Effect of a Fat Free, High Carbohydrate Diet on Diabetic Subjects with Fasting Hyperglycemia

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SUMMARY

Fasting plasma glucose levels and glycosuria were measured in untreated diabetic subjects on basal and on fat free, high carbohydrate diets. On the high carbohydrate diet the mean fasting plasma glucose was slightly, but not significantly, increased by 15 mg./100 ml. and the twenty-four hour excretion of glucose was increased by 56 gm./24 hr. ($p < .02$). Five of these subjects were restudied following insulin or oral sulfonylurea therapy, and four similar patients were studied only while on this therapy. In these treated diabetic subjects receiving the high carbohydrate diet, fasting plasma glucose was significantly decreased by 22 mg./100 ml. plasma ($p < .02$); glycosuria did not change. Thus, among diabetics, only those who remain untreated have worsened glucose tolerance on fat free, high carbohydrate diets. DIABETES *23*:138-42, February, 1974.

We previously reported that subjects with normal fasting plasma glucose levels have a decrease in the fasting level and improved oral glucose tolerance when receiving high carbohydrate meals. A concomitant decrease in fasting insulin levels and no increase in insulin response following oral glucose suggested that this improvement was due to increased peripheral insulin sensitivity,[1] as had been proposed almost forty years ago.[2] These findings help to explain the mechanism for improved carbohydrate metabolism in subjects who are able to secrete some endogenous insulin in response to a glucose challenge, but they cannot be used to design therapeutic programs for the treatment of diabetic subjects who have fasting hyperglycemia. In this study the effects of high carbohydrate feeding in subjects with fasting hyperglycemia have been investigated.[3]

METHODS

Fifteen diabetic subjects with untreated fasting hyperglycemia (plasma glucose above 115 mg./100 ml. after an overnight fast) were studied while hospitalized in a metabolic ward. Five of these subjects were again studied after they had begun insulin or oral sulfonylurea therapy and had stable weight and glucose levels for at least one week. Four additional subjects with fasting hyperglycemia were studied only during therapy.

All subjects ingested meals based on two formula diets. The basal diet consisted of 40 per cent fat, 45 per cent carbohydrate and 15 per cent protein. A high carbohydrate diet contained 0 per cent fat, 85 per cent carbohydrate and 15 per cent protein. Each dietary period was seven to ten days long. The carbohydrate employed in these diets was either dextrose or a mixture of dextrins and maltose (Dextrimaltose). Supplements of multivitamins (Unicap-M), iron and folic acid were added. Both diets were given as five equal feedings at 8 and 11 a.m.. and 2, 5 and 8 p.m. Calories required to maintain body weight were estimated in relation to the degree of obesity.* A mean of 32 calories per kilogram was given for all subjects with a mean ideal body weight of 130 per cent; the thinnest subject (89 per cent) received 38 calories per kilogram and the most obese (175 per cent) received 25 calories per kilogram. The calories were adjusted to attempt to maintain constant body weight (±1 kg.)

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*Based on regression analysis of calories per kilogram/per cent ideal body weight. Cal./kg. $= 52.2 - \frac{15.5 \text{ weight}}{\text{ideal body weight}}$.

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only during the early phase of the basal diet. Additional carbohydrate calories were added to account for changes in glycosuria on both diets where needed.

Plasma glucose drawn three times a week after twelve hours of fasting was measured by the Auto-Analyzer ferricyanide method. Glucose concentration of daily twenty-four hour urine samples was determined by the method of Benedict, and the mean glucose values for each dietary period were calculated. The dosage of insulin or oral sulfonylurea therapy was maintained constant through the study except in two subjects, in whom symptomatic hypoglycemia necessitated decrease of insulin dosage when the high carbohydrate diet was used. In these two subjects the study was temporarily delayed until the fasting plasma glucose was stable on the new dosage of insulin. The values obtained in the studies during each dietary period were compared by the paired *t* test.

One additional subject received the two diets as above and, in addition, a mildly restricted carbohydrate diet (25 per cent carbohydrate) and a severely restricted low carbohydrate diet (5 per cent carbohydrate) (table 2). Fasting glucose and insulin levels were measured as above and, in addition, oral glucose tolerance tests with 100 gm. of glucose were performed after a period of two weeks of each diet. Insulin was measured by a previously reported method.[1]

RESULTS

Untreated subjects. The untreated subjects with fasting hyperglycemia (table 1) had a variable response of fasting plasma glucose levels to the high carbohydrate diet, with a mean increase of 15 mg./100 ml. (p = n.s.). The height of the fasting plasma glucose level on the basal diet did not seem to determine the response of the subject. Twenty-four hour urine glucose

TABLE 1
Effect of high carbohydrate diet on fasting plasma glucose and glycosuria

Subject	Age	% Ideal body wt.*	Therapy		Fasting plasma glucose (mg./100 ml.)		Glycosuria (gm./24 hr.)		Change in weight‡ (kg.)
			Drug	Change†	Basal	High carbohydrate	Basal	High carbohydrate	
No therapy									
LT	45	139	None		130	135	1	16	−2
EPδ	50	175	"		140	166	8	35	0
DP	54	146	"		143	156	2	29	0
DT	61	124	"		145	155	21	26	0
RDe	62	152	"		155	155	1	32	−1
DF	35	162	"		158	177	–	–	0
RB	45	125	"		162	124	48	110	0
HLδ	62	105	"		164	174	11	48	0
OL	43	135	"		204	167	53	29	0
RSδ	23	89	"		212	284	291	352	−7
LB	41	163	"		250	364	81	285	−2
MMδ	55	108	"		268	265	95	187	0
CR	43	153	"		288	308	176	392	−2
NBδ	45	118	"		308	310	184	231	+1
BS	44	159	"		316	316	130	122	0
Insulin or oral sulfonylurea therapy									
NBδ	45	118	Insulin	–	101	82	11	13	0
EA	59	127	Acetohexamide	–	103	100	2	3	−1
HLδ	62	105	Chlorpropamide	–	108	88	3	6	0
RDo//	35	105	Insulin	–	112	97	16	20	0
BC	33	132	Insulin	–	133	125	–	–	0
CW	63	117	Insulin	↓5 units	137	120	30	60	−1
MMδ//	55	108	Insulin	–	189	187	14	24	0
EPδ//	50	175	Chlorpropamide	–	192	135	49	21	0
RSδ//	23	89	Insulin	↓20 units	220	167	134	169	+2

* Metropolitan Life Insurance tables
† Change in therapy from basal to high carbohydrate diet.
‡ During high carbohydrate diet.
δ Subjects studied before and after therapy.
// Subjects studied on high carbohydrate diet first.

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output during the two diets was higher in these subjects on the high carbohydrate diet (mean increase: 56 gm./24 hr., $p < .02$). Some of these subjects lost weight when glycosuria increased and were never in caloric balance, even though an attempt was made to replace the calories lost in the urine by an increase in carbohydrate calories.

Treated subjects. The subjects treated with insulin or oral sulfonylureas (table 1) all had lower fasting glucose levels while receiving the high carbohydrate diet (mean decrease: 22 mg./100 ml., $p < .02$) as compared to the basal diet with therapy. The dosage of insulin therapy had to be decreased for two subjects during administration of the high carbohydrate diet because hypoglycemia developed on the insulin dosage used during the basal diet period. In the two subjects in whom the dosage of insulin was decreased, glycosuria increased. In one subject no data concerning urinary glucose output was available. In the remaining six subjects glycosuria did not change significantly (mean decrease 1.3 gm./24 hr., p = n.s.). No differences in fasting plasma glucose or glycosuria with the diet change were apparent between those subjects treated with insulin and those treated with oral agents. The weight in these subjects was stable throughout both dietary periods. Subjects given the high carbohydrate diet first and then the basal diet had the same responses to high carbohydrate feeding as those studied in the reverse order (table 1).

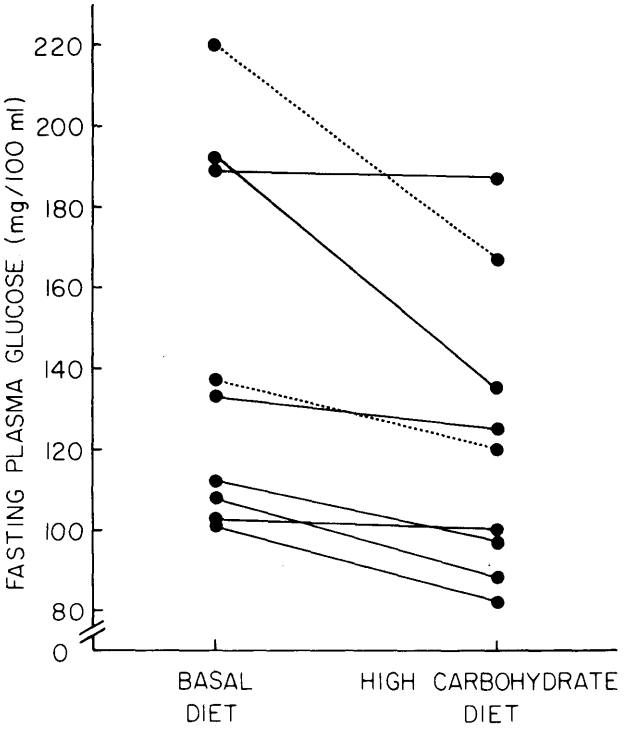

FIG. 1. Fasting plasma glucose levels in treated diabetic subjects on the basal and fat free, high carbohydrate diet. (—): no change in therapeutic dose; (--): dosage of insulin decreased on high carbohydrate diet.

TABLE 2
Effect of low, basal and high carbohydrate diets*

Diet composition (% of calories)		Carbohydrate	5	25	45	85
		Fat	80	60	40	0
		Protein	15	15	15	15
Number of days sampled			7	5	5	5
Fasting glucose†			141	129 (<.001)	124 (<.02)	118
Fasting insulin†			30	31 (<.01)	23 (<.05)	25 (<.001)
Oral glucose: integrated glucose area			39,315	38,017	44,790	36,442
Oral glucose: integrated insulin area			17,332	29,115	17,325	16,282

*Subject was a forty-nine year old male weighing 163 per cent of ideal body weight.
†p values, *t* test for differences between dietary periods.

Subject on low and high carbohydrate diets. A single subject studied on 5, 25, 45 and 85 per cent carbohydrate diets had higher fasting plasma glucose levels with carbohydrate restriction and lower levels with increasing dietary carbohydrate content. The fasting insulin levels on the low carbohydrate diets also tended to be higher (table 2). The integrated area under the oral glucose tolerance curve was less on both the high and low carbohydrate diets as compared to the basal diets, while the area under the insulin response curves tended to be higher with carbohydrate restriction.

DISCUSSION

In the untreated diabetic subjects with fasting hyperglycemia the response of the fasting plasma glucose to the high carbohydrate diet was quite variable, but glucose tolerance as measured by glycosuria worsened. In several of these subjects it was difficult to prevent weight loss with the high carbohydrate diet. Weight loss was due to the increased glycosuria, which most likely resulted in part from increased glycemic excursions during high carbohydrate feeding. In subjects with markedly increased fasting glucose levels, exceeding the renal threshold for glucose

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throughout the entire day was a partial cause.

In contrast, when diabetic subjects treated with insulin or oral sulfonylurea agents for a minimum of one week were studied on the two diets, the fasting glucose level was lower in all subjects on the high carbohydrate diet. This response is similar to that previously reported in subjects with normal fasting plasma glucose levels. Glucose tolerance as measured by glycosuria was not worsened even though the total load of carbohydrate per day was much higher on the high carbohydrate diet—85 per cent of calories (about 600 gm.) vs. 45 per cent of calories (about 315 gm.). Although it would seem unlikely, an increase in the renal threshold for glucose cannot be ruled out as an alternate explanation for the lack of increase in postprandial glycosuria during the period of increased carbohydrate intake. The response appeared to be the same in those few subjects treated with oral sulfonylureas as those treated with insulin. The study diets are not typical of diets available to diabetic patients, being formula diets given in five daily portions. However, any influence of these dietary differences on fasting plasma glucose levels was eliminated, since subjects studied on the basal diet first responded in the same manner as those studied in reverse order. The reversed studies also indicate that the decrease in fasting plasma glucose levels on the high carbohydrate diet was not a result of further improved glucose tolerance due to continued insulin therapy.

The subjects previously reported—normal fasting glucose levels, improved glucose tolerance on the high carbohydrate diet[1]—had an acute insulin response to a rapid intravenous glucose pulse.[4] The subjects in this study with untreated fasting hyperglycemia were worsened by the high carbohydrate diet. However, when insulin was given to these previously untreated subjects, they then responded to the high carbohydrate diet in a manner similar to that of normoglycemic subjects. This improvement of glucose tolerance during the high carbohydrate diet appears to be associated with availability of insulin, whether endogenous or exogenous.

The mechanism for the decrease in fasting glucose levels during administration of the high carbohydrate diet appears to be due to increased insulin sensitivity in the previously reported normoglycemic subjects, since there was no increase in basal insulin levels to account for the fall in glucose levels.[1] The subjects with insulin dependent diabetes also had a decrease in glucose levels with the same or lower doses of insulin. Some of these changes in glucose metabolism may be related to induction of hepatic and gastrointestinal enzyme systems that regulate glucose disposal, as has been shown to occur in animals given high carbohydrate meals.[5-8] Improvement in glucose tolerance with high carbohydrate diets has also been shown in the rat.[9]

Anderson was able to demonstrate improved oral glucose tolerance in normal subjects receiving high carbohydrate meals;[10] also, he demonstrated worsening of glucose tolerance with low carbohydrate diets, but only in subjects with fasting euglycemia who had glucose intolerance.[11] We have observed a comparable phenomenon: Those subjects with the worst oral glucose tolerance (greatest integrated area under curve of oral glucose tolerance curve) had the greatest improvement in oral glucose tolerance (measured as a decrease in glucose area; $r = .75$, $p < .01$, $n = 12$) when the high carbohydrate diet was employed.

On the other hand, low carbohydrate diets have been reported to worsen[12] or improve[13, 14] glucose tolerance. The improvement in glucose levels in some of these studies[13] could easily be accounted for by concomitant weight loss In the study of Grey and Kipnis,[14] regarding the six obese, nondiabetic subjects who lost no weight, glucose levels tended to fall and insulin responses decreased, comparable to our findings, when the basal diet (46 per cent carbohydrate) was replaced by the high carbohydrate diet (62 per cent carbohydrate). Fasting insulin levels were unchanged. However, when the basal diet and the high carbohydrate diet each were compared to a low carbohydrate diet (25 per cent carbohydrate), fasting plasma glucose, fasting insulin levels and oral glucose tolerance insulin responses in these patients all were lower on the low carbohydrate diet. These results suggest that there is improvement with a lower carbohydrate diet. However, in one obese subject in the present study given diets with a wide range of carbohydrate content (table 2), the fasting glucose and insulin levels were higher on low carbohydrate diets and the post-oral glucose insulin area was higher in the 25 per cent carbohydrate diet. However, the glucose areas were lower with both the high and low carbohydrate diets. The reasons for the above differences are not apparent. Perhaps the mild elevation of the fasting plasma glucose with the basal diet in our subject or the use of constant composition formula diets instead of food accounts for the differences.

Thus, treated diabetic subjects do not appear to be adversely affected with respect to glucose and insulin homeostasis by diets high in carbohydrate. The impli-

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cations this has for dietary therapy aimed at the prevention and treatment of atherosclerosis associated with elevated plasma lipid levels are potentially important. Diabetic subjects have an increased risk of atherosclerosis[15] at a premature age[16] and increased plasma triglyceride[17] and, possibly, cholesterol levels.[18] Low fat and, thus, high carbohydrate diets have been shown to decrease plasma cholesterol levels in insulin-treated diabetics[19] as well as in nondiabetic subjects.[20] These same diets also appear to lower plasma triglyceride levels, when the levels are examined over the entire twenty-four hours of the day in nondiabetics,[21] and not to cause an increase in fasting triglyceride levels in insulin-treated diabetics given these diets for prolonged periods of time.[19]

Thus, if and when low fat, high carbohydrate dietary regimes for lowering plasma lipid levels are demonstrated to be beneficial in the prevention of atherosclerosis, there appears to be no reason related to changes in glucose homeostasis to withhold these diets from diabetic subjects, who are prone to both hyperlipidemia and atherosclerosis.

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