Effects of Weight Reduction on Obesity

STUDIES OF LIPID AND CARBOHYDRATE METABOLISM IN NORMAL AND HYPERLIPOPROTEINEMIC SUBJECTS

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ABSTRACT Considerable controversy exists over the purported role of obesity in causing hyperglycemia, hyperlipemia, hyperinsulinemia, and insulin resistance; and the potential beneficial effects of weight reduction remain incompletely defined. Hypertriglyceridemia is one of the metabolic abnormalities proposed to accompany obesity, and in order to help explain the mechanisms leading to this abnormality we have proposed the following sequential hypothesis: insulin resistance → hyperinsulinemia → accelerated hepatic triglyceride (TG) production → elevated plasma TG concentrations. To test this hypothesis and to gain insight into both the possible role of obesity in causing the above metabolic abnormalities and the potential benefit of weight reduction we studied the effects of weight loss on various aspects of carbohydrate and lipid metabolism in a group of 36 normal and hyperlipoproteinemic subjects. Only weak to absent correlations ($r = 0.03 - 0.46$) were noted between obesity and the metabolic variables measured. This points out that in our study group obesity cannot be the sole, or even the major, cause of these abnormalities in the first place. Further, we have observed marked decreases after weight reduction in fasting plasma TG (mean value: pre-weight reduction, 319 mg/100 ml; post-weight reduction, 180 mg/100 ml) and cholesterol (mean values: pre-weight reduction, 282 mg/100 ml; post-weight reduction, 223 mg/100 ml) levels, with a direct relationship between the magnitude of the fall in plasma lipid values and the height of the initial plasma TG level. We have also noted significant decreases after weight reduction in the insulin and glucose responses during the oral glucose tolerance test (37% decrease and 12% decrease, respectively). Insulin and glucose responses to liquid food before and after weight reduction were also measured and the overall post-weight reduction decrease in insulin response was 48% while the glucose response was relatively unchanged. In a subgroup of patients we studied both the degree of cellular insulin resistance and the rate of hepatic very low density (VLDL) TG production before and after weight reduction. These subjects demonstrated significant decreases after weight reduction in both degree of insulin resistance (33% decrease) and VLDL-TG production rates (40% decrease). Thus, weight reduction has lowered each of the antecedent variables (insulin resistance, hyperinsulinemia, and VLDL-TG production) that according to the above hypothesis lead to hypertriglyceridemia, and we believe the overall scheme is greatly strengthened. Furthermore, the consistent decreases in plasma TG and cholesterol levels seen in all subjects lead us to conclude that weight reduction is an important therapeutic modality for patients with endogenous hypertriglyceridemia.

INTRODUCTION

It has been suggested that obesity has an important causal role in the development of hyperglycemia (1), hyperlipemia (2, 3), hyperinsulinemia (4), and insulin resistance (5). However, considerable controversy still exists over the role of obesity in causing the above metabolic abnormalities (6–10), and the mechanisms involved remain quite unclear. Furthermore, although it it commonly accepted that weight loss by obese subjects ameliorates these abnormalities (11–12) there are surprisingly little data to support this widespread belief.

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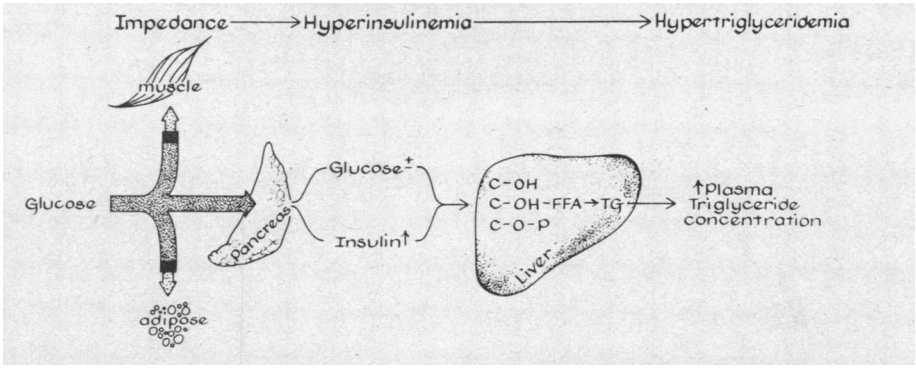

FIGURE 1 Schematic representation of a sequential hypothesis relating insulin resistance to hyperinsulinemia and subsequent hypertriglyceridemia.

Most of the reports to date have involved only a few patients (13–18), and have not examined a wide spectrum of variables (14, 15, 18, 19). Furthermore, even if weight loss does lead to a decrease in hyperglycemia, hyperlipemia, hyperinsulinemia, and insulin resistance, this does not necessarily mean that obesity was the sole cause of these metabolic abnormalities in the first place. For these reasons, and because hyperglycemia (20) and hyperlipemia (21, 22) have been proposed as independent risk factors for the development of coronary heart disease, it seemed important to evaluate the relationship between obesity and various aspects of carbohydrate and lipid metabolism in a large group of normal and hyperlipoproteinemic subjects with varying degrees of obesity; and then to study the effects of weight loss on these variables in the same group of patients.

Plasma triglyceride (TG)[1] concentration is one of the metabolic variables we have measured. To help explain the mechanism leading to hypertriglyceridemia, we have previously proposed a sequential hypothesis (Fig. 1) that states that tissue resistance to insulin-mediated glucose uptake is a common underlying finding in most patients with endogenous hypertriglyceridemia, and that in an effort to maintain glucose homeostasis, insulin-resistant subjects secrete increased amounts of insulin (23, 24). We have also suggested that this hyperinsulinemia may act upon the liver to accelerate very low density lipoprotein (VLDL) TG production rate, which in turn leads to endogenous hypertriglyceridemia (10, 24, 25). The term "endogenous hypertriglyceridemia" corresponds to the primary hyperlipoproteinemias recently defined as types IIb, III, and IV (26). A way to help validate a three-part sequential hypothesis such as this would be to perturb the system and measure the effects of this perturbation on each step of the sequence. If all the changes were in the predicted direction, then the hypothesis would be strengthened, whereas, if one observed a dissociation in the direction of the predicted changes, the argument would be weakened. To test our hypothesis in this manner, and to gain clinical insight into the possible beneficial effects of weight loss, we have studied the metabolic effects of weight reduction in 36 patients.

[1] *Abbreviations used in this paper:* SSPG, steady state plasma glucose levels (degree of insulin resistance); TG, triglyceride; VLDL, very low density lipoprotein.

METHODS

Subjects

36 subjects selected from Stanford's Nutrition and Metabolism Clinic underwent a mean weight loss of 10.9 kg (range 9.1–14.2 kg). The only criteria for selection was the subject's acquisition of more than 10 kg in body weight since age 20 and the subject's willingness to undertake a weight reduction program. Tables I and II list the clinical characteristics and metabolic data of our study group before and after weight reduction. None of our patients were massively obese and the degree of obesity of these patients is similar to the degree of moderate obesity commonly encountered by a physician. By weight history all of them had acquired the bulk of their excess poundage in adulthood. Percentage adiposity was determined according to the anthropometric technique of Steinkamp et al. (27). With this method the mean percentage adiposity of normal adults of this age group ±SD is 27%±7% for men and 31%±10% for women. The mean pre-weight reduction percent adiposity of our male subjects was 32.0% with a range of 23.5%–48.1% and the mean percent adiposity of our female subjects was 40.9% with a range of 36.5%–48.8%. Relative weight was determined by dividing a patient's weight by his "ideal weight" as determined according to the Metropolitan Life Tables. The mean pre-weight reduction relative weight of our study group was 1.21 with a range of 1.00–1.76. We do not wish to imply that a percent adiposity of 27% for men or 31% for women is "ideal": it is merely average, and we consider the "average" American adult to be somewhat overweight. Other than chemical diabetes, as defined by an abnormal oral glucose tolerance test without fasting hyperglycemia (28), no subject had any disease state or was ingesting any drug known to affect carbohydrate or lipid metabolism.

According to the lipoprotein classification system published by the World Health Organization (26), 4 of our patients were type IIa, 6 were type IIb, 3 were type III, 17 were type IV and 6 were normal. In this study, nor-

TABLE I

Clinical Characteristics and Metabolic Data in 36 Patients before Weight Reduction

Patient no.	Age	Sex	Body weight	Relative weight	Adiposity	Lipoprotein electrophoretic pattern	Glucose* response during OGTT	Insulin* response during OGTT	Fasting TG concentration	Fasting cholesterol concentration	VLDL-TG production rate	Insulin resistance SSPG level	Insulin response to formula
			kg		%		*area U*	*area U*	*mg/100 ml*	*mg/100 ml*	*mg/kg/h*	*mg/100 ml*	*area U*
1	33	M	91	1.17	25.31	IV	381	157	212	245	—	—	—
2	59	M	87.1	1.12	23.45	IV	414	267	306	—	11.90	—	—
3	53	M	118.9	1.57	48.10	IIb	587	376	228	254	—	—	—
4	51	M	96.3	1.20	40.30	IV	425	250	357	242	—	307	357
5	58	M	76	1.00	26.63	IV	496	250	279	324	—	—	—
6	50	F	75.7	1.36	40.85	III	356	391	906	408	—	—	—
7	26	F	70.4	1.06	36.47	N	542	223	88	203	10.30	210	174
8	36	F	81.5	1.31	42.40	IIb	399	260	268	342	—	—	—
9	27	M	82.3	1.15	24.14	IIb	424	299	159	274	11.60	—	—
10	39	M	100	1.36	28.30	III	522	426	862	571	—	—	—
11	25	M	90.6	1.31	31.88	IV	393	350	214	253	16.90	257	240
12	55	M	88.4	1.16	29.08	II	493	408	147	343	—	300	258
13	45	M	77.1	1.02	29.76	IIb	326	308	181	295	—	—	—
14	43	M	89.4	1.02	27.91	IV	464	341	204	220	—	—	—
15	61	M	106.8	1.18	39.47	IV	469	507	352	326	23.90	270	510
16	53	M	104	1.17	33.79	N	398	327	136	198	10.60	210	291
17	61	F	77.7	1.11	34.02	IIb	476	352	379	349	17.60	226	213
18	49	M	94.2	1.07	28.95	IIb	345	156	177	286	—	—	—
19	48	M	82.5	1.13	38.60	II	310	145	130	343	—	—	—
20	46	M	84.9	1.04	24.02	IV	361	156	308	278	—	—	—
21	41	M	79.4	1.09	28.19	IV	433	330	171	260	—	—	—
22	42	F	70.5	1.16	44.10	IV	517	574	582	231	—	—	—
23	58	M	78.2	1.09	30.30	IIb	361	189	254	276	—	—	—
24	54	M	94.4	1.25	29.68	IV	568	357	349	206	18.60	276	258
25	44	M	96.1	1.46	41.30	IV	414	672	563	251	16.00	—	—
26	45	F	85	1.35	41.90	IV	459	367	108	228	10.80	107	213
27	46	M	97.5	1.27	—	IV	345	487	479	269	20.70	—	—
28	48	M	115.6	1.30	34.20	IV	429	479	816	248	26.40	—	—
29	50	M	97.5	1.27	30.00	IV	583	303	625	—	—	—	—
30	25	M	87.0	1.20	—	III	382	687	326	429	—	—	—
31	24	M	125.7	1.76	39.80	N	420	364	92	210	—	304	—
32	41	M	86.5	1.07	26.14	IV	537	538	707	269	—	—	—
33	41	F	102.8	1.60	48.82	N	315	309	79	201	—	—	—
34	41	F	74	1.10	38.94	II	267	157	143	283	—	—	—
35	59	M	81.4	1.15	—	IV	410	183	175	242	—	137	—
36	69	M	82.5	1.11	33.61	N	606	193	134	231	9.64	—	—

* Area under the plasma response curve during the 3-h oral glucose tolerance test (COGTT).

TABLE II

Clinical Characteristics and Metabolic Data in 36 Patients after Weight Reduction

Patient no.	Body weight	Relative weight	Adiposity	Glucose* response during OGTT	Insulin* response during OGTT	Fasting TG concentration	Fasting cholesterol concentration	VLDL-TG production rate	Insulin resistance SSPG level	Insulin to response formula
	kg		*%*	*area U*	*area U*	*mg/100 ml*	*mg/100 ml*	*mg/kg/h*	*mg/100 ml*	*area U*
1	78.8	0.94	20.93	349	87	73	199	—	—	—
2	74.0	0.85	15.79	329	105	139	—	2.50	—	—
3	109.2	1.44	40.69	448	336	142	246	—	—	—
4	83.2	1.12	36.01	392	123	157	198	—	134	108
5	63.5	0.83	21.72	412	159	132	312	—	—	—
6	66.6	1.20	30.17	324	185	483	280	—	—	—
7	60.0	0.91	18.29	503	195	65	181	7.26	61	108
8	71.4	1.17	38.70	466	207	134	200	—	—	—
9	73.1	0.99	23.35	424	177	81	181	12.50	—	—
10	88.4	1.20	29.27	324	277	230	155	—	—	—
11	78.9	1.14	30.95	352	240	269	243	11.59	220	159
12	77.4	1.02	28.61	366	169	185	276	—	145	132
13	67.4	0.89	26.33	287	226	108	279	—	—	—
14	78.2	0.89	23.46	318	169	168	168	—	—	—
15	97.7	1.08	36.79	400	140	222	255	14.71	279	243
16	91.5	1.03	30.05	391	281	128	187	8.70	121	219
17	68.1	0.97	31.29	426	213	260	284	9.23	175	81
18	84.5	0.97	25.14	366	264	145	204	—	—	—
19	71.4	0.98	33.15	377	113	79	240	—	—	—
20	75.6	0.88	23.35	428	105	203	201	—	—	—
21	70.1	0.96	25.41	335	266	120	269	—	—	—
22	61.3	1.05	38.62	480	337	355	255	—	—	—
23	68.6	0.95	27.63	319	143	187	259	—	—	—
24	83.8	1.10	30.45	471	153	138	176	13.32	144	150
25	82.9	1.26	35.90	361	389	328	199	15.50	—	—
26	75.3	1.17	38.66	472	429	103	263	12.22	—	162
27	83.6	1.08	—	—	—	126	196	20.30	—	—
28	101.5	1.13	30.80	363	331	253	187	6.20	—	—
29	83.5	1.07	31.60	486	288	392	—	—	—	—
30	77.7	1.04	—	357	139	233	253	—	—	—
31	111.5	1.60	32.91	402	144	90	162	—	261	—
32	77.4	0.87	22.31	383	305	371	230	—	—	—
33	93.6	1.46	44.12	361	288	64	200	—	—	—
34	62.3	0.93	34.17	261	147	102	274	—	—	—
35	72.2	1.00	—	382	142	106	186	—	77	—
36	71.7	0.92	28.49	562	150	93	183	7.60	—	—

* Area under the plasma response curve during the 3-hr oral glucose tolerance test (OGTT).

mality was defined as a plasma TG level less than 150 mg/100 ml and a plasma cholesterol level less than 250 mg/100 ml, and a classification of Type III was confirmed by ultracentrifugation. Subjects were studied and managed either entirely on an outpatient basis, or on a combined outpatient and inpatient basis. The outpatient study is described first.

Experimental protocol

After a careful dietary history and collection of anthropometric measurements, 23 of the 36 subjects were placed on a solid food weight-maintaining diet designed to mimic the typical diet consumed in this country (29, 30) (approximately 15% protein, 43% carbohydrate, and 42% fat with a polyunsaturated: saturated ratio of 0.21). At the end of 1 wk of this weight maintenance period, an oral glucose tolerance test was performed by administering 40 g glucose/m^2 body surface area. Plasma glucose and insulin were determined at 0, 30, 60, 120, and 180 min. After an overnight fast, plasma TG and cholesterol were measured on at least two separate occasions during the 2nd wk of the weight maintenance period. Plasma lipoprotein electrophoresis was performed on one of these two samples. Once these data were collected, subjects were placed on a hypocaloric diet containing 600–1,600 kcal/day. The percentage by calories of carbohydrate, protein, and fat was not changed, only the total amounts consumed. Furthermore, the degree of physical activity was not appreciably changed in any of these patients. After approximately 11 kg of weight had been lost (the period of weight loss was quite variable: the range was from 2 to 10 mo, with a mean of 4.3 mo), each subject was placed again on his original weight-maintaining diet for 2 wk. During this 2-wk period no subject's weight changed by more than 3%, and during the last 10 days of this period no subject's weight changed by more than 1.5%. At the end of the 2nd wk, the anthropometric measurements, oral glucose tolerance test, fasting TG and cholesterol determinations (again, on at least two separate occasions), and plasma lipoprotein electrophoresis were repeated. This study design attempted to isolate weight loss as the only independent variable.

An additional 13 patients were studied in a similar

manner, except that the pre- and post-weight reduction studies were performed while the subjects were hospitalized in the metabolic ward setting of the Stanford General Clinical Research Center. Pre-weight reduction degree of obesity and amount of weight lost were comparable with the outpatient group. During the hospitalization, these subjects consumed a weight maintenance liquid formula diet containing 35 kcal/kg body weight/day. The caloric breakdown was: 43% carbohydrate, 15% protein, and 42% fat with a polyunsaturated: saturated ratio of 0.21. This diet was also designed to closely approximate the content of a diet typical for the United States (29, 30). The formula provided 251 mg cholesterol for every 1021 cal and was consumed daily in four equal feedings. Each feeding was ingested evenly and slowly over a 30-min period. Oral glucose tolerance test, fasting plasma TG and cholesterol measurements, and plasma lipoprotein electrophoresis were performed as was done in the outpatient subjects. Additional studies were performed on these inpatient subjects as follows:

Studies of glucose and insulin responses to formula. On two separate occasions during each hospitalization, plasma was sampled for insulin and glucose just before the 11 a.m. feeding, and again at 12, 1 and 2 p.m. The data are expressed as the mean values of these two studies for each subject.

VLDL-TG production rate studies. This was done according to a previously reported method (25, 31), which is briefly summarized as follows: [^{3}H]glycerol is injected intravenously and becomes incorporated into plasma VLDL-TG molecules. The specific activity decay curve of the endogenously labeled VLDL-TG is measured, and from this curve, the fractional loss rate of the labeled VLDL-TG is calculated. If one assumes plasma volume to be 4.5% of body weight, then the VLDL-TG pool size can be calculated according to the following formula: VLDL-TG pool size = 4.5% × kg body weight × VLDL-TG concentration. Finally, the product of the fractional loss rate and VLDL-TG pool size equals the VLDL-TG removal rate (mg/kg/h). Since the VLDL-TG concentration is in a steady state throughout the study, the VLDL-TG removal rate is equal to the VLDL-TG production rate (25, 31).

Estimate of insulin resistance (or impedance). The method for estimating this variable has been previously reported (23), and the insulin resistance measured by this technique should not be confused with the type of insulin resistance sometimes found in insulin-treated diabetics who develop excessive amounts of anti-insulin antibodies. For this reason we have proposed the term impedance to describe this type of insulin-resistant state and we will use these two terms interchangeably in this report. This study is performed by simultaneously infusing constant amounts of crystalline pork insulin (50 mU/min), glucose (6 mg/kg/min), epinephrine (6 μg/min), and propranolol (0.08 mg/min). The infusion is begun 5 min after a 5-mg loading dose of propranolol, and is constantly administered via a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) over a period of 150 min. Steady state plasma concentrations of insulin and glucose are achieved within 90 min after the start of the infusion, and we then measure these levels every 10 min for an additional 60 min. Insulin resistance is expressed as the mean of the seven steady state plasma glucose levels (SSPG). This approach is based upon the known ability of epinephrine and propranolol to suppress endogenous insulin secretion (32). Confirmation of this action under these particular experimental conditions has been obtained by finding no rise in plasma endogenous insulin levels during extreme hyperglycemia after an infusion of glucose, epinephrine, and propranolol (23). During this study, comparable steady state plasma levels are achieved in all subjects. (Mean steady state plasma insulin level, 102 μU/ml; coefficient of variation, 10%.) Thus, we are able to measure the ability of closely similar circulating levels of exogenous insulin to promote disposal of comparable glucose loads in a variety of subjects. If one assumes that endogenous glucose production is inhibited during this steady state period, then the glucose uptake rate should be equal to the glucose infusion rate. We have verified this assumption by directly measuring the irreversible glucose loss rate (23), and have found it to be identical to the rate of glucose infusion. Thus, since insulin concentration and glucose uptake (infusion rate) are the same for all subjects at the steady state, the height of the SSPG response is a direct reflection of a subject's overall efficiency of insulin-mediated glucose uptake. It should be pointed out that the degree of insulin resistance measured by this technique is a result of the combined efficiencies of glucose uptake of each tissue actively transporting glucose. Thus, this estimate does not provide information as to the relative degrees of insulin resistance of any particular tissues.

Analytical methods

Samples for plasma glucose were collected in potassium oxalate sodium fluoride tubes and measured by the Technicon AutoAnalyzer (Technicon Instruments Corp., Tarrytown, N. Y.), by the ferricyanide method of Hoffman (33). Plasma insulin was measured according to the double-antibody immunoprecipitation techniques of Hales and Randle (34). Cholesterol was determined according to the N-24 AutoAnalyzer method (Technicon Instrument Corp.) (35) on a Folch extract of plasma, and plasma TG was measured by to the chromatropic acid method of Carlson and Wadstrom (36) after acid hydrolysis with a dilute solution of H_2SO_4. Lipoprotein electrophoresis was performed according to the agarose gel method of Noble (37).

Statistical methods

T tests were performed by the two-tailed, paired Student's *t* test (38). Simple correlation coefficients were calculated by the product-moment correlation method (38). Partial correlation coefficients were calculated by the use of multiple regression analysis (38). For correlation analysis the insulin and glucose responses to both formula and oral glucose were expressed as total area under the response curve.

RESULTS

The correlation coefficient between relative weight and percent adiposity was 0.63 for men and 0.81 for women. While these correlations are obviously highly significant, the deviations from perfect correlations indicates that these two estimates are measuring somewhat different things. Consequently, in an effort to understand the relationships among obesity, insulin resistance, and plasma levels of insulin, glucose, TG, and cholesterol, we attempted to quantify, within the entire study group, the impact of obesity as estimated either by percent adiposity or relative weight on each of the metabolic

TABLE III

*Product-Moment Correlation Coefficients (r) between Percent Adiposity and Several Metabolic Variables in Men and Women before Weight Loss**

	Insulin resistance	Fasting insulin level	Insulin area during OGTT	Glucose area during OGTT	Fasting TG level	VLDL-TG production rate	Fasting cholesterol level
Men	0.36 (7)	0.39 (25)‡	0.19 (25)	0.10 (25)	−0.03 (25)	0.43 (9)	−0.17 (23)
Women	—	−0.03 (8)	0.30 (8)	−0.36 (8)	−0.04 (8)	—	−0.36 (8)
	Product-moment r between relative weight and several metabolic variables in the entire group before weight loss						
	0.46 (10)	0.10 (36)	0.33 (36)‡	0.03 (36)	0.12 (36)	0.34 (13)	−0.05 (34)

OGTT, oral glucose tolerance test.

* After each correlation coefficient is the number of observations in parentheses.

‡ $P < 0.05$.

variables measured. These data are shown in Table III. The subjects were divided by sex, and the preweight reduction product-moment correlation coefficients between percent adiposity and the above variables were calculated (Table III, top). These correlations ranged from 0.03 to 0.43. In addition, by using multiple regression analysis, the partial correlation coefficient was calculated between percent adiposity and each variable while holding the effect of all the other variables constant. None of the partial correlation coefficients exceeded 0.22. Therefore, percent adiposity never accounted for more than 18% of the variation in any variable. When a similar analysis was performed with relative weight as the measure of obesity essentially identical relationships were obtained (Table III, bottom). The product-moment correlation coefficients between relative weight and the various metabolic variables ranged from 0.03 to 0.46, and none of the partial correlation coefficients between relative weight and any of the metabolic variables exceeded 0.25. Thus significant correlations did not exist in most instances and in the remaining instances only modest correlations were present. This indicates that while obesity, estimated as either percent adiposity or relative weight, has a modest influence on some of these variables it cannot be implicated as the sole determinant of any of them.

Table IV presents the data for the cross-correlations among the metabolic variables themselves in the entire group. As predicted by our hypothesis (Fig. 1) a highly significant correlation is noted between fasting TG level and both fasting insulin level and insulin response.

Next, we looked at the effects of weight loss on the metabolic variables in question. Fig. 2 summarizes the effects of weight reduction on plasma TG and cholesterol levels. The mean cholesterol and TG levels for each patient were determined before and after weight loss from a minimum of two samples at each stage, and

TABLE IV

Product-Moment Correlation Coefficients among the Indicated Metabolic Variables in the Entire Group of Subjects before Weight Reduction

	Fasting insulin level	Insulin area during OGTT	Glucose area during OGTT	Fasting TG level
Fasting insulin level	—	—	—	—
Insulin area during OGTT	0.50 (36)‡	—	—	—
Glucose area during OGTT	−0.10 (36)	0.23 (36)	—	—
Fasting TG level	0.43 (36)*	0.52 (36)§	0.21 (36)	—
Fasting cholesterol level	−0.08 (34)	0.20 (34)	−0.06 (34)	0.48 (34)‡

OGTT, oral glucose tolerance test.

* $P < 0.01$.

‡ $P < 0.005$.

§ $P < 0.001$.

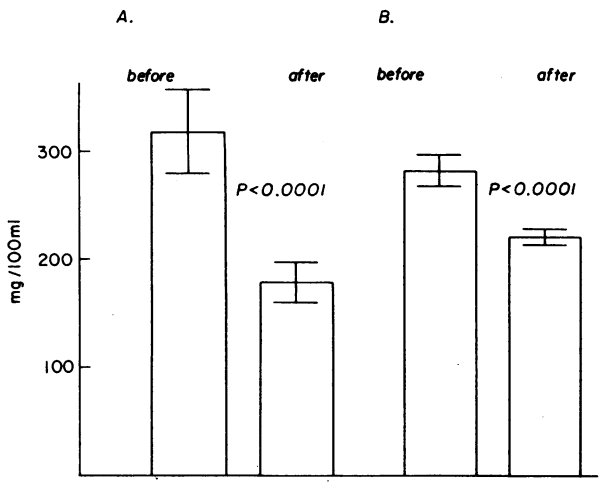

FIGURE 2 Plasma TG (A) and cholesterol (B) concentrations in 36 patients before and after weight reduction. Data are given as means±SEM.

the data are expressed as the means for the entire group. The decreases in both plasma TG (from 319 mg/100 ml to 180 mg/100 ml) and plasma cholesterol levels (from 282 mg/100 ml to 223 mg/100 ml) are both considerable in magnitude and highly significant ($P < 0.0001$). Furthermore, the TG levels of 34 out of 36 subjects and the cholesterol levels of 33 out of 36 subjects fell after weight loss.

To illustrate the magnitude of the post-weight reduction fall in plasma TG and cholesterol in relation to the pre-weight reduction plasma TG level, the patients were divided into quartiles on the basis of their pre-weight reduction plasma TG concentrations (Table V). The average amount of weight loss was the same in all four groups. Going from the lowest to highest quartile the mean decreases in plasma TG level after weight loss were 19 mg/100 ml, 43 mg/100 ml, 140 mg/100 ml, and 347 mg/100 ml. The mean post-weight reduction fall in cholesterol levels showed the same trend with decreases of 24 mg/100 ml, 46 mg/100 ml, 71 mg/100 ml, and 101 mg/100 ml, going from the lowest to highest pre-weight reduction TG quartiles. Thus, the greater the pre-weight reduction plasma TG level, the greater the decrease in plasma TG and cholesterol concentration in both percentage and absolute terms.

The mean plasma insulin and glucose responses during the oral glucose tolerance test before and after weight reduction are shown in Fig. 3. The mean insulin values after weight loss are lower at every time interval (3B) and these differences are statistically significant at 30, 60, 120, and 180 min (an overall 37% decrease in area under the curve). Although not as impressive as the lowering of insulin responses after weight loss, the mean glucose responses are also lower after weight loss (3A), and these differences reach statistical significance at each time point (an overall 12% decrease in area under the curve). Thus, the insulin decrement was approximately three times the glucose decrement. After weight loss, the insulin response to oral glucose decreased in 34 out of 36 subjects and glucose response decreased in 31 out of 36 subjects.

Additionally, the plasma glucose and insulin responses to the 11 a.m. liquid food ingestion were studied in nine inpatient subjects before and after weight loss. These data are presented in Fig. 4, and it can be seen that a post-weight reduction fall in insulin response is quite evident with significant differences noted at each time point (4B). Furthermore, the insulin response to formula

TABLE V

Decrease in plasma TG and cholesterol levels in subjects divided into quartiles

Plasma TG range per quartile	Mean±SE plasma TG levels*				Mean±SE plasma cholesterol levels			
	Before	After	Absolute decrease	Percentage decrease	Before	After	Absolute decrease	Percentage decrease
1st quartile (71–147)	115±8	96±9	19	17	239±16	215±13	24	10
2nd quartile (159–228)	182±8	139±20	43	24	269±12	223±15	46	17
3rd quartile (254–357)	312±13	172±13	140	45	303±24	232±16	71	23
4th quartile	658±60	311±35	347	53	324±35	223±17	101	31

* The 36 subjects are divided into quartiles (9 in each quartile) on the basis of their plasma TG concentrations before weight reduction.
Of the nine subjects in the 1st quartile, six were classified as normal, and three had Type IIa hyperlipoproteinemia.
Of the nine subjects in the 2nd quartile, one was classified as Type IIa, three as Type IIb, and five as Type IV,
Of the nine subjects in the 3rd quartile, three were classified as Type IIb, one as Type III, and five as Type IV.
Of the nine subjects in the 4th quartile, two were classified as Type III and seven as Type IV.

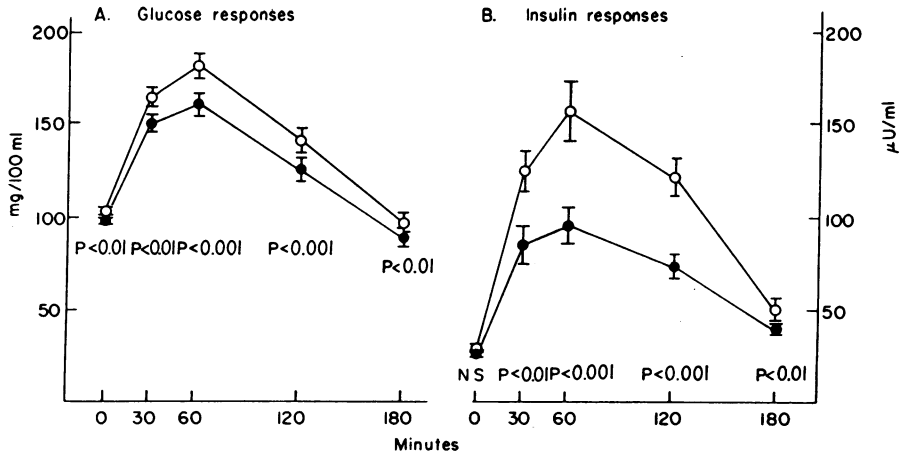

FIGURE 3 Glucose (A) and insulin (B) responses during the oral glucose tolerance test in 36 patients before (○—○) and after (●—●) weight reduction. Data are given as means ±SEM.

decreased in all 9 subjects for an overall mean decrease in area under the curve of 48%. On the other hand, the glucose response to formula was only slightly lower after weight loss (4A) with the only significant difference being at the 12 noon time point (an overall 3% decrease in area under the curve). Thus, in response to formula the post-weight reduction insulin decrement was 16 times the glucose decrement. Comparing Figs. 3 and 4 reveals the post-weight reduction decrement in insulin response to formula to be appreciably greater than the post-weight reduction decrement in insulin response during the oral glucose tolerance test. On the other hand, the post-weight reduction decrement in glucose response to formula is considerably less than the post-weight reduction decrement seen during the oral glucose tolerance test.

Clearly, then, weight reduction reduces each of the metabolic factors studied in almost all subjects. In order to identify the mechanisms which account for these observations, we performed more detailed metabolic studies on the inpatient subgroup. First of all, to examine the mechanism(s) underlying the post-glucose or post-food decrease in insulin and glucose responses after weight loss, the efficiency of insulin-mediated glucose uptake was measured before and after weight reduction in 10 subjects. The degree of insulin resistance (impedance) is expressed as the mean of the SSPG values and the effects of weight reduction on this variable can be seen in Fig. 5A. The mean±SE SSPG before weight loss was 241 mg/100 ml±17, while the mean±SE SSPG after weight loss was 161 mg/100 ml±23. The difference between these values is statistically significant at the $P < 0.001$ level. Furthermore, it can be seen that the degree of insulin resistance decreased in 9 out of 10

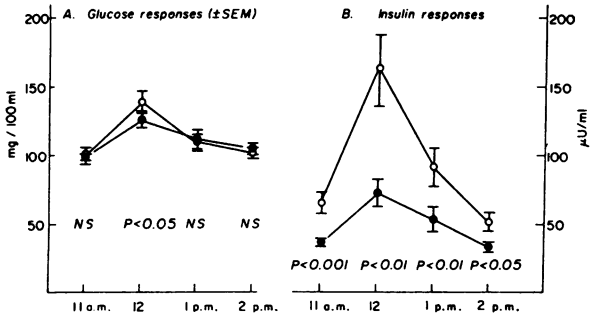

FIGURE 4 Glucose (A) and insulin (B) responses after the 11 a.m. formula feeding in nine inpatients before (○—○) and after (●—●) weight reduction. Data are given as means±SEM.

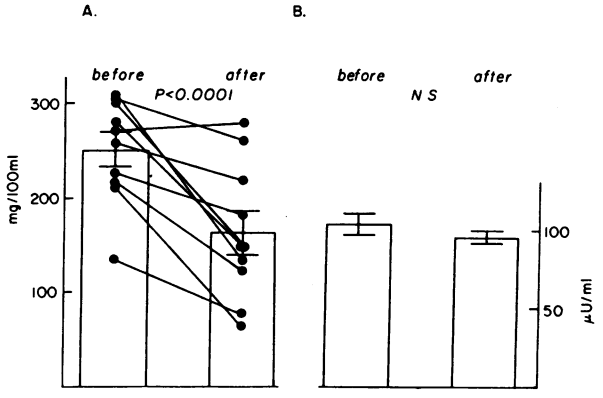

FIGURE 5 SSPG (degree of insulin resistance) level during the infusion study in 10 inpatients before and after weight reduction. The lines connect each patient's before and after value (A). Steady state plasma insulin values before and after weight reduction are shown in B. All data are given as means±SEM.

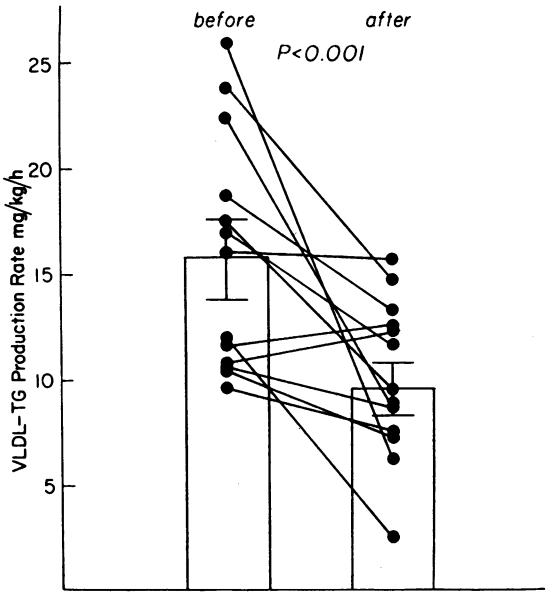

FIGURE 6 VLDL-TG production rates in 13 patients before and after weight reduction. The lines connect each patient's before and after value. Data are given as means±SEM.

subjects after weight loss. Fig. 5B compares the mean steady state plasma insulin levels during these infusion studies for the group before and after weight loss. No significant differences exist between these two mean values, and thus changes in SSPG levels cannot be attributed to changes in concomitant steady state plasma insulin values. According to our previously outlined sequential hypothesis, the decreases in glucose and insulin responses to oral glucose that we have shown in the larger group of 36 patients can be attributed to the decreases in degree of insulin resistance which we have demonstrated in the inpatient studies.

In order to further delineate the mechanism(s) responsible for the fall in plasma TG concentrations after weight loss, VLDL-TG production rates were determined in 13 subjects before and after weight reduction. The results of these studies are displayed in Fig. 6. VLDL-TG production rates decreased in 11 out of 13 subjects after weight loss, resulting in a mean VLDL-TG production rate before weight loss of 15.9±1.9 mg/kg/h and a mean production rate afterward of 9.6±1.3 mg/kg/h. These differences are significant at the $P < 0.001$ level.

Table VI presents the correlation coefficients among the metabolic variables measured in the inpatient subgroup. A significant correlation exists between degree

TABLE VI

Product-Moment Correlation Coefficients between Degree of Insulin Resistance and Insulin Response, Insulin Response and VLDL-TG Production Rate, and VLDL-TG Production Rate and Fasting TG Concentration

	Insulin response during OGTT	Fasting TG concentration
Degree of insulin resistance	0.57 $P < 0.05$	—
VLDL-TG Production rate	0.65 $P < 0.005$	0.82 $P < 0.001$

OGTT, and glucose tolerance test.

TABLE VII

*Comparison of Effects of Weight Reduction in the Five Most Obese and the Five Least Obese Men**

	Weight	Adiposity	Insulin response‡	Glucose response‡	Plasma TG level§	Plasma cholesterol§
	kg	%				
Most obese						
Before	108.70	41.94	434	462	319	257
After	96.9	36.46	226	401	188	212
Difference	11.8	5.48	208	61	131	45
Decrease, %	11	13	48	13	41	18
Least obese						
Before	86.36	24.61	283	425	338	266
After	75.78	21.14	156	384	173	203
Difference	10.58	3.47	127	41	165	63
Decrease, %	12	14	45	10	48	24

* All numbers represent the mean of each observation in five subjects.
‡ Total area under the plasma response curve during the oral glucose tolerance test in each subject.
§ Mean of at least two fasting determinations in each subject.

of insulin resistance and insulin response to oral glucose ($r = 0.57$). Furthermore, insulin response is highly correlated to VLDL-TG production rate ($r = 0.65$) and VLDL-TG production rate is closely correlated to fasting TG concentration ($r = 0.82$). Thus, these correlations offer support for each of the direct individual steps of the hypothesis outlined in Fig. 1. The correlation coefficient between insulin resistance and VLDL-TG production rate is $r = 0.72$, $P < 0.05$ (not shown in Table VI). Although this finding further supports our hypothesis, both of these measurements were made on only seven subjects; consequently due to the small number of observations this correlation just reaches statistical significance and we are reluctant to stress this relationship.

To emphasize the dramatic effects of weight loss, we summarized (Table VII) the data on the glucose responses, insulin responses, and fasting plasma TG and cholesterol levels in the five most obese and five least obese males as determined by their preweight reduction percent adiposity. It can be seen that comparable amounts of weight loss resulted in similar decrements in these variables in the two groups despite a markedly different pre-weight reduction degree of obesity. It is also clear that weight reduction in the five less obese patients had essentially returned them to normal weight, while the five most obese still remain quite obese. These data point out that return to normal weight is not essential in order to realize the benefits of weight reduction.

DISCUSSION

In agreement with other workers (6, 8, 39–42) we have demonstrated (Table III) that the relationships between obesity and insulin resistance, plasma insulin responses, plasma glucose responses, and plasma TG levels are relatively modest if present at all. On the other hand, several investigators have reported significant relationships between obesity and the above variables (1, 2, 4, 5). We routinely estimate obesity by calculating the percent adiposity according to the anthropometric technique (*27*), while most of the above authors use relative weight. However, using relative weight as the estimate of obesity did not alter any of our findings (Table III) and thus, the solution to this apparent disagreement between our results and those of others is not completely clear. One answer might be that we have studied patients who are minimally to modestly obese, whereas other workers (1, 2, 4, 5) have tended to study patients who are much more obese. Furthermore, perhaps another possibility can be found in the fact that due to a high degree of biologic variability, significant but modest relationships between two variables can be masked by merely seeking correlations between these variables within a given population sample, especially if the sample is small. This clearly suggests that obesity is not the major or sole cause of any of these metabolic abnormalities, but rather is one of a variety of known and unknown factors that affect the above variables, i.e., obesity influences but by no means determines a patient's plasma TG level.

We have confirmed the widespread clinical impression that weight reduction is effective in controlling some of the known cardiovascular risk factors related to lipid and carbohydrate metabolism. Specifically, we have shown significant reduction of impressive magnitude in plasma TG and cholesterol concentrations, and a striking direct relationship between the height of the initial plasma TG level and the magnitude of the post-weight reduction decrements in plasma TG and cholesterol concentrations in both percentage and absolute terms. Furthermore, we have observed significant post-weight reduction decreases in both glucose and insulin responses to oral glucose, with the decreases in insulin response being considerably greater. All of these changes occurred after modest amounts of weight loss. The data were collected during states of weight stability before and after the weight reduction periods, so that any metabolic changes we detected could reasonably be attributed to weight loss alone. The post-weight reduction diet was identical in proportion of food constituents to the preweight reduction diet and differed only in total caloric content, since fewer total calories were necessary to maintain isocaloric conditions at the reduced body weight. It should be noted that during the period of hypocaloric intake the percentage of calories derived from carbohydrate was unchanged. Thus, carbohydrate restriction was proportionate to total caloric restriction, and consequently the degree of carbohydrate restriction varied only inasmuch as total caloric restriction varied. This design does not permit conclusions as to the specific metabolic effects of carbohydrate restriction alone, but we attempted to avoid any possible effects of carbohydrate restriction per se by collecting the post-weight reduction data after the 2 wk stabilization period.

Since the glucose challenges were administered on the basis of body size it should be pointed out that in no case was the post-weight reduction administered glucose load less than 90% of the original challenge. For example, a decrease in weight of 11 kg (the mean weight loss of our group) would result in only a 4 g decrease in glucose load during the oral glucose tolerance test (i.e., a 5′10″ 200-lbs subject receives 84 g of glucose while a 5′10″ 177-lbs subject receives 80 g of glucose). Thus the striking post-weight reduction decreases in glucose and insulin responses we observed cannot be attributed to the minor decreases in glucose load administered.

The decreases in plasma cholesterol concentrations that we have shown to accompany weight reduction dif-

fer from the results published by Wilson and Lees (18). These workers reported that weight reduction in six patients (one with type III and five with type IV hyperlipoproteinemia) resulted in no change in total plasma cholesterol, and in fact Wilson and Lees found an increase in the high and low density lipoprotein fractions of plasma. We have observed a highly significant 21% fall in total plasma cholesterol after weight loss, a clear difference from their results. Furthermore, if one assumes a 5:1 ratio between TG and cholesterol in the $S_f > 20$ lipoproteins (43) then 20% of the mean post-weight reduction total plasma TG decrement would give a reasonable estimate of the cholesterol decrement attributable to decreases in plasma VLDL lipoproteins (i.e., 0.20×139 mg/100 ml $= 28$ mg/100 ml). However, the mean post-weight reduction drop in total cholesterol was 59 mg/100 ml, and thus it is unlikely that this fall can be accounted for solely by the fall in $S_f > 20$ lipoproteins. This strongly suggests that the post-weight reduction decrease in cholesterol also occurred in one or more of the other lipoprotein classes. We are not sure how to reconcile our results with those of Wilson and Lees, but perhaps the answer may be found in the fact that they studied a relatively small number of patients and did not collect the post-weight reduction data during a period of weight stability. Thus, at the time of the post-weight reduction studies, it is possible that their patients were in a state of negative caloric balance, and this injects an additional variable that might have an important effect on plasma lipoprotein dynamics. For these reasons, and because of the impressive decreases in plasma TG concentrations we observed in response to modest amounts of weight loss we believe it is reasonable to consider weight reduction as an appropriate therapeutic measure in patients with endogenous hypertriglyceridemia.

We have previously proposed an hypothesis to help explain one of the mechanisms causing endogenous hypertriglyceridemia (primary Types IIb, III, and IV) in man. We have suggested that a basic underlying abnormality is impedance or resistance to insulin-mediated glucose uptake at the cellular level (23). It was our postulate that in order to maintain glucose homeostasis, insulin-resistant individuals secrete increased amounts of insulin that accelerate the hepatic VLDL-TG production rate, which in turn leads to hypertriglyceridemia (10, 24, 25). The significant correlations noted in this study between degree of insulin resistance and insulin response, insulin response and VLDL-TG production rate, and VLDL-TG production rate and fasting TG concentration in the inpatient subgroup, and between group support each step of this scheme (Fig. 1). To help confirm this sequential hypothesis, we have turned insulin response and TG concentration in the entire to a principle often used to establish causal relationships in complex multivariable systems. We have perturbed the system, thus allowing greater insight than is allowed in static situations. Also, by focusing on intraindividual comparisons this study design avoids the confounding effect of excessive interindividual variation when seeking relationships between biologic variables. After the perturbation of weight loss, we observed decreases in both plasma TG concentration and the glucose and insulin responses to oral glucose. Our inpatient studies were designed to uncover the mechanisms behind these changes, and these inpatient studies revealed marked decreases in both degree of insulin resistance and VLDL-TG production rates after weight loss. According to the sequence outlined in Fig. 1, the decrease in degree of insulin resistance leads to decreases in insulin response to both oral glucose and food, and this lowering of plasma insulin levels results in a lowering of the rate of hepatic VLDL-TG production with a subsequent decrease in plasma TG concentration. Furthermore, we found a marked post-weight reduction lowering of insulin response to liquid food containing protein, carbohydrate, and fat in the face of no appreciable fall in glucose response to liquid food. This observation provides evidence that post-weight reduction decreases in insulin response, but not necessarily glucose response, can be expected after food ingestion in the free-living state. This finding, coupled with the marked fall in plasma TG concentration after weight loss, further underscores the important role of an individual's daily postprandial plasma insulin levels in regulating TG metabolism. While these findings are simply associations, and by themselves do not prove causality, we believe that since weight reduction lowered all three of the supposed antecedent variables, which according to our hypothesis, lead to increased plasma TG concentration (i.e., insulin resistance, plasma insulin concentration, and VLDL-TG production rate) the overall validity of the hypothesis is strengthened. We believe this hypothesis applies to the great majority of patients with endogenous hypertriglyceridemia. However, it should be pointed out that increased insulin levels are not present in all cases of hypertriglyceridemia. For example, many ketosis-prone diabetic patients with severe insulin deficiency develop increased TG levels, which obviously cannot be related to hyperinsulinemia.

Lastly, one may speculate as to why an average weight loss of only 11 kg leads to the rather sizable metabolic changes we have observed. In a study such as ours, which compares each individual to himself, the effects of excessive interindividual biologic variability tend to dampen out. This gives greater leverage to the variable allowed to change (in this study weight alone) and its effects are easier to detect. Thus, we believe that obesity

is one of a variety of factors that influence the metabolic variables measured, and that this influence is amplified by our study design. The mechanisms by which weight loss initiates the changes we have observed remain unclear. Acquired weight gain has been associated with enlarged adipocytes, and Salans, Knittle, and Hirsch (44) have shown enlarged adipocytes to be insulin-resistant. One might reason then that post-weight reduction decreases in insulin and glucose responses are simply due to the decrease in mass of insulin-resistant adipose tissue. However, Bjorntorp, Krotkiewski, Larsson, and Solmo-Szucs, and Bjorntorp, Berchtold, Holm, and Larsson have pointed out that adipose tissue appears to account for less than 5% of an individual's total glucose consumption (45, 46), and thus, modest changes in the amount of adipose tissue present are not likely to appreciably affect the body's overall insulin and glucose economy. It is obvious, then, that further information is needed before a mechanism can be suggested whereby modest decreases in weight can initiate profound changes in the metabolic sequence we have described.

Whatever the mechanism, these studies clearly demonstrate the potent beneficial effects of modest amounts of weight reduction in patients with varying degrees of obesity on some of the known metabolic cardiovascular risk factors.

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