Effect of Dialysis Treatment on Glucose Metabolism in Uremic Patients

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To study the carbohydrate metabolism in uremic patients, the intravenous glucose tolerance test (iv GTT) and insulin sensitivity test were investigated on 69 patients with chronic renal failure, 27 of whom were under the dialysis treatment. 1) Abnormal K-values averaging 1.05 were obtained in uremic patients (creatinine clearance less than 20 ml/min). 2) Carbohydrate intolerance in uremic patients was corrected with regular dialysis and the improvement was correlated with the duration of dialyses. 3) The mechanisms of improvement in carbohydrate metabolism were different between the short-term dialysis group (less than 12 months of dialysis) and the long-term group (more than 12 months). Enhanced secretion of insulin seemed to be the main cause of this improvement in the former, while the correction of impaired sensitivity to insulin in peripheral tissues in the latter.——— glucose intolerance; chronic renal failure; dialysis treatment

Carbohydrate intolerance associated with chronic renal failure has been known for the past half century (Myers and Bailey 1916; Hamman and Hichmann 1917; Linder et al. 1924). However, the exact mechanism of the development of this intolerance has not yet been elucidated.

In order to clarify the mechanism, we studied changes of blood glucose levels and plasma insulin response to an intravenous glucose administration in uremic patients. Furthermore, sensitivity to an intravenously administered insulin as also examined.

MATERIALS AND METHODS

Sixty-nine patients with renal diseases consisting of 63 with chronic glomerulonephritis, 2 with acute glomerulonephritis, each 1 with chronic pyelonephritis, hydronephrosis, horse shoe kidney and cystic kidney, and 14 normal controls were studied. The patients were 43 males and 26 females, aged 16 to 73 years with a mean of 38.6. 5 patients showed nephrotic syndromes. 27 of 69 patients were maintained on peritoneal dialysis or hemodialysis. Peritoneal dialyses were usually performed twice a week (total of 14 to 18 hr per week) with dialysates containing 1.3 to 7% of glucose. Hemodialyses were performed twice a week (total of 12 to 14 hr per week) with a coil dialyser of the single pass system using dialysates containing glucose of 0 to 1.2%.

Received for publication, September 10, 1976.
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When the patients had fallen into a uremic state requiring dialysis, they were usually
dialysed through the peritoneal route initially. Peritonitis occurred frequently and
severe uremia was not controlled satisfactorily with this treatment alone. In these
circumstances hemodialysis was started, replacing the peritoneal dialysis partly at first,
and entirely later on.

Patients were hospitalized in the Department of Nephrology, Toranomon General
Hospital, Kanagawa at least for several days before the test. All patients and control
subjects had no history of diabetes mellitus. The patients and controls were not obese.

Control subjects had a mean body weight of 101.8% (estimated ideal weight=100%),
uremic patients without dialysis 91.7%, and those with dialysis 89.4%.

They were divided into four groups according to the renal function and the duration
of dialysis as follows: group 1, normal subjects with creatinine clearance more than 70
ml/min; group 2, uremic patients without dialysis (creatinine clearance less than 20 ml/
min); group 3, short-term dialysis group (dialysed for less than 12 months); and group 4,
long-term dialysis group (dialysed for more than 12 months).

The intravenous glucose tolerance test (ivGTT) was performed on both patients
and control subjects; they were taking a diet containing at least 320 g of carbohydrate
daily. After an overnight fast, 0.5 g of glucose per kg body weight was injected over a 3-
min period and samples of venous blood were drawn at 0, 10, 20, 30, 60, 90 and 120 min
after injection through an indwelling needle for the measurement of blood glucose and
plasma insulin.

After intravenous injection of glucose, logarithm of the blood glucose level declined
linearly with time. The slope of this line, expressed as functional decrement constant K
\( K = \log_{2} (t)\times100 = 0.693/t^{1/2} \times 100 \) percent per min was used as an index of glucose tolerance
(Lundbaek 1962). Blood glucose was determined with enzymatic methods (glucose oxidase,
peroxidase, o-dianisine system, Boehlinger Mannheim, blood sugar test, TC-M). Plasma
insulin was analysed by a double antibody immunoassay method (Yalow and Berson 1960).

The insulin tolerance test was performed on the subjects after an overnight fast.
Four units of regular insulin were injected into an antecubital vein and heparinized
blood samples were collected through an indwelling needle at 0, 10, 20, 30, 60, 90 and 120 min
after injection.

RESULTS

The \( K \)-values in four groups are shown in Fig. 1. The values in the control
group (group 1) and also in the long-term dialysis group (group 4) were within
normal range (more than 1.5), but in the uremic group (group 2) and in the short-
term dialysis group (group 3) abnormally low \( K \)-values (less than 1.5) were found

Fig. 2 demonstrates plasma insulin response to ivGTT. The fasting serum
insulin level in the group 1 was 12.8±1.0 \( \mu U/ml \) which increased soon after
insulin injection to reach a peak of 101.0±11.3 \( \mu U/ml \) at 3 min. Plasma
insulin fell rapidly in 60 min along an almost straight line, followed by a more
gradual return to the baseline level at the end of the test. In the uremic
(group 2) and short-term dialysis group (group 3), fasting insulin levels were
slightly high but the initial response to the glucose load was almost the same
as in the control group (group 1) and in the long-term dialysis group (group 4)
In the following 60 min, however, the insulin levels in the former 2 groups decline
at a slower rate than in the latter 2 groups so that in the later part of the test
plasma insulin levels remained significantly above normal.

Group 3 patients could be divided into two subgroups; those who had norm
Fig. 1. The $K$-values in control subjects (group 1: creatinine clearance 70 ml/min), uremic patients (group 2: creatinine clearance 20 ml/min), short-term dialysis group (group 3: dialysed for less than 12 months) and long-term dialysis group (group 4: dialysed for more than 12 months). Mean±s.e.

Fig. 2. Plasma insulin response to ivGTT in control subjects, uremic patients, short-term dialysis group, and long-term dialysis group. ○--○ normal (n=9); ●--● uremic (n=13); △--△ short-term dialysis group (n=22); ▲--▲ long-term dialysis group (n=22). Each value is expressed as mean±s.e.
The insulin response to ivGTT differed in these two subgroups as shown in Fig. 3. The normal K subgroup showed a higher insulin secretion than the delayed K subgroup. Fasting levels of insulin or its 3 min levels after glucose load in normal K patients were higher than those in normal controls, but in the later part of the test the levels went down to almost normal. Delayed K patients had also slightly higher values in insulin levels before and 3 min after glucose injection than the control group. Thereafter, the insulin levels declined rather slowly and slightly higher values were found in the later part of the test.

The group 4 patients (dialysed for more than 1 year) could also be divided into subgroups as group 3 patients; normal K patients and delayed K. But there was no great difference in the insulin response between these two subgroups (Fig. 4). Fasting insulin levels in both subgroups were slightly lower than those of the control group.

The 3-min values were also lower. As revealed by a closer examination of Fig. 4, the delayed K patients had lower levels of insulin than normal K patients at 3-min after the load. At 10 to 30 min after glucose injection, lower insulin levels were also found in both subgroups, they rose to normal levels in the later course of the test.
Fig. 4. Plasma insulin response to ivGTT in normal K subgroup and abnormal K subgroup dialysed for more than 12 months. ○-○, normal K group (K>1.5, n=19); ●-●, abnormal K group (K<1.5, n=9). Each value is expressed as mean±s.e.

Fig. 5. Intravenous insulin tolerance test in control subjects, uremic patients, short-term dialysis group, and long-term dialysis group. ○-○ normal (n=14); ●-● uremic (n=7); △-△, short-term dialysis group (n=12); ▲-▲, long-term dialysis group (n=6). Each value is expressed as mean±s.e.
Fig. 5 demonstrates the glucose response to an intravenous injection of insulin. After intravenous injection of insulin, the long-term dialysis group (group 4) showed a more rapid fall in plasma glucose level at the initial phase of the test and then a more rapid rise in the later phase than the short-term dialysis group (group 3); thus the group 4 patients showed an almost normal curve as seen in the group with normal renal function (group 1).

**DISCUSSION**

Improvement of carbohydrate metabolism in uremic patients as a result of dialysis treatment has been reported by many investigators (Sagild 1962; Alefrey et al. 1966; Hampers et al. 1970). Hampers et al. (1966, 1970) described that glucose intolerance, insulin insensitivity and abnormal response to intravenous tolbutamide were corrected with hemodialysis and this was accompanied by increased insulin levels in response to ivGTT. In disagreement with this study, Hutchings et al. (1966) reported that patients on chronic dialysis were found to have abnormal carbohydrate metabolism in spite of normal insulin levels in response to an intravenous glucose.

The results of the present study indicate that the improvement of carbohydrate metabolism in uremic patients as a result of dialysis treatment is related to the duration of dialysis.

Increased insulin levels were found in response to ivGTT in the short-term dialysis group (less than 12 months of dialysis) but not in the long-term group (more than 12 months of dialysis), indicating that tissue sensitivity to insulin is impaired in the former, but has restored to normal in the latter group.

Hampers et al. (1966) reported that the glucose intolerance could be corrected with the frequent hemodialysis within about 2 weeks. On the contrary, the present study demonstrated that long duration of dialysis treatment (2 or 3 times per week for more than 12 months) was necessary to improve the glucose metabolism in uremic patients. The difference in these two studies may be explained by the adequacy of the dialysis. The relation between the improvement of carbohydrate metabolism in uremic patients and the duration of dialysis has, hitherto, never been studied.

From the results of the present study, it appears that the K-value, the insulin response to ivGTT, and the insulin tolerance test in patients treated with dialysis are dependent on the duration of dialyses.

*K-value*. As the renal function deteriorated down to a creatinine clearance of 20 ml/min or lower, the K-value also worsened to a level of 1.5 or less (Amatuzio et al. 1953; Perkoff et al. 1958; Horton et al. 1967; Hampers et al. 1968). The carbohydrate intolerance in uremic patients, however, could be corrected with dialysis treatment. The degree of improvement in carbohydrate metabolism was significantly higher in the long-term dialysis group than in the short-term group.

*Insulin response*. In uremic stage, insulin response to the intravenous glucose
load showed an abnormal pattern (Cohen and Lindall 1969; Tchobroutsky et al. 1969; Hampers et al. 1970; Lowrie et al. 1970; Lindall et al. 1971), but in the patients with dialysis, the pattern was almost normal (Sagild et al. 1962; Hampers et al. 1966).

Relating to the duration of dialysis, recovery of insulin response to ivGTT was better in the long-term dialysis group than in the short-term group. On the contrary, relating to the duration of dialysis and K-value, the initial phase of the test showed supernormal responses to glucose administration in normal K group dialysed for less than 12 months. There were, however, no differences in the results between normal and abnormal K subgroups dialysed for more than 12 months. These results suggest that the improvement of carbohydrate metabolism in the short-term dialysis group may be attributable to supernormal secretion of insulin at the initial phase of the test (Alefrey et al. 1966, 1967; Lowrie et al. 1970). This mechanism is not shared with the long-term dialysis group.

**Insulin sensitivity test.** In the long-term dialysis group, the insulin sensitivity was almost the same as in the control group, and quite different from that in the short-term group. These results suggest a possibility that abnormal metabolism of peripheral tissues induced by uremia is one of the important factors relating to the carbohydrate intolerance (Perkoff et al. 1958; Westervelt and Scribner 1962; Teuscher et al. 1963; Briggs et al. 1967; Horton et al. 1967; Hampers et al. 1970).

These results suggest that it requires a long-term dialysis treatment to improve the glucose intolerance in uremia because abnormal metabolic states at the organ-tissue-enzyme levels are not so quickly corrected with hemodialysis performed 2 or 3 times per week. In the short-term dialysis group, the most important factor contributing to the improvement of carbohydrate intolerance as a result of dialysis may be oversecretion of insulin, but in the long-term dialysis group it may be the correction of peripheral insulin resistance.

**Acknowledgment**

We gratefully acknowledge Prof. Kaoru Yoshinaga and Dr. Keishi Abe, the Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai for the advice about this study. Our thanks are also due to Dr. Yasuo Hatakeyama, Master of Iwaki-Kyoritu General Hospital, Iwaki and Dr. Hiroshi Nihei, the Department of Nephrology, Toranomon General Hospital, Kanagawa.

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