Glucose, Insulin, and Free Fatty Acids in Uremia

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SUMMARY

Glucose intolerance in uremia is well known. In response to the elevated blood glucose, serum insulin rises. We have again demonstrated this rise in serum insulin, especially after the first hour during glucose tolerance testing. Regardless of the mechanism or appropriateness of the insulin response, plasma FFA in uremic patients are markedly depressed when glucose is elevated or small amounts of insulin are infused. The low concentration of FFA accompanying glucose intolerance may be a significant abnormality in the metabolic economy of the uremic patient. DIABETES *22*:111-14, February, 1973.

Many studies have demonstrated glucose intolerance in uremic patients.[1-13] The mechanism of this abnormality remains obscure, although a number of factors have been proposed as having a role. Insulin insensitivity related to growth hormone, acidosis, potassium depletion, and nitrogenous toxins have been suggested as contributing to glucose intolerance. Recent studies have focused attention on the lipemia of uremia.[14-20] Hypertriglyceridemia is well documented in uremia and may be an integral part of the metabolic processes involving carbohydrate intolerance and insulin insensitivity. Little has been written concerning the levels of FFA during glucose loading. This study was undertaken to evaluate the effects of glucose elevation and of insulin infusion on the concentration of FFA in the uremic patient.

METHODS

Eleven uremic male patients and five normal subjects were studied after overnight fasting. They were given carbohydrate orally in an amount equivalent to 75 gm. glucose. Chilled Glucola was used as the source of carbohydrate because it is well tolerated by uremic patients. Patients selected for study were able to take a 50- to 60-gm. protein diet with adequate carbohydrate intake; each specifically denied recent vomiting. Blood samples were drawn before administration as well as fifteen and thirty minutes and at one, two, and three hours after Glucola. Blood samples were collected in heparinized tubes and immediately chilled, and the plasma was separated by centrifugation and frozen. Aliquots of plasma were analyzed for glucose (Somogyi-Nelson),[21] insulin (radioimmunoassay)[22,23] and FFA (Ko-Royer).[24] In additional studies, six normal subjects and six uremic patients were given an infusion of Regular insulin after overnight fasting. Iletin (Lilly) was diluted in 0.9 per cent saline to make a solution containing 1 U. per milliliter. The patients and subjects were given a slow drip infusion of 0.9 per cent saline. Regular insulin was introduced directly into the intravenous tubing at the venipuncture site with a constant infusion pump; the amount was 0.005 U. per kilogram body weight followed by an infusion of 0.0005 U. per kilogram per minute for thirty minutes.* Dilutions of insulin were made in the same manner for each study and were used immediately. Blood specimens were drawn from the opposite arm prior to infusion and at five, ten, twenty, and thirty minutes for estimation of glucose, insulin, and FFA.

To evaluate FFA during prolonged glucose elevation, blood specimens were also taken from three uremic patients prior to peritoneal dialysis and ½, 1, 6, 24, and 48 hours after the start of dialysis.

RESULTS

The age, weight, blood urea nitrogen, serum creatinine, and serum carbon dioxide content of the patients on the morning of the glucose tolerance study are shown in table 1. Although the four dialyzed patients had slightly lower glucose levels (less intolerance), they were included because their insulin and FFA levels during the glucose tolerance test were comparable to those of the uremic undialyzed patients.

The mean age of the patients was 41.0 yr., and their

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*One subject experienced symptoms of hypoglycemia one hour after slow infusion of 1 U. of Regular insulin, with a fall of plasma glucose to 36 mg./100 ml. Since 1 U. of insulin will produce a significant and predictable rise in serum levels, the enhanced effect of slow infusion must be anticipated. After this experience, patients and volunteer subjects were given oral carbohydrate at the conclusion of the infusion.

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mean weight was 77.1 kg.; comparable figures for the normal subjects were 35.3 yr. and 77.7 kg.

The mean values and standard errors for plasma glucose, insulin, and FFA for the five normal subjects and eleven uremic patients are plotted in figure 1. The glucose tolerance curve illustrates the typical intolerance of uremic patients, with statistically higher glucose levels at one, two, and three hours. The curve is not unlike that of patients with diabetes mellitus. Insulin concentrations in the uremic plasma are elevated at two and three hours in response to the hyperglycemia. The FFA in the uremic patients continue to fall and reach levels of 219, 160, and 148 μEq. per liter at one, two and three hours, respectively, compared with the normal subjects' mean of 322, 296, and 298 μEq. per liter.

Table 2 shows the mean plasma concentrations of glucose, insulin, and FFA for six normal subjects and six uremic patients during infusion of a small amount of Regular insulin. The FFA concentration again is much lower in the uremic patients but under the same conditions, their mean glucose does not differ significantly from that of volunteer subjects. In the normal subjects, the FFA drop to 83 per cent of the fasting level at thirty minutes, but in the uremic patients the FFA reach 43 per cent of fasting level.

Figure 2 illustrates the decrease in plasma FFA in three uremic patients during the first forty-eight hours of

TABLE 1

Data concerning eleven uremic patients immediately prior to study of plasma glucose, insulin and FFA during glucose tolerance testing

Patient	Renal Diagnosis	Age	Weight (kg.)	CO_2 Content (mEq./L.)	BUN (mg./100 ml.)	Creatinine (mg./100 ml.)
K.A.	Polycystic	46	72	19	82	11
D.D.	Polycystic	37	77	22	98	12
C.W.	G.N.	54	78	20	110	20
T.W.	Pyelonephritis	46	92	20	110	20
G.B.	G.N.	36	92	22	145	12
N.D.	G.N.	32	86	18	94	5
V.Y.	Nephrosclerosis	44	76	21	230	17
R.R.*	Polycystic	44	77	17	100	12
R.K.*	G.N.	39	63	21	117	13
W.Z.*	G.N.	36	73	20	185	14
J.J.*	G.N.	38	62	18	81	9
	Uremic patients (11)	41.0	77.1	19.8	123	13.2
	Normal subjects (5)	35.3	77.7			

* Patient had hemodialysis; last dialysis at least forty-eight hours before study.

G.N. = chronic glomerulonephritis.

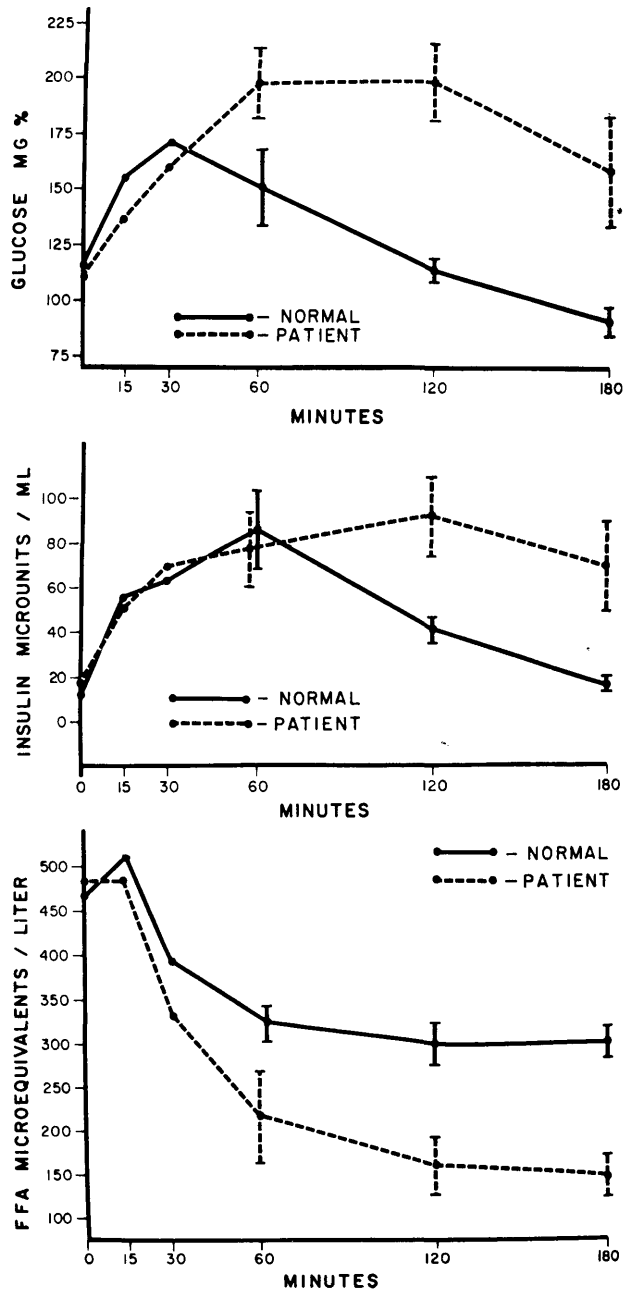

FIG. 1. Glucose, insulin, and FFA concentrations for five normal subjects and eleven uremic patients during three-hour glucose tolerance testing, mean ± S.E.

peritoneal dialysis. Glucose and insulin are elevated and FFA remain very low throughout the dialysis. This is comparable to levels seen during the three-hour glucose tolerance test in uremic patients.

DISCUSSION

There are many studies concerning the insulin response to glucose elevation in uremia.[6-13] Most studies

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TABLE 2

Changes in plasma glucose, insulin, and FFA during infusion of small amounts of Regular insulin

		Normal Subjects (6)	S.E.	Uremic Patients (6)	S.E.	P.
Glucose (mg./100 ml.)	Fasting	104	9	103	6	n.s.
	5 min.	105	13	102	6	n.s.
	10 min.	91	13	98	5	n.s.
	20 min.	90	9	91	8	n.s.
	30 min.	84	8	87	7	n.s.
Insulin μU./ml.	Fasting	8	3	8	2	n.s.
	5 min.	52	5	41	3	n.s.
	10 min.	36	4	33	5	n.s.
	20 min.	28	4	29	4	n.s.
	30 min.	36	5	27	4	n.s.
FFA μEq./L.	Fasting	572	48	471	56	n.s.
	5 min.	651	77	437	50	<.02
	10 min.	628	58	352	52	<.005
	20 min.	552	66	266	43	<.005
	30 min.	473	44	204	30	<.001

n.s. = not significant.

show that the insulin levels are higher in uremic patients during glucose tolerance testing, especially after the first hour. In this study the insulin concentrations in the plasma at two and three hours are significantly higher than in normal subjects. This is an agreement with published observations of others.[10] The variability of insulin response in any condition of glucose intolerance may be influenced by levels of insulin secretion prior to the study.[14] Small elevations of insulin may have important effects on other metabolic processes.

Most striking is the fall in FFA during glucose tolerance testing in the uremic patient. The fall in FFA when blood glucose and insulin are elevated is greater in the uremic patients, while normal subjects under the same conditions have a lesser drop in FFA. The concentration of FFA in the serum of control subjects levels off at the second and third hour after oral glucose, while in the uremic patients the FFA are significantly lower ($P < .01$).

This difference between healthy subjects and uremic patients was also demonstrated when small amounts of Regular insulin were infused over a period of thirty minutes. Unlike the glucose tolerance study, in which there was considerable elevation of the insulin concentration, the insulin levels were comparable in the control subjects and the patients during insulin infusion. In spite of this, the fall in FFA in the uremic patients was greater.

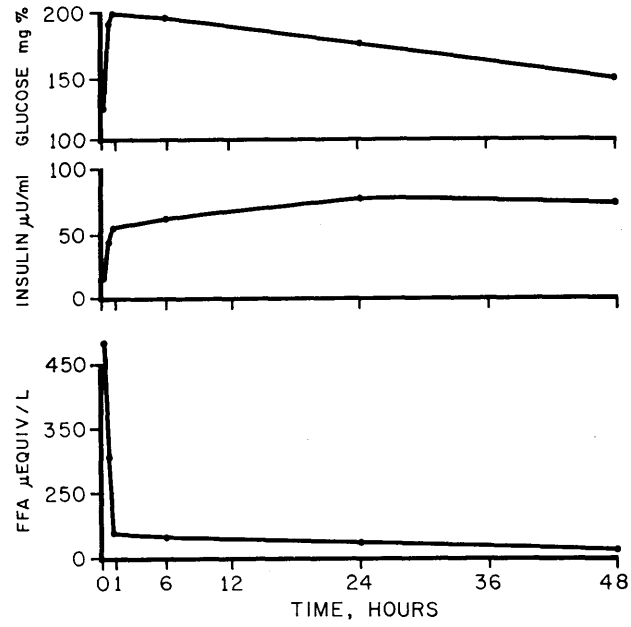

FIG. 2. Mean plasma glucose, insulin, and FFA concentrations in three uremic patients prior to and during the first forty-eight hours of peritoneal dialysis. The infused dialysate fluid contained 1,500 mg./100 ml. glucose with exchange every ninety minutes.

Meade et al.[25] have shown in dogs that insulin infused in physiologic amounts will lower FFA with minimal effect on glucose. Zierler and Rabinowitz[26] have demonstrated a selective fall in FFA without effect on glucose in the human forearm by infusing small amounts of insulin. They concluded that insulin is responsible for decreasing the release of FFA from adipose tissue. Mirsky[27] reported that with controlled insulin infusion FFA could be decreased without influencing glucose concentration in the plasma of dogs. Jones and Arky[28] believe this effect of insulin is one of inhibition of lipolysis. Relative hyperinsulinemia may be a major factor responsible for the low plasma FFA in the uremic patient during glucose tolerance testing. The greater drop in FFA during insulin infusion suggests an additional sensitivity to insulin in uremia. Whether this drop is partly from increased utilization of FFA or entirely from decreased liberation of FFA from fat stores is not clear. Postheparin lipolytic activity is low and plasma triglycerides are high in uremia,[15-17] also suggesting that the defect is one of decreased lipolysis. Further studies are necessary to clarify the interrelationships of triglyceride, FFA, and insulin as well as the significance of lipolytic factors.

Goodner[18] has demonstrated, in normal and diabetic adults, that prolonged hyperglycemia favors delivery of FFA to the serum. Our studies indicate that the uremic

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patient is unable to sustain an adequate level of FFA following a glucose load.

During peritoneal dialysis the FFA remain low for prolonged periods, again under conditions of hyperglycemia. Figure 2 illustrates the mean plasma glucose and insulin and the abrupt fall of FFA to low levels, which persisted during forty-eight hours of continuous peritoneal dialysis, in three patients. The levels are comparable to those reported by Barter et al.[19] during prolonged sucrose consumption combined with insulin infusion in man.

The unusually low plasma FFA may be a significant metabolic defect in the patient with chronic uremia. These patients often receive low protein diets and depend upon carbohydrates for adequate caloric intake. In this study, very low plasma concentrations of FFA were induced in uremic patients by oral carbohydrate or insulin infusion. Low levels of FFA persisted for prolonged periods during peritoneal dialysis. The role of depleted FFA as a factor in uremic neuropathy is speculative at this time. Glucose intolerance improves with adequate hemodialysis,[7] and there is evidence that the very low FFA concentrations also improve.[20]

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