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Insulin Resistance in Uremia

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Abstract

In chronic renal failure the abnormal carbohydrate metabolism is characterized by normal or slightly elevated fasting plasma glucose level, significantly increased plasma glucose concentration following glucose administration, hyperinsulinemia and insulin resistance. The present study was conducted on 20 uremic patients, 10 of them were under hemodialysis and 10 were not. 10 normal individuals served as control subjects. For each the following was done: Blood urea and serum creatinine, creatinine clearance, oral glucose-insulin tolerance test extended for 2 hours serum K^+ during OGTT.

The analysis of data obtained by the study had led to the following conclusions: there was a significant state of insulin resistance which was manifested by significant increase in the blood glucose samples following glucose administration with simultaneously elevated plasma insulin level in all samples. There was no significant difference in the state of insulin resistance as regard the progress of renal failure, this was shown by the findings of non significant differences in the indices that measure insulin resistance among patients under dialysis and those who are not. There was no significant improvement of the state of insulin resistance after dialysis.

Introduction

GLUCOSE intolerance has long been recognized as a common feature of patients with uremia. This state of impaired glucose tolerance has been proved by both oral and intravenous glucose tolerance

tests which revealed normal or slightly increased fasting plasma glucose level and significantly increased plasma glucose concentration following glucose administration in uremic patients [1].

Considerable evidence has accumulated to implicate peripheral tissue, primarily muscles, as the tissue responsible for the defect in insulin-mediated glucose utilization in uremic patients [2].

There is evidence that implicated post receptor events [3], mainly, the ability of insulin to promote hexose transport and glucose oxidation, to explain insulin resistance [4]. Recent studies provided evidence that at least two intracellular metabolic defects i.e. in the glycolytic and glucose oxidative pathways, contribute to the insulin resistance of chronic uremia [5].

Material and Methods

This study was conducted on 20 uremic pateints, 10 of them were under hemodialysis for the last year and the other 10 were under conservative treatment. They included 13 males and 7 females and their age ranged between 34 and 60 years with a mean of 43.7 ± 8.06. The patients were compared to 10 normal individuals of matching age and sex.

All cases were subjected to history taking clinical examination to exclude factors which may produce glucose intolerance or insulin resistance such as obesity, diabetes mellitus or liver diseases.

For each subject the following investigation was done: Kidney function tests including blood urea, serum creatinine and creatinine clearance, oral glucose-insulin tolerance test extended for 2hours, serum potassium during the OGTT, serum insulin determination.

In the serum samples studied, insulin was quantitiated by solid-phase 125_I radioimmunoassay [6,7].

The principle of the procedure is that 125_I- labeled insulin competes with insulin in the patients sample for sites on insulin-specific antibody immobilized to the wall of a polypropylene tube. After incubation, isolation of the antibody-bound fraction is achieved simply by decanting the supernatant.

Interpretation of the Results:

Assessment of the Insulin Sensitivity:

The "A" value, reffering to the peripheral insulin activity is calculated from the results of the OGTT as follows:

$$A = \frac{10^4}{\text{Peak glucose x peak insulin level}}$$

Decreased "A" value as compared with the control subjects indicates the presence of peripheral insulin resistance [8].

The insulin area under the OGTT curve is computed by the following formula:

Insuiin area = 0.25 (fasting value + 0.5 (half-hour value) + 0.75 (one - hour value) + 0.5 (two-hour value)

Thus the insulin area values could represent the magnitude of integrated serum insulin concentrations in response to oral glucose load.

A high value of insulin area as compared with control subjects may indicate hyperinsulinemia and resistance [9].

Glucose/insulin value, this is a third way used by Mbanya et al [10] as an insulin sensitivity. They limited their study to the fasting samples but we extended this ratio to the whole levels of OGTT. The higher the insulin resistance the lower the ratio [10].

Results

The results of the three groups are shown in table 1 and Figs. 1, 2, 3, 4, 5.

Table (1): Mean Values ± Standard Deviation of the Different Groups.

	Contral	Group I	Group II
Age (Years)	46.1 ± 7.7	44.5 ± 7.41	42.9 ± 8.58
Height (cms)	164.7 ± 7.15	161.6 ± 4.56	160.5 ± 6.87
Weight (kg)	64.1 ± 11.53	57.55 ± 7.11	58.25 ± 7.81
Urea (mg / dl)	17.9 ± 4.68	139.7 ± 38.94	142.9 ± 27.24
Creatinine (mg / dl)	0.695 ± 0.19	9.42 ± 3.19	10.83 ± 3.38
Creatinine clearance (ml / min)	122.75 ± 26.86	9.58 ± 4.15	7.77 ± 3.07
Serum k^+ (0) (MEq / L)	4.23 ± 0.52	4.96 ± 0.88	6.97 ± 0.43
Serum K^+ (1h) (MEq / L)	4.32 ± 0.49	4.73 ± 0.88	6.77 ± 0.48
Serum K^+ (1h) (MEq / L)	4.54 ± 0.57	4.73 ± 0.84	5.9 ± 0.43
Serum K^+ (1h) (MEq / L)	4.21 ± 0.6	4.88 ± 0.84	6.94 ± 0.40

Serum K+ during the OGTT (0. 1.2 h)
Group I :- Patients not under dialysis
Group II :- Patients under dialysis.

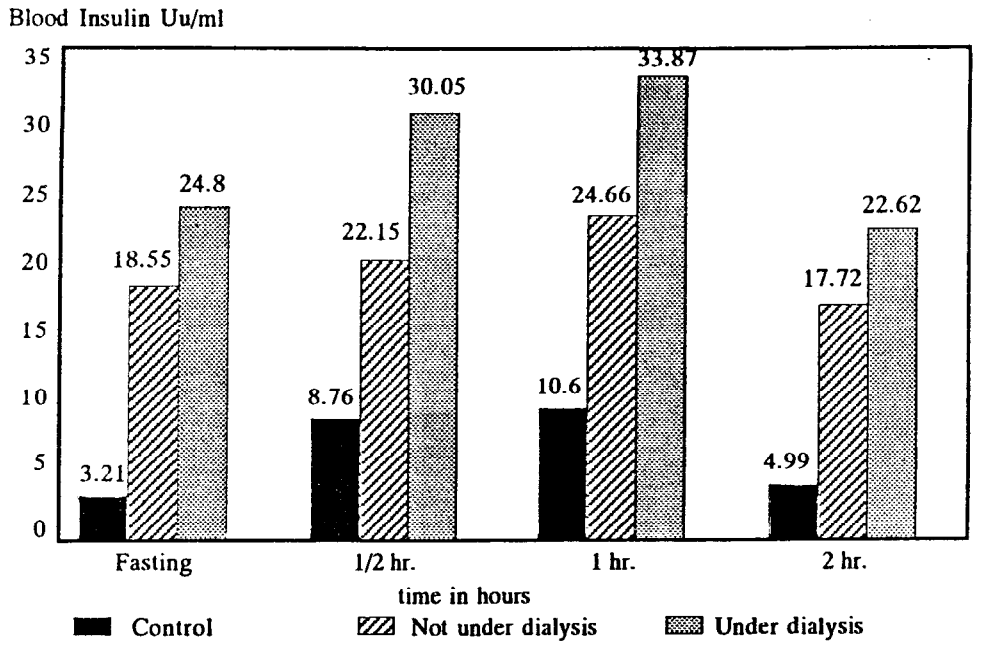

Fig. (1): Mean insulin level.

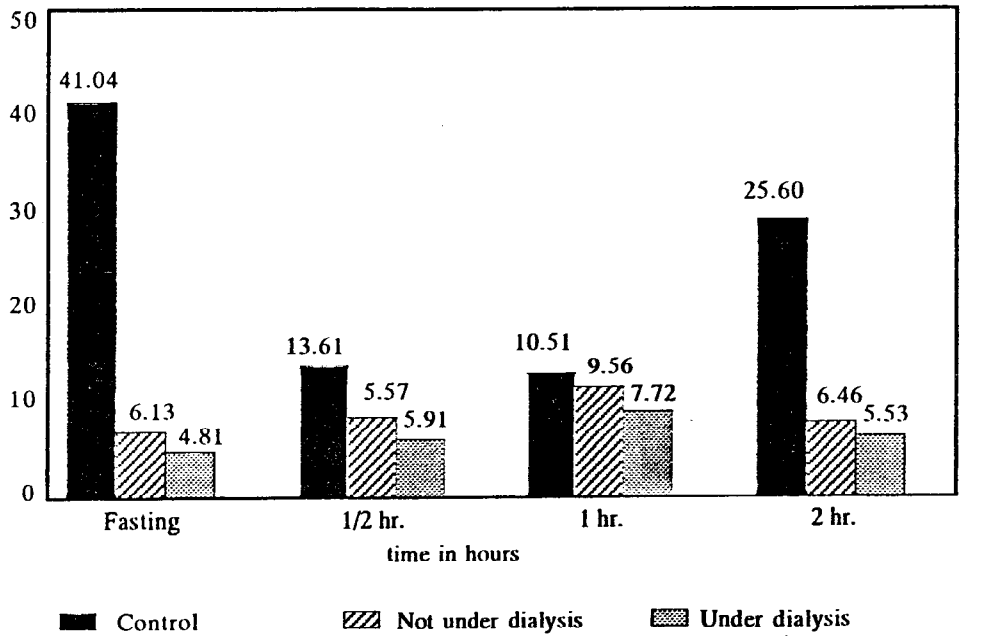

Fig. (2): Glucose insulin ratio.

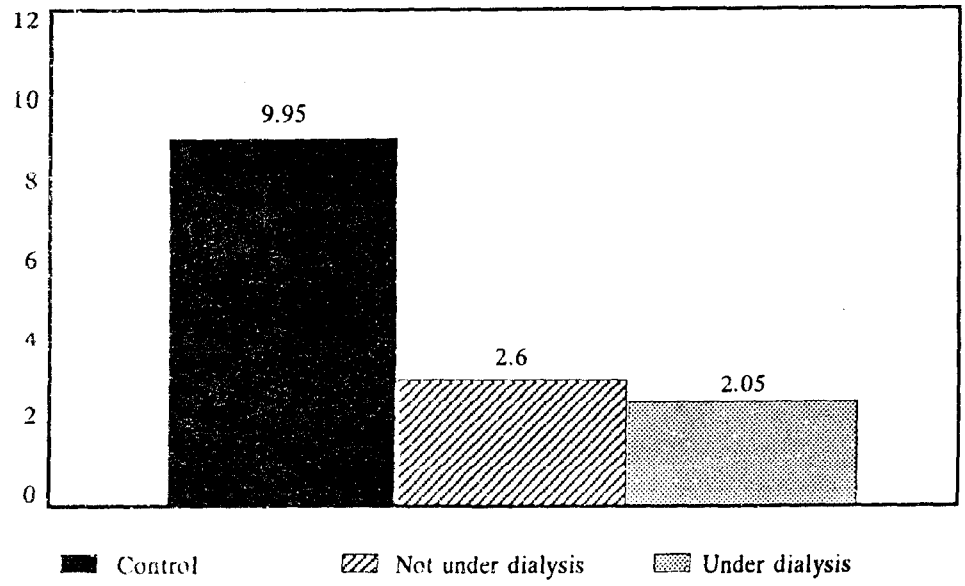

Fig. (3): A value.

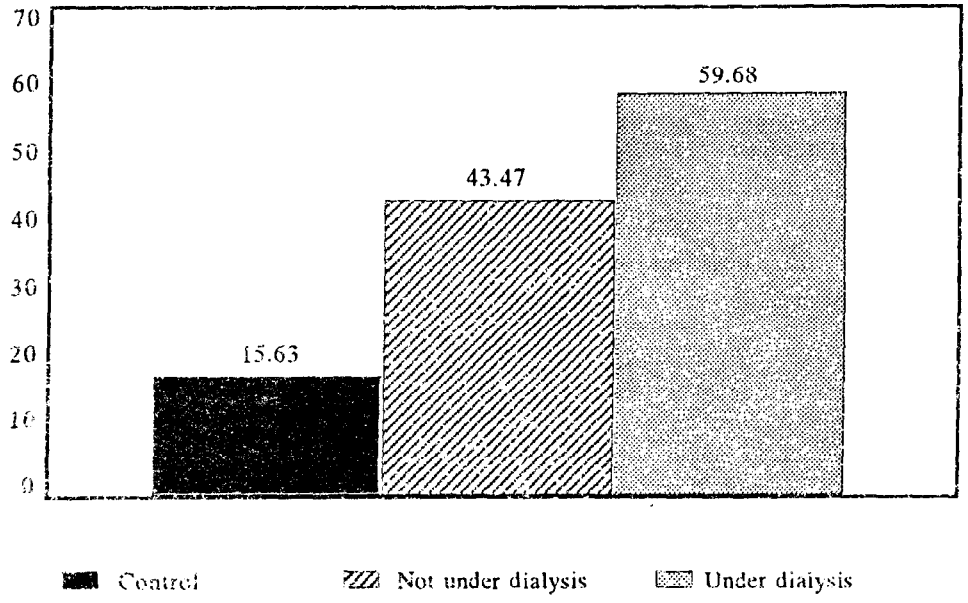

Fig. (4): Insulin area.

Discussion

Significant hyperinsulinemia with relative hyperglycemia was present in both groups of patients when compared with the control, there was significant hyperinsulinemia which rose to more significant values durig the rest of the curve

In spite of this significant hyperinsulinemia, the glucose level during the insulin stimulated state was significantly higher than the control group but not to a diabetic state.

This in itself is an indicator of insulin resistance in these patients.

Besides, the A values for the uremic patients were significantly less that obtained from the controls. Its mean value was 2.33 as compared to 9.95 for the controls ($p < 0.1$) This implies significant resistance as shown by application of the equations.

The equations of insulin area in the patients as compared to control subjects, indicated hyperinsulinemia and insulin resistance. Our patients showed a mean of 51.57 as compared to 15.63 in the control subjects ($p < 0.1$). This again implies hyperinsulinemia and insulin resistance in our patients.

Lastly, the fasting glucose/insulin ratio was used as an index of insulin sensitivity in contrast to the study obtained by Mbanaya group (which showed reduction of the ratio in addition to higher insulin level. The mean value of the fasting glucose/insulin ratio in our patients was 5.47 as compared to 41.4 in the control group ($p < 0.1$).

In addition, we didn't restrict our study to he fasting ratio, but we extended the statistical analysis to the values of the GTT with the following results:

1/2 hour ratio 6.74 as compared to 13.61 for the control

1 hour ratio 8.64 as compared to 25.6 for the control ($p < 0.1$).

2 hours ratio 6 as compared to 25.6 for the control ($p < 0.1$).

Again, these findings showed significant insulin resistance. We could not elicit a fine correlation between the three methods in spite of proving resistance by all of them. This can be simply due to the fact that each of them depend on different parameters.

Now a question arises whether the state of insulin resistance increased with deterioration of renal function or not.

The present study which was done on two groups of patients, those not under dialysis and others under dialysis representing end stage renal failure revealed:

* No significant difference in level of insulin during oral glucose tolerance test ($p > 0.1$).

* The indices of insulin resistance:

- p value was > 0.1 for the A value.
- $p > 0.1$ for the insulin area
- $p > 0.1$ for the glucose-insulin ratio during glucose tolerance test.

This may suggest that the state of insulin resistance develops with the occurrence of renal failure till it reaches a steady state, then continue when the kidney function reaches the end stage renal failure.

To study the effect of dialysis on the level of insulin, state of insulin resistance and glucose tolerance in patients with uremia, most but not all authors observed normalization of glucose tolerance and insulin levels after the initiation of intensive regular dialysis [11].

The same observation was confirmed by Ferrannini et al [9] where both the metabolic clearance and the secretory rates of insuline which were markedly reduced prior to initiation of regular dialysis, were partially improved after several months of regular dialysis.

The present study revealed no significant differences in patients under dialysis and those who were not, as regards the level of insulin sensitivity as well as glucose tolerance. Thus, the possibility of presence of small molecular weight peptide, that causes insulin resistance in uremic patients and which can be removed by dialysis [13] could not be proved in this study and this is in contrast with the clinical observations that glucose tolerance and insulin sensitivity improve dramatically when chronically uremic patients are started on hemodialysis [14] whether this controversy is due to a wrong assumption of the presence of this small molecular weight peptide or due to inefficient or irregular dialysis for the patients studied will need further study.

The pathogenesis that could be responsible for insulin resistance in uremia was studied by Ferrannini et al [15]. They found that the peripheral tissue and not the liver appear to be the site of insulin resistance. This was evidenced by observation that hepatic glucose release was normal in the fasting state and was normally inhibited by hyperinsulinemia. DeFronzo et al [16] demonstrated that splanchnic glucose uptake is not enhanced by rise in plasma insulin level when euglycemia is maintained. Furthermore, this splanchnic uptake constitutes only 8% of the glucose disposal.

Therefor, the reduced insulin-stimulated glucose utilization occurs in extra splanchnic tissue.

The brain is not involved since being an obligatory site of glucose consumption, it uses glucose at maximal rate even in the basal state.

Therefore, skeletal muscle are the probable site of insulin resistance in patients with chronic renal failure.

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