Glucose, Insulin, and Triglyceride Responses to High and Low Carbohydrate Diets in Man *

JOHN W. FARQUHAR,[†] ARTHUR FRANK,[‡] RICHARD C. GROSS,[§] AND GERALD M. REAVEN WITH THE TECHNICAL ASSISTANCE OF E. P. BROWN

(*From the Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif.*)

Several reports have recently been published which suggest that abnormalities of glucose metabolism are common in patients with fasting hypertriglyceridemia. Metabolic defects reported in these patients have included abnormal glucose (1, 2) and tolbutamide tolerance tests (3), and a diminished blood glucose response to exogenous insulin (2, 4). However, conflicting reports have been obtained in measurements of endogenous plasma insulin response to oral glucose loads in hypertriglyceridemic patients. Kane, Longcope, Pavlatos, and Grodsky have reported normal insulin levels measured by bioassay and immunoassay (2). On the other hand, preliminary reports from our group and from Davidson and Albrink suggest that elevated plasma insulin is a common response in such subjects when measured either by bioassay (5, 6) or immunoassay (6, 7). Although further evidence for abnormal insulin metabolism is suggested by the report of supranormal increases in plasma insulin-like activity after intravenous tolbutamide (3), tolbutamide's effect on insulin metabolism is not well understood and is clearly not analogous to the effect of ingested carbohydrate.

These differences in published results may be partly due to variations in experimental design and patient selection. Since plasma triglycerides are known to vary greatly depending on the amount and type of carbohydrate fed in isocaloric feeding programs (8, 9), dietary control should aid in establishing the relative degree of triglyceride abnormality in patient groups. Only one study has included such careful dietary control, but glucose and insulin-like activity were measured together only after intravenous tolbutamide (3). Furthermore, since plasma triglycerides are altered after chronic ingestion of these diets, insight into possible mechanisms of the hypertriglyceridemia might come from postprandial measurements of plasma glucose and insulin on defined diets.

In the study we report here, patients were selected with varying triglyceride levels as measured on ad libitum diets, and their insulin and glucose responses to an oral glucose load were measured. They were then placed on isocaloric liquid formula diets, varying only in percentage of fat and carbohydrate, and insulin and glucose studies were repeated in direct response to these meals. Patients with fat-induced lipemia (8) were excluded by dietary means and measurement of plasma postheparin lipolytic activity.

This paper confirms preliminary evidence (5–7) that hyperinsulinemia is a common response to single oral glucose loads in patients with hypertriglyceridemia. We also extend these observations to conclude that there is a high correlation between the magnitude of triglyceride response to high and low carbohydrate diets and the plasma insulin and glucose response to these diets.

Methods

Subjects. Table I summarizes the clinical features of the 15 experimental subjects. Two patients had psoriasis (W.W. and E.M.), and the remaining 13 had clinical evidence for premature atherosclerosis. All were ambu-

latory, and their fasting blood glucose concentrations were less than 100 mg per 100 ml.

Procedures. Calories were supplied in four daily equicaloric feedings of a liquid formula diet (10). Two diets were used; each contained 15% of calories from protein. One diet was high in fat (68% of calories), and the other was high in carbohydrate (85% of calories). All of the protein was derived from skimmed milk powder.[1] In both diets 17% of calories were from the carbohydrates of skimmed milk powder, and these carbohydrates were composed of over 99% lactose and less than 0.5% monosaccharides. Fat and carbohydrate were varied by equicaloric replacement of corn oil[2] and dextrins.[3] The carbohydrates of the 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. All subjects were fed the high fat diet for 2 to 10 weeks and the high carbohydrate diet for 2½ to 7 weeks. In seven subjects the two diet program was repeated one or more times, and in eight subjects 125 mg per day of chlorpropamide was given during a repeat feeding study. The duration of ingestion of each formula was considered an important variable, and care was taken to ensure that it was consumed steadily over a 30-minute period. Finally, body weight was closely maintained to within ± 0.5 kg during each dietary period. A rapid gain or loss of approximately 1.0 kg occurred on shifting from a high fat to a high carbohydrate diet, or vice versa. This weight difference, presumed to result from

gain or loss of fluid, was maintained during the duration of either diet (Table I).

Oral glucose tolerance tests were performed on all patients immediately before the dietary studies. Concentrations of blood glucose (11), plasma immunoreactive insulin,[4] and insulin-like activity (12) were determined on the fasting, 1-, 2-, and 3-hour samples of the glucose tolerance tests. After the diet periods started, blood was drawn at 8 a.m. twice weekly; the plasma lipids were extracted with chloroform: methanol (13) and analyzed for total cholesterol (14), phospholipid (15), and triglyceride by a modification of the method of Lofland (16). During one of the paired high fat, high carbohydrate periods, additional measurements of plasma glucose (17) and immunoreactive insulin (18) concentrations were obtained in ten subjects. These studies, termed "all-day" insulin-glucose tests, were performed after 2 to 3 weeks of each dietary period and before termination of these periods. The patients ingested their formulas as before (at 8 a.m., 11 a.m., 2 p.m., and 5 p.m.), and blood was drawn for plasma glucose and immunoreactive insulin hourly from 8 a.m. to 2 p.m., and every half-hour from 2 to 5 p.m. A weighted average of both the glucose and insulin concentrations was obtained by assuming straight lines between points on a plot of concentration against the 9 hours of the test. The weighted average represents an estimate of the area units under a concentration "curve."

One additional patient, M.M., a 54-year-old woman (not listed in Table I) was studied for 3 weeks before

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[1] Carnation Instant, Carnation Co., Los Angeles, Calif.
[2] Mazola, Corn Products Co., New York, N. Y.
[3] Dexin, Burroughs Wellcome & Co., Tuckahoe, N. Y.

[4] These assays were performed through the courtesy of Dr. Roger Unger, The University of Texas Southwestern Medical School, Dallas, Texas.

TABLE I

General description of patients studied

| | | | Weight* | | | | Clinical characteristics‡ | | | |
| | | | | | | | | | Xanthomata | |
Patient	Age	Sex	HF	HC	Height	Relative weight†	ASHD	ASO	Tendon	Tuberous
	years		*kg*		*cm*					
1. W.W.	56	M	65.2	65.4	169	104.2	O	O	O	O
2. J.P.	48	M	73.9	74.5	174	111.2	X	X	X	O
3. F.W.	45	F	65.4	66.0	163	121.2	X	O	X	O
4. G.B.	52	M	72.9	74.5	171	108.0	X	O	O	O
5. N.T.	39	M	66.0	67.0	174	100.4	X	O	O	O
6. L.Mc.	52	M	77.2	78.4	171	110.7	X	O	O	O
7. C.B.	54	M	69.4	70.5	175	103.5	X	O	O	O
8. E.M.	48	M	78.4	80.6	179	111.5	O	O	O	O
9. R.L.	51	M	77.2	77.9	183	105.8	X	O	O	O
10. J.H.	50	M	89.4	91.2	180	116.6	X	O	O	O
11. S.S.	39	M	90.5	91.1	178	121.0	X	O	O	O
12. R.N.	47	M	71.3	71.8	173	108.7	X	O	O	O
13. M.F.	61	F	57.7	59.4	160	111.1	X	O	O	O
14. E.C.	40	M	89.0	89.8	165	136.9	X	X	O	X
15. P.G.	52	M	73.7	74.5	178	106.8	X	X	O	O

* Mean daily body weights during high fat (HF) and high carbohydrate (HC) diets.
† Relative weight = per cent of ideal weight calculated from Metropolitan Life Insurance Co. tables.
‡ X = characteristic present; O = characteristic not present. ASHD = arteriosclerotic heart disease, either angina pectoris or previous myocardial infarction; ASO = arteriosclerosis obliterans.

TABLE II

Effect of diet on plasma lipid concentration

Patient	High fat period Plasma lipids*			High carbohydrate period Triglycerides					Means of 1 through 4 weeks		
	TG	Chol	PL	1 week	2 weeks	3 weeks	4 weeks	Terminal†	TG	Chol	PL
	mg/100 ml plasma			*mg/100 ml plasma*					*mg/100 ml plasma*		
1. W.W.	72	134	207	122	97	121	112	122(5½)	113	121	213
2. J.P.	158	352	303	169	200	179	172	205(6)	180	361	231
3. F.W.	88	351	395	151	218	210	190	(4)	192	451	446
4. G.B.	122	196	205	286	288	306	323	286(6)	301	217	241
5. N.T.	199	231	247	286	294	382		(3)	321	270	264
6. L.Mc.	138	198	234	348	436	394	452	503(5½)	408	250	312
7. C.B.	110	174	200	449	436			(2)	443	207	263
8. E.M.	125	196	188	507	466	572	470	360(6½)	504	218	257
9. R.L.	110	254	250	620	563	706	510	(4)	600	308	390
10. J.H.	267	179	236	741	898	744	898	(4)	820	240	396
11. S.S.	1,101(738)‡	356	477	918	1,000	785		(3)	901	290	406
12. R.N.	196	225	236	849	1,053	1,134		(3)	1,012	279	338
13. M.F.	385	127	191	1,020	1,030			(2)	1,025	166	268
14. E.C.	650	251	296	971	1,025	1,052	1,060	974(7)	1,027	309	387
15. P.G.	877(710)	349	398		1,714	1,489	1,346	1,408(5)	1,516	444	606
Group means	305	238	271						624	276	335

* TG = triglyceride; chol = cholesterol; PL = phospholipid.
† The number in parentheses after the terminal triglyceride value represents the total duration of the period in weeks. The terminal value is the final triglyceride value for periods exceeding 4 weeks.
‡ The values in parentheses were obtained by subtraction of the chylomicron particulate triglyceride (derived from dietary fat, see Results) from total plasma triglyceride.

surgical removal of an insulin-secreting pancreatic adenoma. Her diet was derived from solid foods and contained approximately 350 g of carbohydrate per day. In addition to solid foods, consumed in frequent meals between 8 a.m. and 8 p.m., she received 150 g of glucose intravenously between 8 p.m. and 8 a.m. On 5 successive days food was withheld at 8 a.m., and blood was obtained at 8, 9, 10, and 11 a.m. for measurement of glucose, immunoreactive insulin, and triglyceride concentrations.

Results

Effect of diet on plasma lipid concentrations. The plasma triglyceride, cholesterol, and phospholipid concentrations present in the 15 patients when on the high fat and high carbohydrate diets are seen in Table II. For the high fat period, the average values are listed, and each number is derived from the mean of 4 to 16 samples obtained twice weekly. Since it has been suggested that the triglyceride response to a high carbohydrate diet may be abolished with time (19), weekly triglyceride values (mean of biweekly measurements) are given for the high carbohydrate period. In seven patients, the high carbohydrate period lasted for more than 4 weeks, and the triglyceride values for the terminal week are also seen in Table II. The mean lipid values for the high carbohydrate period are the average of weekly concentrations during the first 4 weeks.

The patients are listed in order of increasing mean triglyceride concentration. It should be noted that in patients with the most elevated high carbohydrate triglycerides, there also was persistence of moderate hypertriglyceridemia (above 300 mg per 100 ml plasma) on the high fat diet (Table II). This phenomenon is noted in patients M.F., E.C., P.G., and S.S., but it is shown most clearly in patient S.S., who alone had a higher triglyceride concentration on the high fat than on the high carbohydrate diet. Therefore, all patients but S.S. had some degree of rise in triglyceride concentration when changed from the high fat diet to the high carbohydrate diet. However, activities of plasma postheparin lipolytic activity of patients S.S. and P.G. (the two with the highest "high fat" triglyceride levels) were within normal limits,[5] indicating that they do not have fat-induced lipemia (8, 20). Also, when the contribution of dietary fat as plasma chylomicron triglyceride (21) was subtracted from the triglycerides of patient S.S., the high fat triglyceride value was appreciably less than the mean value of the high carbohydrate period (see second footnote to Table II). Plasma cholesterol and phospholipid changes

generally paralleled the triglycerides but were lesser in magnitude.

Effect of chlorpropamide on plasma triglyceride concentration. Eight patients received 125 mg of chlorpropamide per day for a 4-week period while on a high carbohydrate diet in an attempt to lower the triglyceride concentration. Four of these patients (L.Mc., J.F., E.C., and P.G.) had mildly abnormal oral glucose tolerance tests by the criteria of Fajans and Conn (22). However, in all cases fasting blood glucose concentration was less than 100 mg per 100 ml when tested before chlorpropamide, and in no instance was hypoglycemia detected with administration of this drug. The results of these experiments are seen in Table III. Each weekly value for triglyceride concentration is the average of two determinations, and, as before, the weekly and terminal triglyceride values are illustrated for each patient.

Ideally, all patients would have had three consecutive high carbohydrate dietary periods, with chlorpropamide administered during the middle period. This was achieved only in three patients.

and the variation in experimental design makes statistical evaluation difficult. Analysis of two consecutive dietary periods, in which chlorpropamide was given during the second period, was possible in seven patients. By use of either the Wilcoxon signed ranks test (p = 0.04) or the *t* test (p = 0.03), chlorpropamide significantly lowered plasma triglyceride concentration. However, the magnitude of the chlorpropamide effect was not very great in most patients, and it is possible that this was a function of time rather than treatment. Consequently, we felt that additional investigation will be necessary to establish the effectiveness of chlorpropamide in lowering triglycerides.

Correlation of plasma lipid measurements and relative body weight with plasma glucose and insulin values. Correlation between the mean plasma triglyceride concentration attained on either diet was sought with the following: *a*) the mean of the fasting, 1-, 2-, and 3-hour blood glucose values of a standard oral glucose tolerance test done just before beginning the special diets; *b*) the mean

TABLE III

Effect of chlorpropamide on plasma triglyceride

Patient	Test period*	Weeks of high carbohydrate diet					Mean of weeks 1–4
		1	2	3	4	Terminal†	
		mg triglycerides/100 ml plasma					
J.P.	HC + chlor	192	214	196	180	179(8)	196
	HC	169	200	179	172	205(6)	180
F.W.	HC	151	218	210	190	(4)	192
	HC + chlor	201	193	147	161	(4)	176
	HC	282	238	203	198	222(5)	230
L.Mc.	HC	348	436	394	452	503(5½)	408
	HC + chlor	398	311	346	348	412(6)	351
M.F.	HC	437	529	517	384	322(6)	467
	HC + chlor	284	371	310	246	(4)	303
	HC	237	384	376	304	242(5)	350
E.M.	HC	507	466	572	470	360(6½)	504
	HC + chlor	343	332	312	212	217(7)	300
R.N.	HC	1,199	547	849	877	(4)	868
	HC + chlor	775	735	714	592	734(5½)	704
	HC	849	1,053	1,134		(3)	1,012
E.C.	HC	1,202	1,036	755	1,121	(4)	920
	HC + chlor	780	856	1,075	969	(4)	971
P.G.	HC		1,714	1,489	1,346	1,408(5)	1,516
	HC + chlor		1,223	1,713	1,220(8)	1,468

* All test periods were consecutive. HC = high carbohydrate; chlor = chlorpropamide.
† The terminal value is the final triglyceride value of periods exceeding 4 weeks. The number in parentheses represents the total duration of the test period in weeks.

TABLE IV

Summary of data used in correlation of plasma lipid measurements with glucose and insulin values

Patient	Ad libitum diet								High fat diet		High carbohydrate diet				
	Glucose tolerance test*			Plasma lipids			Glucose area†	Insulin area‡	Plasma lipids			Glucose area	Insulin area
	Glu-cose	Insu-lin	ILA	Chol	PL	TG			Chol	PL	TG		
	mg/100 ml	μU/ml	μU/ml	mg/100 ml					mg/100 ml				
1. W.W.	92	42	250	134	207	72	791	384	121	213	113	901	446
2. J.P.	80	77	209	352	303	158	998	274	361	231	180	938	268
3. F.W.	78	58	477	351	395	88			451	446	192		
4. G.B.	100		580	196	205	122	921	189	217	241	301	1,012	887
5. N.T.	93	82	242	231	247	199	879	156	270	264	321	985	166
6. L.Mc.	111		890	198	234	138			250	312	408		
7. C.B.	125	343	803	174	200	110			207	263	443		
8. E.M.	111	76	239	196	188	125	911	230	218	257	504	1,089	647
9. R.L.	82	87	252	254	250	110			308	390	600		
10. J.H.	98	101	580	179	236	267	1,039	283	240	396	820	1,158	1,019
11. S.S.	108		1,345	356	477	1,101 (738)§	1,023	337	290	406	901	1,240	1,828
12. R.N.	117	144	1,190	225	236	198	929	450	279	338	1,102	1,104	808
13. M.F.	158	172	830	127	191	385	1,118	669	166	268	1,025	1,715	1,963
14. E.C.	125	221	1,054	251	296	650			309	387	1,027		
15. P.G.	131		1,334	349	398	877 (710)§	948	465	444	606	1,516	1,372	1,178

* Mean of fasting, 1-, 2-, and 3-hour specimens. Insulin = immunoreactive insulin; ILA = insulin-like activity.
† Serum glucose area in mg per 100 ml plasma during the period between 8 a.m. and 5 p.m. of "all-day" tests (see Methods).
‡ Plasma immunoreactive insulin area in microunits per milliliter during the all-day tests.
§ These values were reduced by subtracting chylomicron particulate triglyceride from total triglyceride. Only the first "uncorrected" value was used in seeking correlations.

of the fasting, 1-, 2-, and 3-hour values for insulin by bioassay and by immunoassay during the glucose tolerance test of the ad libitum diet period; *c*) the areas (in microunits per milliliter or milligrams per 100 ml during 9 hours) of the hour and half-hour plasma insulin and glucose measurements during the all-day insulin-glucose tests performed at the end of each dietary period; and *d*) relative body weight (Table I). The data other than relative weight used for these correlations are seen in Table IV, and the results are listed in Tables V and VI.

Two methods of calculating correlation coefficients were used, the usual product moment correlation (PMC) (23) and the Spearman rank product moment correlation (RPMC) (24). Although these two methods gave closely similar results, correlations were generally higher with the rank method, a finding that suggests a nonlinear relationship between the variables tested. For simplicity, the comments that follow will emphasize the rank data. The most striking over-all impression is that all measurements of glucose and insulin response correlate very well (usu-

TABLE V

*Correlation of tests done before dietary studies with lipid values and relative weight**

Test	Statistical method†	Lipid values						Relative weight
		High carbohydrate diet			High fat diet			
		TG	PL	Chol	TG	PL	Chol	
Glucose	PMC	0.69	0.11	−0.27	0.42	0.16	−0.35	0.10
tolerance	RPMC	0.76	0.13	−0.26	0.53	−0.30	−0.35	0.01
Insulin-like	PMC	0.78	0.57	0.22	0.75	0.35	0.13	0.36
activity	RPMC	0.73	0.60	0.15	0.59	0.23	0.09	0.18
Immuno-reactive	PMC	0.47	−0.03	−0.22	0.38	−0.28	−0.29	0.14
insulin	RPMC	0.74	0.20	0.08	0.56	−0.21	−0.24	0.09

* Correlations are between the various "tests" on the vertical axis against items on the horizontal axis. Units for the measurements are as previously described. Underlined correlation coefficients are significantly different from zero, p < 0.05.
† PMC = product moment correlation, RPMC = rank product moment correlation.

ally > 0.7, Tables V and VI) with triglyceride response. Closer inspection of these data reveals that the correlations were generally higher for the high carbohydrate period than for the high fat period. It seems possible that this difference is due to inclusion of triglyceride values in the high fat data, which are spuriously high (Table II) due to their content of some exogenous (chylomicron) triglyceride. However, correlations were generally poorer (< 0.4) for these same glucose and insulin responses with either the plasma cholesterol and phospholipids or with relative weight. A somewhat greater correlation was present with phospholipid than with cholesterol, a finding consistent with the higher content of phospholipid than of cholesterol in the $S_f > 20$ lipoprotein.

Metabolic studies on a patient with a pancreatic insulin-secreting adenoma. Table VII presents values from this patient (M.M.) for mean plasma levels of glucose, immunoreactive insulin, and triglycerides obtained immediately after her overnight glucose infusion, and hourly in the postinfusion period between 8 and 11 a.m. For comparison's sake, Table VII also includes similar data for two patients (group I) with the least, and four patients (group II) with the greatest, triglyceride responses to a high carbohydrate diet. The results show that the glucose values for both the immediate postinfusion sample and for the three subsequent fasting samples were very low in patient M.M. when compared with plasma glucose

TABLE VI

Correlation of all-day tests with dietary lipid responses and relative body weight*

Test†		Statistical method	TG	PL	Chol	Relative weight
			mg/100 ml			
All-day glucose	HC diet	PMC	0.76	0.42	0.46	0.35
		RPMC	0.94	0.84	0.21	0.41
All-day glucose	HF diet	PMC	0.40	0.22	0.14	0.58
		RPMC	0.70	0.21	0.04	0.62
All-day glucose	Combined	PMC	0.71	0.42	0.13	
		RPMC	0.83	0.59	0.24	
All-day insulin	HC diet	PMC	0.67	0.42	0.04	0.62
		RPMC	0.75	0.68	0.01	0.44
All-day insulin	HF diet	PMC	0.31	0.04	−0.17	0.12
		RPMC	0.43	0.07	−0.22	0.05
All-day insulin	Combined	PMC	0.65	0.40	0.03	
		RPMC	0.64	0.46	−0.05	

* Correlations are between the tests on vertical axis against items on the horizontal axis. See Table V for explanation of abbreviations. Underlined correlation coefficients are significantly different from zero, p < 0.05.
† HC = high carbohydrate; HF = high fat; combined = data from both diets.

concentrations of the other patients. On the other hand, insulin concentrations in plasma of patient M.M., drawn at the same time, are considerably higher than those found in patients with the lowest triglycerides either fasting or postprandially and are similar to the elevated plasma insulin values found in the patients with marked hypertriglyceridemia postprandially (group II). However, in spite of the increase in plasma insulin levels, plasma triglyceride concentration of patient M.M. was not elevated.

TABLE VII

Studies of a patient (M.M.) with a pancreatic islet cell tumor

Patients	Fasting plasma triglyceride*	Plasma glucose		Plasma insulin	
		Fasting	Postprandial	Fasting	Postprandial
	mg/100 ml	*mg/100 ml*		*μU/ml*	
M.M.	196(3)†	47(12) ±11	58(8) ±13	126(11) ±42	157(4)
Group I (W.W. and J.P.)	148(2)	80(2)	101(6)	25(2)	82(2)
Group II (J.H., S.S., M.F., P.G.)	1,063(4)	90(4)	163(12) ±50	22(4)	178(12) ±127

* Fasting refers to the samples obtained after an overnight fast (Groups I and II) or to the samples obtained from patient M.M. 1, 2, and 3 hours after cessation of the intravenous glucose infusions (9, 10, and 11 a.m.). For Groups I and II, postprandial refers to the mean values of 1-, 2-, and 3-hour samples of the all-day test of the high carbohydrate period. For patient M.M., postprandial refers to the samples obtained at 8 a.m. immediately before stopping the preceding 12-hour continuous intravenous glucose infusion.
† The number in parentheses refers to the number of measurements used to obtain the mean. When present, numbers below the mean = ± standard deviation.

Discussion

The effects of diets either low or high in carbohydrate on plasma triglyceride concentration have been documented in 15 patients. All demonstrated some increase in endogenous triglyceride concentration as a result of the high carbohydrate diet. Previous studies from our laboratory have established a precise relationship between the concentration and turnover rate of $S_f > 20$ triglycerides in man (25) and demonstrated that increased hepatic triglyceride production is the primary cause of endogenous hypertriglyceridemia. The current studies were undertaken in an effort to correlate certain measures of glucose and insulin metabolism with the degree of increase in plasma triglyceride concentration (and hepatic production) resulting from a high carbohydrate diet. The wide variation in triglyceride response suggests that carbohydrate-induced lipemia (8) is not an all or none phenomenon, but rather that the majority of patients will increase their triglyceride production and concentration to a variable extent as a consequence of a high carbohydrate diet. Furthermore, our results indicate that one may accurately predict the magnitude of this triglyceride response. When tested during an ad libitum diet period, the more abnormal the glucose tolerance test and the higher the accompanying rises in plasma insulin-like activity and immunoreactive insulin, the greater the subsequent triglyceride rise on ingestion of a high carbohydrate diet. Finally, the degree of the triglyceride response on either a low or high carbohydrate diet correlated very well with the estimated integral of both plasma and glucose concentrations during the 9 hours of a representative day of ingestion of these diets.

If this apparent relationship is a causal one, there are at least two possible explanations. Hyperglycemia and hyperinsulinemia may cause hypertriglyceridemia, or conversely, a rise in plasma triglyceride concentration may secondarily increase plasma glucose and insulin concentrations. However, we find that the return of glucose and insulin values to normal antedates by a few days the return of elevated $S_f > 20$ triglyceride to normal when hypertriglyceridemic patients are changed from high to low carbohydrate diets. Since we have previously found prolonged half-

lives of $S_f > 20$ triglyceride in such patients (26), we can predict this gradual return of triglyceride concentration to normal after the stimulus to lipid production is diminished. In view of these observations, the second alternative proposed above seems less likely but cannot be entirely excluded.

Although our data do not clearly distinguish between the possible relative importance of glucose and insulin in determining triglyceride response, certain comments are possible. First, it seems unlikely that plasma insulin concentration alone may control hepatic triglyceride synthesis and thereby plasma triglyceride concentration. Plasma triglycerides were not elevated in the subject with hyperinsulinism secondary to an islet cell adenoma, despite the ingestion of a high carbohydrate diet and the presence of plasma insulin levels comparable to those present in patients with marked lipemia. However, this patient also had hypoglycemia. In contrast, patients with lipemia had hyperinsulinism and moderate hyperglycemia. However, it does not follow that hyperglycemia alone is sufficient to produce hyperlipemia, for if this were the case, all patients with diabetes and hyperglycemia would have hyperlipemia. Since this is not so, hyperglycemia does not inevitably "cause" an elevation of plasma triglycerides. A clue to the solution of this problem may lie in the recent suggestion of Berson and Yalow (27) that patients with maturity onset diabetes may be separated into those with higher than normal and those with lower than normal plasma insulin concentrations. A few studies have been carried out in our laboratory on patients with maturity onset diabetes, hyperglycemia, and low levels of plasma insulin. None of these patients has developed hypertriglyceridemia in response to high carbohydrate diets. If these results are subsequently confirmed, they would suggest that hypertriglyceridemia can only develop in patients who have both hyperglycemia and hyperinsulinemia.

If, as much evidence indicates, the liver is readily permeable to glucose without the need for insulin facilitation of its transport (28), then the liver of certain patients will be subjected to episodes of marked hyperinsulinism and moderate hyperglycemia throughout much of the day. Could these factors directly stimulate an otherwise normal liver to synthesize larger quantities of triglyceride? Recent *in vitro* studies (29) sug-

gest that this may well be, but experimental proof will require further knowledge of the rate-controlling steps in hepatic triglyceride synthesis and secretion in man. It would also be of interest to know the dependence of the hepatic triglyceride synthetic system on plasma free fatty acid concentrations in view of the evidence that FFA levels are modestly raised in hypertriglyceridemic subjects (2, 30). In any event, further study is needed to determine the relative importance of plasma glucose, plasma insulin, and plasma free fatty acids in control of triglyceride synthesis, secretion, and turnover.

If high insulin levels do enhance hepatic triglyceride synthesis and secretion in man, can this response be prevented in patients with hypertriglyceridemia? Evidence exists that chlorpropamide may produce a concomitant lowering of both blood glucose and insulin-like activity in patients with diabetes mellitus (12). If the modest triglyceride-lowering effect of chlorpropamide reported here can be confirmed, this may be mediated by the action of this drug on glucose and insulin metabolism. Current studies include further evaluation of the effect of chlorpropamide and other oral hypoglycemic agents, weight reduction, altered rates of dietary carbohydrate ingestion, and high fat diets on the glucose, insulin, FFA, and triglyceride responses of individuals with either normal or elevated fasting blood sugars. Perhaps these observations will help to clarify further the relationship of various types of diabetes to premature atherosclerosis and hyperlipidemic states.

Finally, our data show clearly that within the broad spectrum of triglyceride response to a high carbohydrate diet, there is little evidence of "adaptability" of this response during periods of 4 to 6 weeks of high carbohydrate feeding. A report has appeared (19) of a return of triglycerides to previous levels after 6 months of continued ingestion of low fat diets in a group of white South African prisoners. Further study is needed to see if such adaptation would commonly occur in individuals whose propensity for lipemia is greater and if the adaptation is associated with a commensurate amelioration of the glucose and insulin abnormalities. Furthermore, it is important to know if the type of carbohydrate ingested determines the duration of these responses. Such studies would be relevant to the question of the wisdom of wide-spread use of high carbohydrate-low fat diets in the prevention of coronary arterial disease.

Summary

We administered alternating high fat and high carbohydrate diets to 15 patients and encountered a wide spectrum of plasma triglyceride response. An attempt was made to correlate this response with various measures of glucose and insulin metabolism. Glucose tolerance tests were performed just before the dietary studies, and the observed elevations of plasma glucose, insulin-like activity, and immunoreactive insulin correlated well with the magnitude of the triglyceride response that resulted from the subsequent ingestion of the higher carbohydrate diet. A similar high degree of correlation existed between the plasma triglyceride response and the average levels of plasma glucose and immunoreactive insulin reached during 9 hours of a representative day of ingestion of either the high fat or the high carbohydrate diet. However, despite the presence of hyperinsulinism, a high carbohydrate diet did not produce hypertriglyceridemia in a patient with hypoglycemia secondary to an islet cell adenoma. We suggest that hyperinsulinemia, in the presence of normal to moderately elevated levels of plasma glucose, may be an important cause of the enhanced hepatic triglyceride production that underlies endogenous hypertriglyceridemia.

Acknowledgments

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