least 3 days before testing. The protein intake of the uremic patients was restricted to less than 30 g/day. At the time of testing, 4 patients were receiving α-methyldopa and one furosemide (80 mg/day). The subjects were tested in the early morning following a 10-hr overnight fast. After resting for 30 min in a quiet room, 0.2 μg of glucagon/kg of body weight was administered intravenously. Blood samples were taken at 0, 10, 20, 30, 60, 90, and 120 min through an indwelling needle placed in an antecubital vein.

Blood urea and serum electrolytes were measured on the AutoAnalyser (Technicon). Blood sugar was estimated on the AutoAnalyser by the method of Hoffman (11). Serum insulin was assayed by a modification of the

double antibody method of Morgan and Lazarow (12) on serum stored at —20°. A standard human serum was included in each assay and over the period of the study its value varied from 190 to 240 μU/ml (coefficient of variation 6.8%). In order to minimize interassay variations, serum insulin samples from both patients and control subjects were measured in the same assay.

Results. The mean age of the control subjects was 38 years (range 29–46) and the uremic patients 42 years (range 26–55). All subjects were within 15% of their "ideal" body weight with the exception of 2 patients with renal failure who were 20% below their "ideal" weight. The mean blood urea of the patients was 129 mg/100 ml (range 70–223 mg/100 ml). The serum potassium, chloride, sodium, and carbon dioxide concentrations of all the subjects were within normal limits with the exception of one patient who had a carbon dioxide content of 12 meq/liter. The blood sugars of all the control subjects at 120 and 150 min after oral glucose administration were below 110 mg/100 ml, while the uremic patients showed marked glucose intolerance with elevated blood sugar levels (greater than 120 mg/100 ml at 120 and 150 min). Moreover, the serum insulin levels of the patients were higher than those of the normal subjects (2).

The mean fasting blood sugar in the control subjects was 71 mg/100 ml (SD ±7); while in the patients, it was 97 mg/100 ml (S ±5) ($p = < 0.001$). After the administration of glucagon, the rise of blood sugar was greater in the patients with chronic renal failure than the control subjects and this was significant at 30 min ($p = < 0.05$) (Fig. 1). The peak blood sugar increase was 35 mg/100 ml above fasting in the control subjects (20 min) and 45 mg/100 ml in the uremic patients (30 min). Although the mean fasting serum insulin level was slightly increased in the patients, this was not significant. The maximum increase of serum insulin occurred at

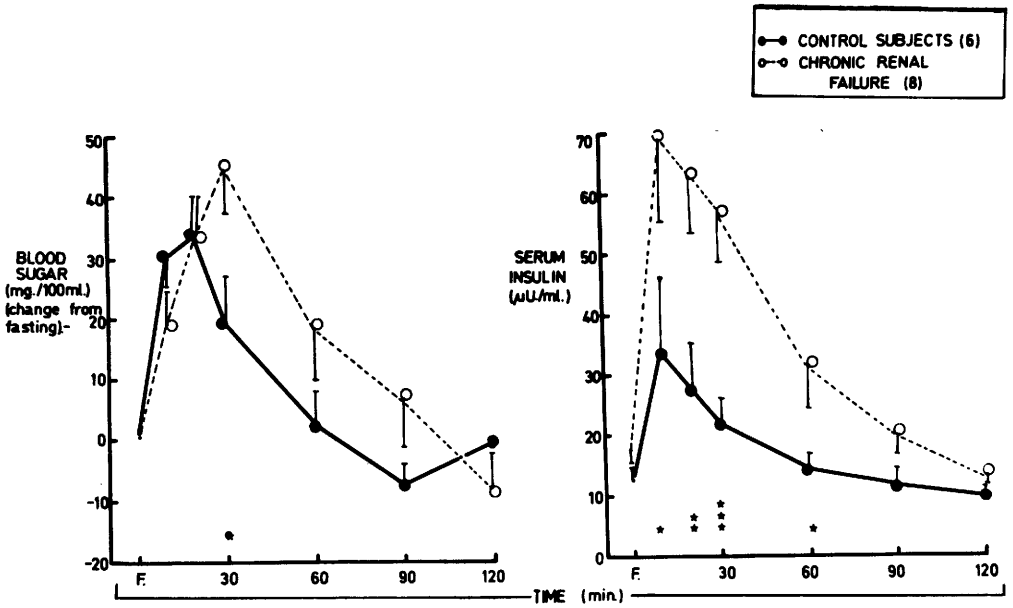

FIG. 1. Glucagon tolerance test in chronic renal failure: The blood sugar and serum insulin responses to intravenous glucagon in the patients with chronic renal failure and the control subjects. The asterisks indicate the significant differences between the patients and the control subjects: $*p = <0.05$; $** p = <0.025$; and $*** p = <0.005$.

10 min in both groups. The mean levels were considerably greater in the patients with renal failure than in the controls at 10 min ($p = 0.05$), 20 min ($p = 0.025$), 30 min ($p = 0.005$) and 60 min ($p = 0.05$). At 1 hr the mean serum insulin concentration of the control subjects had returned to basal values, while the uremic subjects still had elevated levels.

Discussion. Linder *et al.* (13) observed a rapid increase in the respiratory quotient following the administration of glucose to uremic subjects. From these results, they concluded that the metabolism of glucose to carbon dioxide through the tricarboxylic acid cycle was normal and postulated that the glucose intolerance of uremia was due to impaired glycogen synthesis in the liver.

There have been conflicting reports concerning hepatic glycogen stores in animals with renal disease. Drabkin and Marsh (14) produced acute fulminating nephrosis in rats with nephrotoxic serum; and, in addition to fasting hypoglycemia, observed a threefold decline in liver glycogen stores. In rats rendered uremic with surgical procedures, Cohen (3) demonstrated decreased glycogen stores only in those animals who became hyperglycemic. On the other hand, Boucot *et al.* (15) could find no alterations in blood sugar or hepatic glycogen concentration in rats with both acute and chronic renal failure.

Indirect evidence for the adequacy of hepatic glycogen stores can be obtained by the administration of epinephrine and glucagon, for the early rise in blood sugar in response to these hormones is quantitatively related to the level of hepatic glycogen (4) and does not occur when liver glycogen stores are depleted (16). Although glucagon also stimulates gluconeogenesis in the intact animal and the isolated perfused liver, the rise in blood sugar from this source occurs after a delay of approximately 30 min, is prolonged in duration and initially, and is of lesser magnitude than that following glycogenolysis (17). Our results indicate that the absolute rise in blood sugar following glucagon is adequate in uremia, although the patients attained maximum blood sugar levels at 30 min (compared to 20 min in the controls). Other authors have also observed a normal blood sugar response to glucagon in renal disease (7–10). On the other hand, Cohen (3) demonstrated a decreased glycogenolytic response to both glucagon and epinephrine in azotemic subjects. The reason for this impaired blood sugar response is unknown, but it seems possible that some of his subjects were malnourished in addition to being uremic.

Uremic subjects have an impaired ability to clear both oral and intravenous galactose loads (3). Since the clearance of galactose is largely dependent on hepatic activity this was interpreted as further evidence favoring the importance of the liver in the pathogenesis of glucose intolerance. However, recent work by Luke *et al.* (18) has shown that galactose tolerance may be normal in uremia. Furthermore, fructose and xylitol, which are also metabolized by the liver, are efficiently utilized in the uremic state (19).

Samols *et al.* (5) and Turner and McIntyre (6) reported that glucagon stimulates the pancreas to release insulin. It is unlikely that the insulin response is secondary to hyperglycemia, for glucagon directly stimulates insulin secretion from pancreatic slices *in vitro* and high levels of serum insulin have observed as early as 1 min after glucagon administration, although the maximum blood sugar response occurs later (20). The exaggerated insulin response to glucagon in the patients with chronic renal failure suggests that absolute insulin deficiency is unlikely to account for their glucose intolerance. Rather, the elevated insulin levels observed support previous observations that a state of insulin antagonism is present. It is of interest that the insulin response to glucagon is also exaggerated in obesity (20), a condition characterized by the presence of hyperinsulinism and insulin antagonism.

The persistent elevation of serum insulin observed after glucagon administration is attributed to the decreased degradation of insulin. This phenomenon has been well described in patients with chronic renal disease and results in the prolonged half disappearance time of insulin (2). Following the administration of exogenous insulin, uremic subjects demonstrate hypoglycemic unrespon-

siveness (2, 3, 10). This is marked by a delayed and diminished return of the blood sugar to fasting levels. Although it has previously been suggested that this is related to decreased hepatic glycogen concentration with inadequate glycogenolysis (3), it could also be explained by the long half-life of insulin in these patients.

Summary. The blood sugar and serum insulin response to glucagon was evaluated in 8 patients with chronic renal disease and 6 control subjects. When compared to the controls, the patients demonstrated a normal blood sugar rise together with an exaggerated response of serum insulin. These observations indicate that hepatic glycogen stores are adequate and that impaired insulin secretion is not a major factor in the pathogenesis of the glucose intolerance of chronic renal failure.

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