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Role of Insulin in Endogenous Hypertriglyceridemia *

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Abstract. Dietary carbohydrate accentuation of endogenous triglyceride production has been studied in 33 patients. A broad and relatively continuous spectrum of steady-state plasma triglyceride concentrations was produced in 31 of the 33 subjects during 3 wk of a high carbohydrate (fat-free) liquid formula diet. Two patients developed plasma triglyceride concentrations in excess of 2000 mg/100 ml, and these were the only patients we have studied in which carbohydrate induction of hypertriglyceridemia seemed to be associated with a defect in endogenous plasma triglyceride removal mechanisms. In the remaining 31 patients the degree of hypertriglyceridemia was highly correlated with the insulin response elicited by the ingestion of the high carbohydrate formula ($P < 0.005$). No significant correlation existed between fasting plasma triglyceride concentration and either plasma glucose or free fatty acid concentrations after the high carbohydrate diet, nor was the degree of hypertriglyceridemia related to degree of obesity. It is suggested that hypertriglyceridemia in most subjects results from an increase in hepatic triglyceride secretion rate secondary to exaggerated postprandial increases in plasma insulin concentration.

Introduction

We have recently reported that the magnitude of plasma triglyceride response in man to diets either high or low in carbohydrate was highly correlated with both the plasma glucose and insulin responses elicited by that diet (1). However, all our patients had normal fasting glucose concentrations, and there was less than a twofold difference between those with the highest and lowest total glucose response to a high carbohydrate diet. In contrast, within this same population, there was a greater than sevenfold difference in the range of insulin responses. On the basis of our data we tentatively proposed that carbohydrate accentuation of triglyceridemia was secondary to repetitive postprandial elevations of plasma glucose and insulin which increased hepatic triglyceride secretion (1). In this proposal the liver was considered the unwitting victim of an excess supply of potential substrate for triglyceride synthesis and of a hormone which may enhance the synthetic process. It was also observed that incorporation of glucose-^{14}C into hepatic triglyceride in vitro is stimulated by insulin administered to the experimental animal (2). However, a significant insulin effect was only seen when liver slices were incubated in media containing high

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concentrations of glucose. Therefore, in an attempt to distinguish in vivo, and in man, between the relative importance of hyperglycemia and hyperinsulinemia in the carbohydrate induction of hypertriglyceridemia, we have extended our studies of postprandial metabolic response to include patients with fasting hyperglycemia. Furthermore, since plasma free fatty acid (FFA) concentrations have been reported to be moderately elevated in hypertriglyceridemic subjects (3), we have also correlated FFA responses to a high carbohydrate diet with the degree of hypertriglyceridemia produced by that diet.

In this paper we describe plasma glucose, insulin, FFA, and triglyceride responses to a high carbohydrate diet in 33 patients. The results confirm our previous finding of a high correlation between insulin and triglyceride responses. However, with inclusion of hyperglycemic patients there was no correlation found between plasma glucose response and the magnitude of the triglyceride elevation produced by the high carbohydrate diet. Finally, there was no correlation between hypertriglyceridemia and degree of obesity, or magnitude of the FFA response.

Methods

Subjects. Patients were selected from among those referred to our clinical research group, and reflect the nature of our clinical interests. Since we were attempting to define the relationship between plasma triglyceride, glucose, insulin, and FFA through a wide range of triglyceride concentrations, no effort was made to seek out patients on the basis of triglyceride levels. The two primary criteria for selection were willingness to cooperate in these long-term studies and good general health. Patients with liver disease, congestive heart failure, and known endocrine disease (other than diabetes mellitus) were excluded. Table I summarizes some clinical features of the patient population, as well as the reasons for referral to us. In several instances, more than one clinical abnormality had been documented by the referring physician.

Diets. Calories were supplied in four equicaloric feedings of a liquid formula diet given at 8 and 11 a.m. and 2 and 5 p.m. Each formula was ingested during a 30 min period. Two diets were employed in these studies. One, a control formula diet, consisted of 15% protein, 42% fat, 43% carbohydrate, and was an attempt to approximate the average American diet. The other diet, a high carbohydrate formula, consisted of 15% protein and 85% carbohydrate. All the protein and 17% of the calories from carbohydrates in both diets were derived from skimmed milk powder. The remaining carbohydrates came from Dexin (Burroughs Wellcome & Co., Tuckahoe, N. Y.). The carbohydrates of Dexin are obtained by partial hydrolysis of starch, yield entirely glucose on complete hydrolysis, and consist of the following components: 62% dextrins, 18% maltodextrins, and 19% maltose. The fat in the control formula diet was obtained from a mixture of egg yolk, lard, and butter. Body weight was closely maintained to within ± 0.5 kg during each dietary period. A prompt gain of approximately 1 kg occurred on shifting to the high carbohydrate diet; a phenomenon previously reported (1).

Experimental protocol. Although hospitalized, patients remained ambulatory throughout the study. They were maintained for the first week on the control formula diet. At the end of this time, an oral glucose tolerance test was performed, using 7 oz of a synthetic carbohydrate beverage (Glucola, Ames Co., Inc., Elkhart, Ind.) as the standard challenge. Blood was obtained for measurement of glucose and insulin concentrations before, and 1, 2, and 3 hr after, the oral glucose load. Patients were then started on the high carbohydrate diet, and were maintained on this for 3 wk. During this period blood was obtained twice weekly for measurement of fasting triglyceride concentration. In addition, glucose, insulin, and FFA responses to the high carbohydrate diet were measured twice weekly during the 3 wk period. In our previous study (1) glucose and insulin were measured at hourly intervals between 8 a.m. and 5 p.m. Analysis of these data revealed that the succesive increments and decrements in glucose and insulin concentration after the 8 a.m., 11 a.m., and 2 p.m. feedings were essentially identical, and that a representative sample of the total day's response could be assessed simply by measuring the changes after any one of the formula feedings. Consequently, for these studies, we have estimated the combined effects of the overnight fast and the daily response to the high carbohydrate diet by drawing blood before the 8 a.m. formula and 1 and 2 hr after the feeding was started (8–9–10 a.m. response).

Analytical procedures. All blood was drawn free-flowing into tubes containing EDTA. Plasma was obtained after separation in a refrigerated centrifuge, and frozen quickly in acetone–dry ice. Plasma lipids were extracted with chloroform: methanol (5), and analyzed for triglycerides by a modification (6) of the method of Lofland (7). Plasma glucose (8) and FFA (9) concentrations were determined with an autoanalyzer. In the latter instance a manifold designed by Technicon Co. (Chauncey, N. Y.) was substituted for the one originally described. Plasma immunoreactive insulin concentrations were measured by a modification of the method of Hales and Randle (10) using insulin-^{125}I and insulin-binding reagent obtained from the Radiochemical Centre, Amersham, England. Turnover rates of plasma $S_f > 20$ triglycerides were determined as previously described (11).

Analysis of data. Mean fasting plasma triglyceride concentrations for the last 2 wk of the 3 wk high carbohydrate period were obtained by averaging five separate measurements. This figure has been used as the measure of the triglyceride response. Mean values for glucose,

TABLE I

Clinical characteristics

Patient	General description					Reasons for referral				
	Age	Sex	Height	Weight	PI*	ATH‡	PL§	Diabetes	Obesity	Psoriasis
			cm	*kg*						
H.H.	68	M	181.6	60.6	14.02			X		
W.W.	56	M	167.6	69.0	12.38					X
J.P.	48	M	174.0	73.7	12.63	X				
G.L.	45	F	170.0	68.0	12.62	X				
G.B.	53	M	171.5	79.3	12.10	X				
D.M.	52	M	168.8	114.8	10.55			X	X	
A.T.	51	F	154.9	44.7	14.32		X			
N.T.	41	M	174.0	66.2	13.04	X				
F.Bu.	57	M	185.4	72.8	13.45	X	X			
E.A.	61	F	154.9	57.9	12.13			X		
H.G.	76	F	158.0	70.1	11.62			X		
W.K.	41	M	174.0	106.0	11.14	X				
F.Ba.	59	M	175.3	86.2	12.05	X				
R.D.	45	M	172.8	94.8	11.48	X		X		
E.D.	58	F	152.4	68.2	11.30			X		
F.H.	68	M	175.3	77.9	12.44			X		
E.M.	48	M	180.3	73.2	13.06					X
P.M.	47	F	162.0	111.0	10.18			X	X	
E.K.	59	F	159.0	67.4	11.90	X		X		
C.L.	53	M	175.3	71.2	12.82	X				
C.D.	56	M	172.4	69.6	12.71	X		X		
J.H.	50	M	180.0	90.2	12.17	X				
S.S.	39	M	178.0	90.3	12.02	X	X			
E.C.	41	M	165.1	90.2	11.15	X		X		
R.N.	47	M	173.0	71.0	12.66	X				
M.F.	61	F	160.0	58.6	12.49	X				
L.K.	47	M	180.3	78.6	12.77	X				
J.B.	54	M	168.9	64.0	12.80	X		X		
W.G.	48	M	177.8	96.0	11.75			X		
P.G.	52	M	178.0	75.8	12.75	X				
D.H.	51	F	157.4	66.8	11.76		X			
W.C.	57	M	172.7	67.9	12.70	X	X			
G.R.	42	M	160.3	85.2	11.04			X		

* PI = Ponderal Index, an estimate of obesity $= \frac{\text{height(inches)}}{\sqrt[3]{\text{weight(pounds)}}}$ (4). The lower the index, the greater the relative degree of obesity.

‡ Clinical atherosclerosis, including patients with either coronary artery disease, lower extremity arteriosclerosis obliterans, or cerebral vascular disease.

§ PL = plasma lipid abnormality, either hypercholesterolemia or lactescent plasma.

insulin, and FFA concentrations at 8, 9, and 10 a.m. were determined from six measurements of each during the high carbohydrate period. There was no significant change in the magnitude of these responses during the three weeks of study. Averages of the mean 8–9–10 a.m. concentrations $[(C_8 + C_9 + C_{10}) \div 3]$ of glucose, insulin, and FFA were obtained, and this figure was used as an estimate of the glucose, insulin, and FFA response to the high carbohydrate diet. The use of the average concentration as the measurement of these responses was chosen because it is simple, yet approximates very closely the mean integrated concentration derived from measurement of area under a concentration curve. However, in contrast to estimates of total area, the average gives equal weight to all data points. For similar reasons, plasma glucose and insulin responses during the glucose tolerance test have also been expressed as the average of the four measured concentrations. Finally, correlation coefficients have been calculated by use of the usual product moment correlation (r). In certain instances (designated in the text) these correlations have also been calculated by Kendall's Rank Correlation Coefficient (12).

Results

Triglyceride response to a high carbohydrate diet. In all instances plasma triglycerides were higher than when patients were on the control formula diet. The range of plasma triglyceride concentrations produced by the high carbohydrate diet is illustrated in Fig. 1. Approximately half the patients had triglyceride concentrations between 300 and 600 mg/100 ml. Two patients (W.C. and G.R.) had triglyceride concentrations greater than 2400 mg/100 ml.

A previous report from our laboratory, in which labeled glycerol was used as a precursor for $S_f >$

20 lipoprotein triglyceride, defined a close relationship between plasma $S_f > 20$ triglyceride concentration and hepatic triglyceride secretion rate which was characterized by early saturation of plasma $S_f > 20$ triglyceride removal sites (11). These studies have been continued, and $S_f > 20$ triglyceride hepatic secretion rates have now been determined 44 times under a variety of dietary conditions. In Fig. 2, $S_f > 20$ hepatic triglyceride secretion rates are plotted against the log of plasma $S_f > 20$ concentrations for these 44 studies. A highly significant correlation was observed in 42 instances. It is clear from the logarithmic relationship defined in Fig. 2 that plasma $S_f > 20$ triglyceride concentration is not a simple linear function of hepatic secretion rate, and early saturability of the removal system enables small increments in hepatic secretion rate to produce great increases in plasma triglyceride concentration. Two patients (W.C. and G.R.) exhibit a significant deviation from this relationship, in that markedly elevated plasma triglyceride concentrations are present in the absence of the expected increases in hepatic triglyceride secretion rate. These are the same two patients who had plasma triglyceride concentrations in excess of 2400 mg/100 ml after the high carbohydrate diet. For both reasons these patients will be discussed separately, and excluded from the general correlations made between triglyceride, glucose, insulin, and FFA responses to the high carbohydrate diet.

Glucose and insulin responses to an acute oral glucose load. The glucose responses illustrated in Fig. 3 demonstrate that one-third of the patients had an average plasma glucose concentration during the tolerance test of less than 120 mg/100 ml. These patients would be generally classified as having a normal glucose tolerance, e.g., an average concentration of 120 mg/100 ml would result from plasma glucose concentrations (mg/100 ml) of 80, 180, 140, 80 at 0, 1, 2, and 3 hr respectively. Approximately another one-third of the patients exhibited modest impairments of glucose tolerance, while the remaining one-third demonstrated unequivocal hyperglycemia.

In Fig. 4 the average glucose response observed during the tolerance test is plotted against the average insulin response for each patient. It is

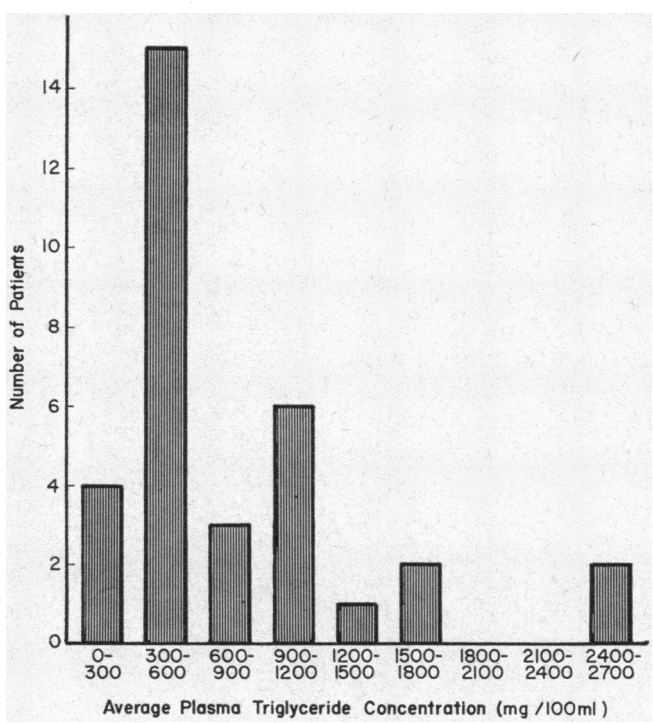

FIG. 1. DISTRIBUTION OF STEADY-STATE PLASMA TRIGLYCERIDE CONCENTRATION AFTER A HIGH CARBOHYDRATE DIET IN 33 SUBJECTS.

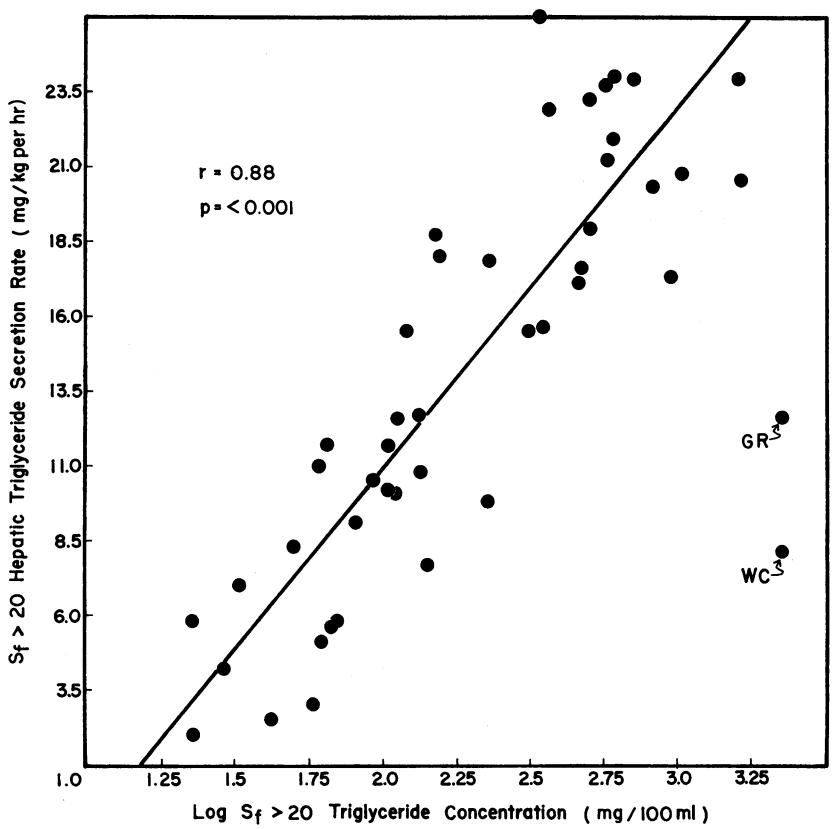

FIG. 2. RELATIONSHIP BETWEEN PLASMA $S_f > 20$ TRIGLYCERIDE CONCENTRATION AND TURNOVER RATE. These 44 studies were conducted during periods of steady-state plasma triglyceride concentrations, and turnover rate is equal to hepatic triglyceride secretion rate. The best fit line was derived by the standard least squares technique.

clear that there is no simple relationship between glucose and insulin response. However, it appears that increasing hyperglycemia is accompanied by greater insulin responses, until, in the instances of marked deterioration of glucose tolerance, the insulin response is again noted to be low. In any case, the lowest insulin responses are seen in patients with both the least and the most hyperglycemia.

Correlation between glucose tolerance test results and triglyceride responses produced by the high carbohydrate diet. Table II presents the degree of correlation between glucose and insulin responses to an acute oral glucose load and the eventual triglyceride response produced by the high carbohydrate diet. It is apparent that a high degree of correlation existed between the magnitude of insulin response and the average fasting plasma triglyceride concentration. In contrast, there was no significant correlation between hyperglycemia and hypertriglyceridemia. The explanation for this difference in degree of correlation between glucose and insulin responses is implicit from the data in Fig. 4, which indicate that the lowest insulin responses were seen in patients with either the least or the greatest degree of hyperglycemia. Since triglyceride concentrations were low in patients with low levels of insulin, patients with the severest degree of hyperglycemia were therefore not hyperglyceridemic.

Correlations between triglyceride, glucose, insulin, and FFA responses to the high carbohydrate diet. The means of the biweekly 8–9–10 a.m. measurements of glucose, insulin, and FFA concentrations produced by the 3 wk high carbohydrate diet are seen in Table III. The average of the mean values for the three time points was correlated with the average fasting plasma triglyceride

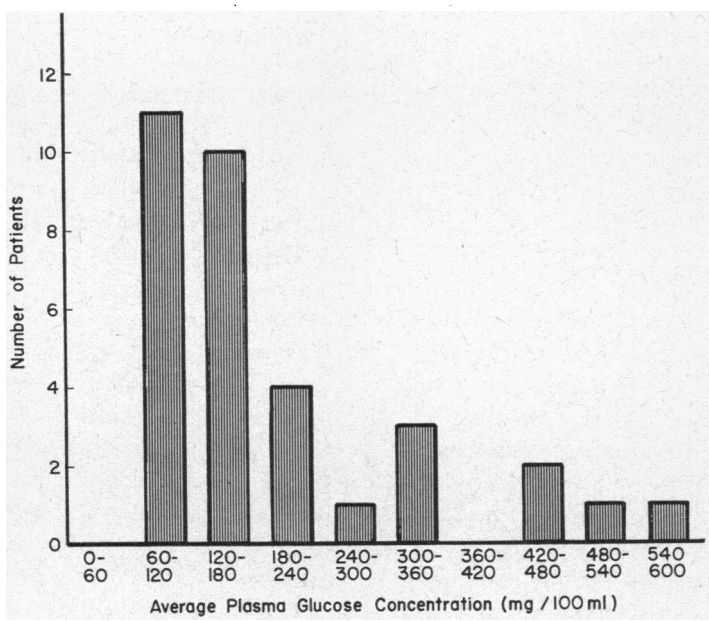

FIG. 3. DISTRIBUTION OF GLUCOSE RESPONSES TO A SINGLE ORAL GLUCOSE LOAD IN THE 33 SUBJECTS BEFORE BEGINNING THE HIGH CARBOHYDRATE DIET.

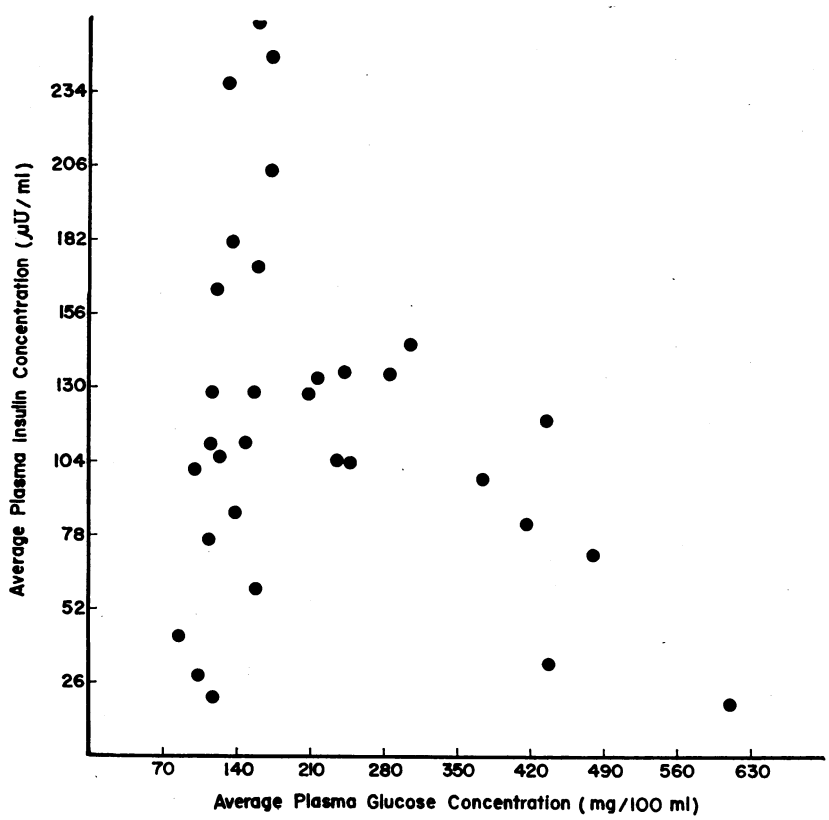

FIG. 4. RELATIONSHIP OF PLASMA GLUCOSE AND INSULIN RESPONSES TO A SINGLE ORAL GLUCOSE LOAD BEFORE THE HIGH CARBOHYDRATE DIET WAS STARTED.

TABLE II

Correlation between glucose tolerance test responses and degree of hypertriglyceridemia produced by the high carbohydrate diet

	Triglyceride response	
Glucose response	$r = -0.19$, $P < 0.3$	$r^* = 0.08$, $P < 0.6$
Insulin response	$r = 0.64$, $P < 0.001$	$r = 0.59$, $P < 0.001$

* Kendall's Rank Correlation Coefficient (12).

concentration, and the relationship between glucose, insulin, and FFA response and plasma triglyceride concentration is seen in Figs. 5, 6, and 7. These results indicate that the magnitude of the insulin response produced by the high carbohydrate diet correlated very well with the triglyceride response to the diet. The glucose response was not significantly correlated with the triglyceride response, and the explanation for this is the same as discussed previously in reference to the glucose tolerance test results. Finally, there was no correlation between FFA and triglyceride responses. Further attempts were made to seek correlation between FFA response and triglyceride response by using other aspects of FFA metabolism, i.e. fasting concentrations and ease with which FFA concentration is lowered by dietary ingestion, and in neither case did a significant relationship emerge.

Correlation between obesity and triglyceride response. There was no significant relationship between ponderal index (which has a high correlation with kilograms of body fat; reference 4) and plasma triglyceride concentration ($P < 0.4$). Furthermore, there was no significant correlation between ponderal index and the insulin response to the high carbohydrate diet ($P < 0.2$).

Patients W.C. and G.R. A summary of the metabolic data for these two patients is seen in

TABLE III

Means of plasma triglyceride, glucose, insulin, and FFA concentrations observed during the high carbohydrate diet period

Patient	TG* 8 a.m.	Plasma glucose				Plasma insulin				Plasma FFA			
		8 a.m.	9 a.m.	10 a.m.	Avg	8 a.m.	9 a.m.	10 a.m.	Avg	8 a.m.	9 a.m.	10 a.m.	Avg
		mg/100 ml				*μU/ml*				*μEq/liter*			
H.H.	110	334	686	844	621	14	19	24	19	563	496	261	440
W.W.‡	113	79	116	101	99	18	62	53	44				
J.P.‡	180	103	118	97	106	16	41	21	26				
G.L.	243	88	164	112	121	10	177	131	106	375	204	190	256
G.B.‡	301	73	225	114	137	9	145	95	83				
D.M.	316	302	466	533	434	21	41	54	39	970	549	419	646
A.T.	316	84	198	154	145	14	172	136	107	343	188	147	226
N.T.‡	321	94	111	119	108	15	26	13	18				
F.Bu.	352	83	196	174	151	11	90	60	54	311	175	144	210
E.A.	367	121	265	309	232	14	112	160	95	417	217	211	282
H.G.	420	331	525	585	480	36	62	82	60	1082	614	346	681
W.K.	434	85	188	165	146	28	276	207	170	423	212	198	278
F.Ba.	449	88	171	146	135	29	292	218	180	428	256	200	295
B.D.	460	81	229	293	201	27	155	193	125	588	491	380	486
E.D.	495	179	471	465	372	26	117	153	99	767	411	252	477
F.H.	498	115	292	290	232	14	117	156	96	512	395	282	396
E.M.‡	504	95	137	122	118	16	132	62	70				
P.Mc.	509	236	488	533	419	41	112	91	81	1020	689	330	680
E.K.	579	240	534	525	433	77	151	134	121	614	400	255	423
C.L.	615	91	156	124	124	18	268	212	166	459	226	213	299
C.D.	788	132	239	267	213	48	194	150	131				
J.H.‡	820	91	158	131	127	20	225	80	108				
S.S.‡	901	95	188	131	138	49	353	300	234				
E.C.	995	123	313	321	252	76	787	1030	631	478	321	283	361
R.N.	1012	85	117	100	101	18	194	69	94				
M.F.‡	1025	103	208	209	173	38	340	234	204				
L.K.	1069	87	229	222	179	49	356	323	243	464	185	164	271
J.B.	1138	120	399	400	306	63	202	164	143				
W.G.	1264	108	302	328	246	32	165	210	136	507	309	194	337
P.G.‡	1516	92	188	168	149	38	208	129	125				
D.H.	1680	97	186	158	147	51	389	321	254				
W.C.	2424	70	162	142	125	6	164	191	120	486	266	229	327
G.R.	2440	145	345	361	284	32	198	176	135	811	485	381	559

* Mean plasma triglyceride concentration during the last 2 wk of the high carbohydrate dietary period.
‡ Data from these patients have appeared in our earlier publication in a somewhat different form (1).

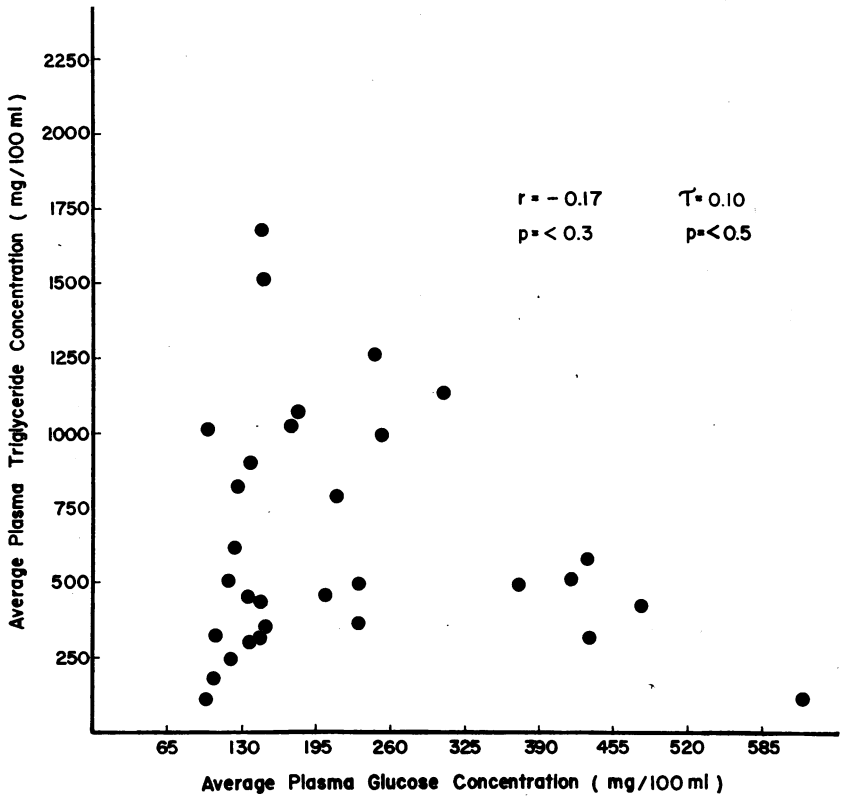

FIG. 5. RELATIONSHIP BETWEEN PLASMA GLUCOSE AND TRIGLYCERIDE RESPONSE PRODUCED BY THE HIGH CARBOHYDRATE DIET. Correlation coefficients have been calculated by the usual product moment correlation (r) and Kendall's Rank Correlation Coefficient (τ).

Table IV. Plasma triglyceride concentrations of these two patients, on either diet, were markedly elevated as compared to the remaining 31 subjects. This severe degree of hypertriglyceridemia was not associated with an appropriate increase in hepatic $S_f > 20$ triglyceride secretion rate in either patient (Fig. 2), and the cause of the marked hypertriglyceridemia seems to be related to a primary impairment in plasma triglyceride removal efficiency. In this regard, these two patients appear to be unique among this group. They do not have "fat-induced lipemia" as triglyceride concentration increased when they were switched from the control formula diet (42% fat) to the high carbohydrate diet (0% fat). Furthermore, they did not have obvious deficiencies in lipoprotein lipase activity.[1] Although they seem to have in common the abnormality in triglyceride removal efficiency, in most other respects they are quite dissimilar. W.C. is a relatively thin patient, with normal glucose tolerance and relatively low levels of FFA. In contrast, G.R. is younger and heavier, with moderately severe diabetes and high levels of FFA. They had approximately similar insulin responses to both the glucose tolerance test and the diet, but their degree of hypertriglyceridemia was not proportionate to their degree of hyperinsulinemia.

[1] These measurements were performed through the courtesy of Dr. Edwin Bierman and Dr. Daniel Porte, Jr., University of Washington School of Medicine, Seattle, Wash.

Discussion

In 1961, Ahrens et al. (13) subdivided patients with hypertriglyceridemia into two general categories based on the plasma triglyceride response to antecedent diet. As a result of this distinction the previous designation of "essential hyperlipemia" was replaced by the physiological concepts of "fat-induced" and "carbohydrate-induced" lipemia. Primary fat-induced lipemia has been defined as a

rare clinical syndrome, characterized by the relative inability of such patients to dispose of newly absorbed chylomicrons, and currently thought to result from an inherited deficiency of lipoprotein lipase (14–16). More recently, it has been suggested that hypertriglyceridemia in some patients with myxedema (17) and with mild diabetic ketoacidosis (18) might be due to an acquired deficiency of the same enzyme, producing another variety of fat-induced lipemia. Thus, the operational definition of fat-induced lipemia, based on the plasma triglyceride response to diet, has been replaced by more specific clinical entities, apparently directly related to the activity of at least one enzyme required for normal clearance of exogenous chylomicrons.

The phenomenon of carbohydrate induction of hypertriglyceridemia has not been as precisely defined, nor is it clear that it represents a specific pathological entity. It appears likely from our data that the majority of individuals, with the exception of those with fat-induced lipemia, will undergo some increase in plasma triglyceride concentration when carbohydrate is isocalorically substituted for fat in their diets. An attempt has been made to clarify this response by differentiating between a "normal" and "abnormal" degree of carbohydrate induction of hypertriglyceridemia (19). However, the distribution of plasma triglyceride concentrations seen in our patient population indicates that there is a relatively continuous spectrum of carbohydrate-induced steady-state plasma triglyceride concentrations ranging from 110 to 1680 mg/100 ml. Furthermore, this is related to a continuous rise in $S_f > 20$ triglyceride hepatic secretion rates. Thus, there does not appear to be any clear separation into two populations, normal and abnormal, until plasma triglyceride concentrations exceed 2000 mg/100 ml. 2 of 33 patients studied attained levels of plasma triglyceride concen-

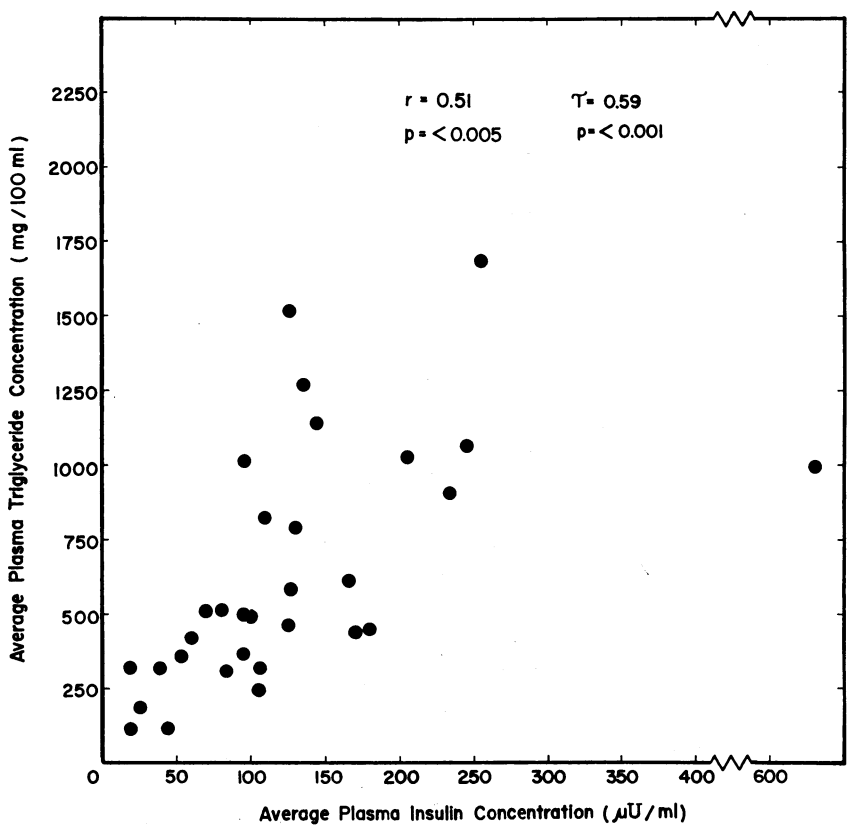

FIG. 6. RELATIONSHIP BETWEEN PLASMA INSULIN AND TRIGLYCERIDE RESPONSE PRODUCED BY THE HIGH CARBOHYDRATE DIET. Correlation coefficients have been calculated by the usual product moment correlation (r) and Kendall's Rank Correlation Coefficient (τ).

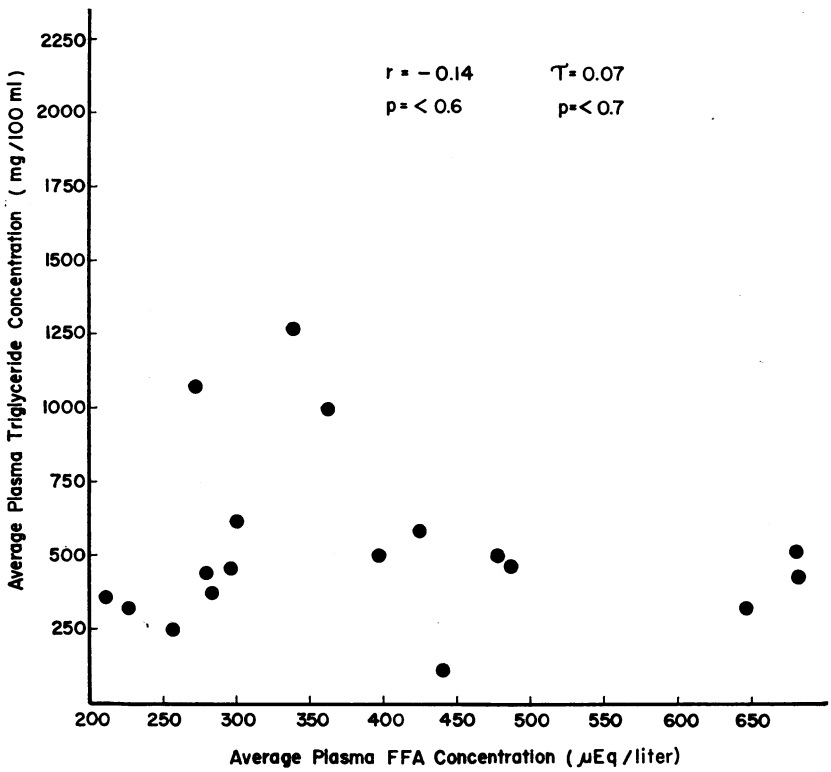

FIG. 7. RELATIONSHIP BETWEEN PLASMA FFA RESPONSE AND TRIGLYCERIDE RESPONSE PRODUCED BY THE HIGH CARBOHYDRATE DIET. Correlation coefficients have been calculated by the usual product moment correlation (r) and Kendall's Rank Correlation Coefficient (τ).

tration greater than 2000 mg/ml as the result of a high carbohydrate diet, and these two are the only ones of 44 patients studied in which hypertriglyceridemia appeared to be related to a primary defect in the disposal of plasma triglycerides. These patients do not have fat-induced lipemia; lipoprotein lipase activity was not decreased, and plasma triglyceride concentration fell when the proportion of fat in the diet was increased. Obviously further study is necessary in order to characterize more carefully such patients, and to define the reason for their apparent inability to clear plasma triglycerides as efficiently as the majority of individuals do.

On the other hand, in the remaining 31 patients, and probably in the majority of individuals, the factors responsible for carbohydrate-induced elevations of plasma triglyceride concentration are becoming increasingly clear. In these patients the primary cause of elevated triglyceride concentrations are carbohydrate-induced increases in hepatic triglyceride secretion rates (11, 20). The

TABLE IV

Summary of data for patients W.C. and G.R.

	Control formula diet				High carbohydrate diet				
	Plasma lipids		Glucose tolerance test*		Plasma lipids		8–9–10 a.m. response‡		
Patient	TG§	Chol‖	Glucose	Insulin	TG	Chol	Glucose	Insulin	FFA
	mg/100 ml		*mg/100 ml*	*μU/ml*	*mg/100 ml*		*mg/100 ml*	*μU/ml*	*μEq/liter*
W.C.	1061	349	85	37	2424	641	125	120	327
G.R.	755	350	230	57	2440	577	284	135	559

* Average of concentrations at 0, 1, 2, and 3 hr.
‡ Average of mean 8–9–10 a.m. concentrations.
§ Average fasting plasma triglyceride concentration.
‖ Average fasting plasma cholesterol concentration.

increases in hepatic triglyceride secretion rates (and in triglyceride concentrations) produced by a high carbohydrate diet have been shown to be highly correlated with the plasma insulin response produced by that diet. The current results differ from our earlier studies (1) in which the plasma glucose response correlated equally well with the triglyceride elevations produced by a high carbohydrate diet, and the reason for this disparity is apparent. Patients with fasting hyperglycemia were excluded from our earlier study, and within the original patient population there was also a direct correlation between the magnitude of the glucose and insulin response to a high carbohydrate diet. The inclusion in the present study of patients with fasting hyperglycemia resulted in a group of patients with varying degrees of hyperglycemia and hyperinsulinemia. Patients with the least insulin response, irrespective of their degree of hyperglycemia, did not become hypertriglyceridemic. Thus, we were able to differentiate between the relative importance of the glucose response as compared to the insulin response, and could demonstrate that it was only the insulin response to the high carbohydrate diet which correlated with the increase in hepatic secretion rate and plasma triglyceride concentration produced by that diet.

It has been suggested that obesity is the primary determinant of the insulin response to a glucose load (21). Although other studies have not been in complete agreement with this postulate (22), a significant correlation between degree of obesity and carbohydrate induction of hypertriglyceridemia might have been anticipated. However, we could not document this relationship, and this difference between our results and those of Albrink and Meigs (23) may be related to the inclusion within our population of obese, hyperglycemic patients with a low insulin response to the high carbohydrate diet. However, if a much larger population were studied, or if more sophisticated anthropometric measures were employed, it is possible that degree of obesity and triglyceride response might be correlated.

The role of FFA metabolism in the genesis of hypertriglyceridemia is not clearly defined. Previous studies have suggested that exposure of liver to increased levels of FFA can stimulate the production and secretion of lipoproteins (24, 25). Intrahepatic FFA concentration could theoretically be elevated by an increase in FFA influx from peripheral tissues or by an increase in net hepatic FFA uptake. The report that fasting plasma FFA concentrations are moderately elevated in patients with hypertriglyceridemia (3) lends support to the notion that increased FFA influx might stimulate hepatic triglyceride production and plasma triglyceride concentration. However, we could not correlate fasting FFA concentrations, their ability to be suppressed by dietary ingestion, or the over-all plasma FFA response to the high carbohydrate diet with the magnitude of triglyceride elevation. Since we did not measure plasma FFA turnover rates, it is still possible that there might be a correlation between plasma FFA turnover and triglyceride response to the high carbohydrate diet. For example, if patients with the greatest FFA response (Fig. 7) had the lowest FFA turnover rates, a direct relationship might have emerged between FFA and triglyceride responses. However, an extremely significant correlation was noted between glucose and FFA responses to the high carbohydrate diet ($r = +0.57$, $P < 0.002$), e.g., the more hyperglycemic, the higher the plasma FFA levels. Consequently, in order to establish a direct correlation between FFA and triglyceride response it would be necessary to make the unlikely assumption that the more diabetic a patient, the less would be his FFA turnover rate. On the other hand, there are reports suggesting that insulin can both increase the hepatic uptake of FFA (26) as well as increase hepatic lipogenesis from glucose in liver slices from normal animals (2). Consequently, increased intrahepatic availability and utilization of FFA could well result from increased levels of plasma insulin, and might represent a method by which insulin stimulates hepatic triglyceride production.

In conclusion, it would seem that in most patients the degree to which a high carbohydrate diet stimulates hepatic triglyceride secretion is directly related to the insulin response produced by that diet. The precise manner in which increased insulin concentrations might stimulate hepatic triglyceride production and secretion is not clear, although recent studies have suggested a possible animal model in which to study this question (2). Finally, the primary abnormality leading to the increased insulin response remains to be established.

Our current view is that this is related to some impedance in peripheral glucose uptake. In an attempt to compensate for this difficulty in transporting glucose into the cell, insulin secretion could be stimulated in order to maintain cellular glucose uptake at some minimal level. The ensuing hyperinsulinemia and hyperlipoproteinemia (and most likely accelerated atherogenesis) is the price paid to maintain a normal rate of glucose transcellular transport and utilization.

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