Metabolic Effects of Weight Loss in Obese Subjects

Changes in Plasma Substrate Levels, Insulin and Growth Hormone Responses

R. K. Kalkhoff, M.D., H. J. Kim, M.D., J. Cerletty, M.D., and C. A. Ferrou, M.D., Milwaukee

SUMMARY

Oral glucose tolerance and intravenous tolbutamide, glucagon and insulin tolerance were assessed in six obese patients before and after an average weight loss of eighty-five pounds and a reduction from 83 to 27 per cent above ideal body weight. Results were compared to ten nonobese subjects of similar age.

Before treatment fasting plasma glucose, free fatty acids and immunoreactive insulin exceeded normal levels. Total plasma alpha-amino acid nitrogen levels were unaffected by obesity. Post-challenge insulin responses during the first three tolerance tests were two to four-fold above control responses, and increments of immunoreactive growth hormone during insulin tolerance were subnormal in the obese. After weight reduction only minor differences in mean values existed between obese and control groups.

These findings indicate that disturbances in fasting plasma substrate levels as well as plasma insulin and growth hormone responses in obese individuals are reversible after substantial weight reduction. DIABETES *20*:83-91, February, 1971.

Over thirty years ago Newburgh and Conn reported that middle-aged obese patients frequently have delayed utilization of carbohydrate and impaired glucose tolerance tests. Reversal of weight gain corrected the metabolic defect in more than 90 per cent of instances.[1] Subsequently, a number of investigators have reported that greatly increased plasma immunoreactive insulin responses to glucose, tolbutamide and glucagon are observed in these patients which suggests that insulin antagonism is primarily responsible for diabetogenic stress among the overweight.[2-5] Additional studies also have revealed that elevations of plasma immunoreactive growth hormone in response to appropriate stimuli are blunted in the obese subject.[6-8]

In the present investigation, six obese patients were evaluated before and after weight loss to determine if these two hormonal disturbances are acquired and reversible or persistent regardless of body weight. Effects of weight reduction on fasting plasma substrate levels were examined also.

METHODS

More than one-hundred patients currently are being followed in cooperative obesity research and treatment programs in the Clinical Research Center of Milwaukee County General Hospital and in Deaconess Hospital. From this population three men and three women were selected for the present investigation. Each had achieved substantial weight loss during a period of supervised meal planning and follow-up visits ranging from ten to eighteen months. Female patients were given 1000 calorie diets; obese men were placed on 1200 to 1400 calorie regimens. Carbohydrate content varied between 20 and 40 per cent of total daily calorie intake.

Before treatment, patients were hospitalized and placed on 300 gram carbohydrate, 2300 calorie diets. Weights remained stable throughout an eight to ten day period. After Day 3, standard 100 gram oral glucose, 1 gm. intravenous tolbutamide, 1 mg. intravenous glucagon and intravenous insulin tolerance tests were performed after overnight ten-hour fasts on successive days. Tolbutamide and glucagon were infused during a one minute period and Regular insulin was given rapidly intravenously (0.1 unit/kg. body weight). All intravenous tests were timed from the beginning of injection. After weight loss the patients were rehospitalized. The same 2300 calorie, 300 gram carbohydrate diets

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From the Metabolism Division, Department of Medicine, Marquette School of Medicine, the Clinical Research Center, Milwaukee County General Hospital, and Deaconess Hospital, Milwaukee, Wisconsin.

TABLE 1

Ages and weights of control and obese subjects

Group	Age years	Weight pounds	Per cent above IBW*	Weight loss pounds
A. Control				
mean	48 ± 3†	153 ± 9	1 ± 2	—
B. Obese				
1	57 M‡	364 (217)§	123 (33)	147
2	47 F	276 (200)	112 (54)	76
3	33 M	274 (207)	84 (39)	67
4	59 F	234 (186)	64 (30)	48
5	30 M	293 (182)	70 (6)	101
6	46 F	210 (146)	43 (0)	64
mean	45 ± 5†	275 ± 22 (190 ± 10)	83 ± 12 (27 ± 8)	85 ± 14

*IBW: Ideal body weight (Metropolitan Life Insurance Tables, 1959).
†Values are mean ± standard error of the mean.
‡M and F: male or female subjects.
§Numbers in parentheses indicate values after weight loss.

were instituted. After the fifth day, tolerance tests were repeated in succession as before. Patients 1-4 (table 1) who did not achieve ideal body weight were restudied after weight remained stable for a period of eight weeks. Patients 5 and 6 were evaluated a second time within two weeks of achieving their goals.

Similar studies were performed on five male and five female nonobese, age-matched control subjects after at

TABLE 2

Fasting substrate and hormone concentrations in control and obese subjects

Group	Glucose mg./100 ml.	Free fatty acids μEq./L.	Alpha-amino acid nitrogen mg./100 ml.	Insulin μU./ml.	Growth hormone mμg./ml.
A. Control					
mean	81 ± 1	484 ± 18	5.1 ± .2	8 ± 1	2.1 ± .5
B. Obese					
1	98 (89)	593 (539)	5.5 (5.6)	28 (21)	1.3 (1.0)
2	88 (84)	647 (540)	5.7 (4.7)	38 (26)	1.1 (3.0)
3	87 (84)	540 (437)	4.2 (5.6)	30 (21)	1.2 (1.5)
4	93 (84)	568 (498)	5.4 (4.8)	20 (14)	1.9 (4.3)
5	90 (86)	597 (563)	5.6 (5.7)	19 (10)	1.2 (1.5)
6	84 (80)	653 (374)	4.6 (4.8)	14 (4)	1.2 (1.8)
mean	90 ± 2 (85 ± 1)	599 ± 18 (492 ± 30)	5.1 ± .3 (5.2 ± .2)	25 ± 4 (16 ± 3)	1.3 ± .1 (2.2 ± .5)
p value *	<.005	<.005	NS	<.001	NS
p value †	<.005	<.05	NS	<.001	NS
p value ‡	NS	NS	NS	<.025	NS

Each individual value is the average of fasting determinations performed on three separate days. Values are mean ± S.E.M. Parentheses indicate levels after weight reduction.
*Significance of the difference between mean values before and after weight loss within the obese group.
†, ‡Significance of the difference between mean values of the control and obese groups before (†) and after (‡) weight reduction.

least three days of a similar 300 gram carbohydrate diet. Tests were done on an out-patient basis after overnight ten-hour fasts with the exception of the insulin tolerance test which was performed after overnight hospital confinement. In both obese and control groups, tolerance tests were begun after one hour of absolute bed rest. All patients were in good health, were receiving no medications other than vitamins and had negative family histories of diabetes mellitus.

Blood samples were obtained by forearm veni-puncture, placed in heparinized tubes on ice, centrifuged at 4° C., and plasma samples were frozen until analyses were performed in duplicate. Plasma glucose was determined by an automated glucose oxidase procedure.[9] Plasma free fatty acids, alpha-amino acid nitrogen, immunoreactive plasma insulin and growth hormone were measured by technics previously described.[10-13] All plasma samples obtained from a patient before and after treatment were analyzed on the same day in a single procedure together with specimens obtained from at least one control subject.

Total plasma insulin responses are defined as the area circumscribed by the total plasma insulin response curve above fasting levels during a given tolerance test. This value was calculated by planimetric measurements of individual curves drawn to the same scale and expressed in arbitrary units.

RESULTS

Patient weights: After several months of a planned reducing regimen, the mean body weight of the obese group fell from 275 to 190 pounds and the degree of obesity was decreased from a mean of 83 per cent to 27 per cent above ideal body weight (table 1).

Effects of weight loss on fasting plasma constituents: Fasting plasma levels of glucose, free fatty acids (FFA) and insulin were significantly higher in the obese group before weight loss than corresponding concentrations in the control subjects (table 2). After weight loss insulin levels, though lower, were still significantly above control

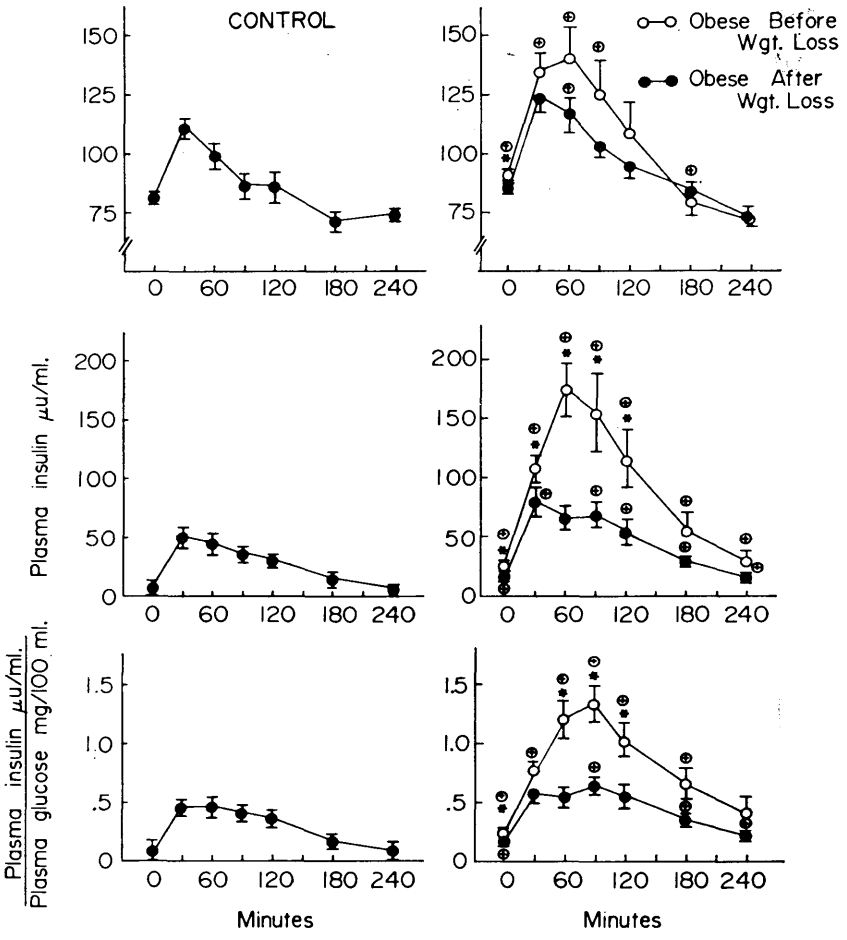

FIG. 1.

Plasma glucose and insulin responses and insulin-glucose (I/G) concentration ratios in six obese patients before and after weight reduction and in ten nonobese control patients. Values here and in subsequent figures are mean ± S.E.M. Asterisk (*): significance of differences between corresponding means in the obese group before and after treatment by paired data analysis, $p < .05$. Plus sign (+): significance of differences between corresponding means of obese and control subjects by unpaired data analysis, $p < .05$.

values, but plasma glucose and FFA concentrations were not different from the normal group. Fasting plasma alpha-amino acid nitrogen was unchanged by weight loss and was not different from normal concentrations. Fasting plasma growth hormone levels tended to rise following weight reduction but were not different statistically from control levels before or after treatment.

Influence of weight reduction on plasma glucose and insulin responses to glucose, tolbutamide and glucagon administration: Before treatment obese patients had significantly higher glucose levels during the initial ninety minutes of oral glucose tolerance than did the control group (figure 1). Both individual plasma insulin levels and corresponding insulin-glucose (I/G) concentration ratios were higher than control values throughout the procedure, indicating that insulin responses relative to a given glucose level were accentuated in the obese group.

After weight loss carbohydrate tolerance improved, and only sixty and one-hundred and eighty minute glucose values remained above control levels (figure 1). There was a significant decrease in plasma insulin concentrations and I/G ratios during the first 120 minutes of glucose tolerance after weight loss, but values still remained significantly higher than normal at most time intervals.

In the obese group there was over a three-fold increase in total plasma insulin response above control values during oral glucose tolerance tests (figure 4). After weight loss the magnitude of hormonal response decreased significantly from pretreatment values, but still remained above the control group's response.

Glucose responses during tolbutamide tolerance tests were impaired relative to control values before treatment (figure 2). The fall in plasma glucose was sluggish and nadirs were not reached until sixty minutes. This occurred despite insulin concentrations that were considerably higher than control levels (figure 2), and total plasma insulin responses that were two to three-fold greater than normal (figure 4). After weight loss glucose responses returned to normal patterns in association with plasma insulin levels (figure 2) and total plasma insulin responses (figure 4) that were similar in magnitude to the control group.

During glucagon tolerance tests, weight loss effected reductions of plasma glucose at zero and sixty minutes, but the curves generally were similar to control subjects before and after treatment (figure 3). Nevertheless, glucagon administration to the obese group before weight reduction augmented plasma insulin levels to a significantly greater degree than in control patients, and the total insulin response was higher than normal (figure 4). All individual insulin concentrations were

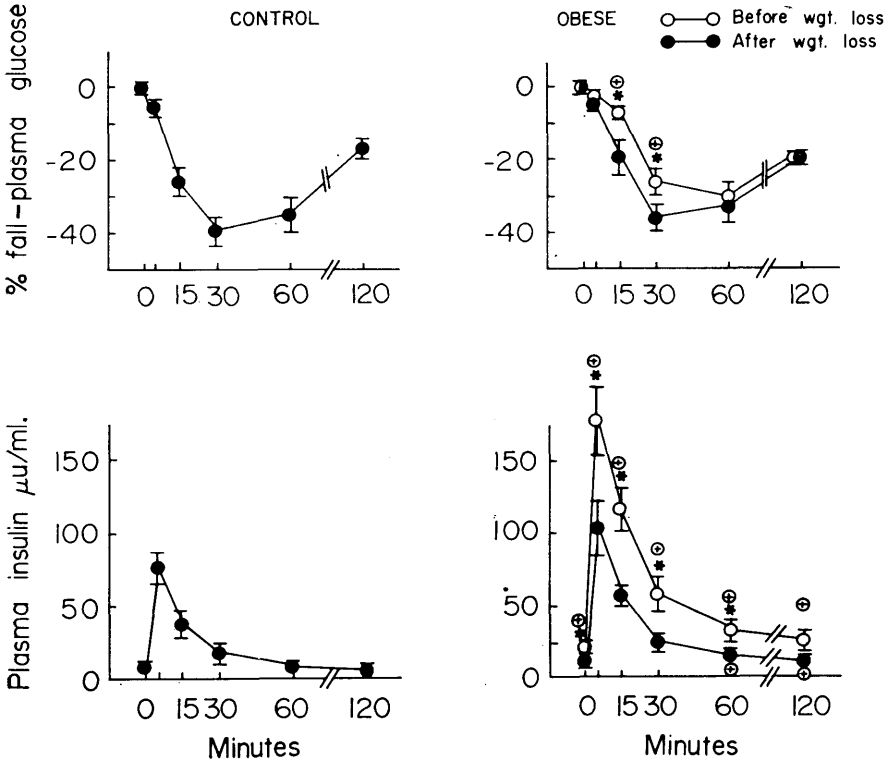

FIG. 2.

Plasma glucose and insulin responses during tolbutamide tolerance tests in six obese and ten control patients. Asterisks (*) and plus signs (+) are explained in figure 1.

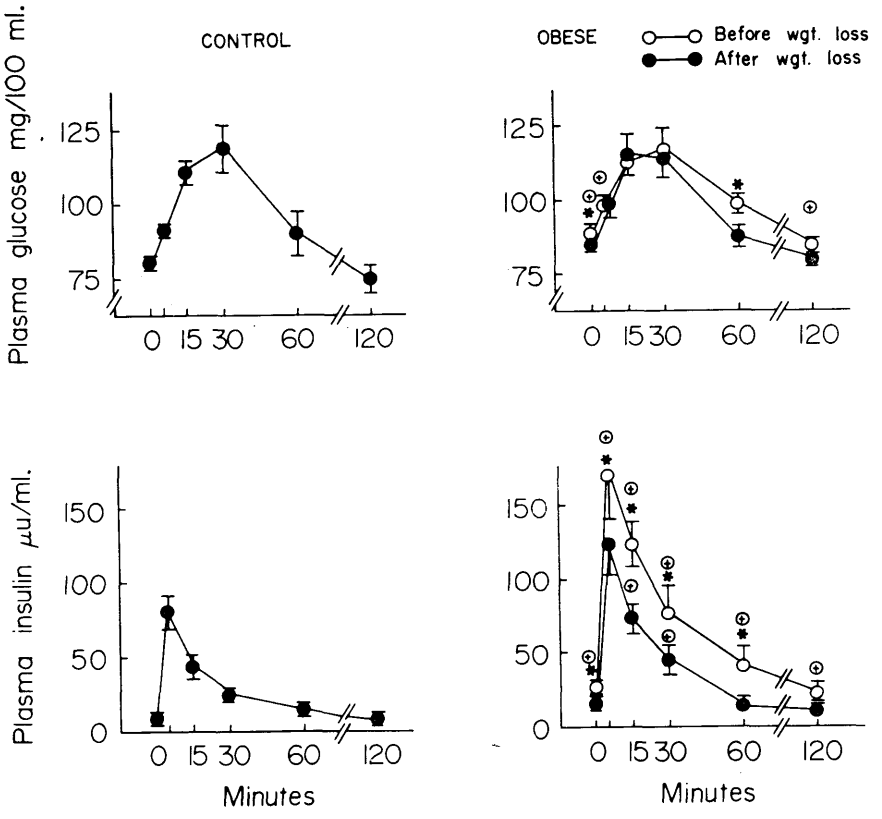

FIG. 3.

Plasma glucose and insulin responses during glucagon tolerance tests in six obese and ten control patients. Asterisks (*) and plus signs (+) are explained in figure 1.

decreased significantly after loss of weight, but the fifteen and thirty minute insulin levels remained significantly above normal values (figure 3). Total hormonal responses were not different from control values after treatment (figure 4).

It should be mentioned that patients who remained significantly obese after treatment (table 1) had plasma insulin responses that improved but which were generally higher than mean control values. Patients 5 and 6, who were closest to their ideal body weight after treatment, had responses that were in the range of nonobese control patients during each of the three tolerance tests.

Growth hormone responses to insulin-induced hypoglycemia: Intravenous insulin produced comparable degrees of hypoglycemia in both control and overweight subjects (figure 5). Each patient exhibited more than a 50 per cent fall in plasma glucose from fasting levels, and lowest concentrations were below 50 mg. per 100 ml. Before treatment all obese patients had subnormal elevations of plasma growth hormone relative to control responses at sixty, ninety and one-hundred and twenty minutes. After weight loss, growth hormone responses were higher than pretreatment levels and differences at the sixty minute interval were significant. After weight reduction, no differences in hormonal response existed between control and obese groups.

DISCUSSION

Exaggerated plasma insulin responses following administration of glucose, tolbutamide or glucagon to obese patients that were demonstrable in the present study are consistent with a number of previous reports.[2-5] Since the hormonal response relative to corresponding glucose concentrations (I/G ratios) during glucose tolerance tests are disproportionately high, hyperinsulinemia in this instance appears to be an indirect measure of insulin antagonism.[3,4] It suggests further that pancreatic islets have become more responsive to insulinogenic stimuli to adapt to contra-insulin changes and preserve normal glucose homeostasis. Histologic evidence of islet hypertrophy in obese human subjects supports this concept.[14]

In the present study, weight loss was associated with a significant reduction of total plasma insulin responses and individual insulin concentrations during each of the three tolerance tests. Despite lower insulin levels, glucose responses during glucose and tolbutamide tolerance

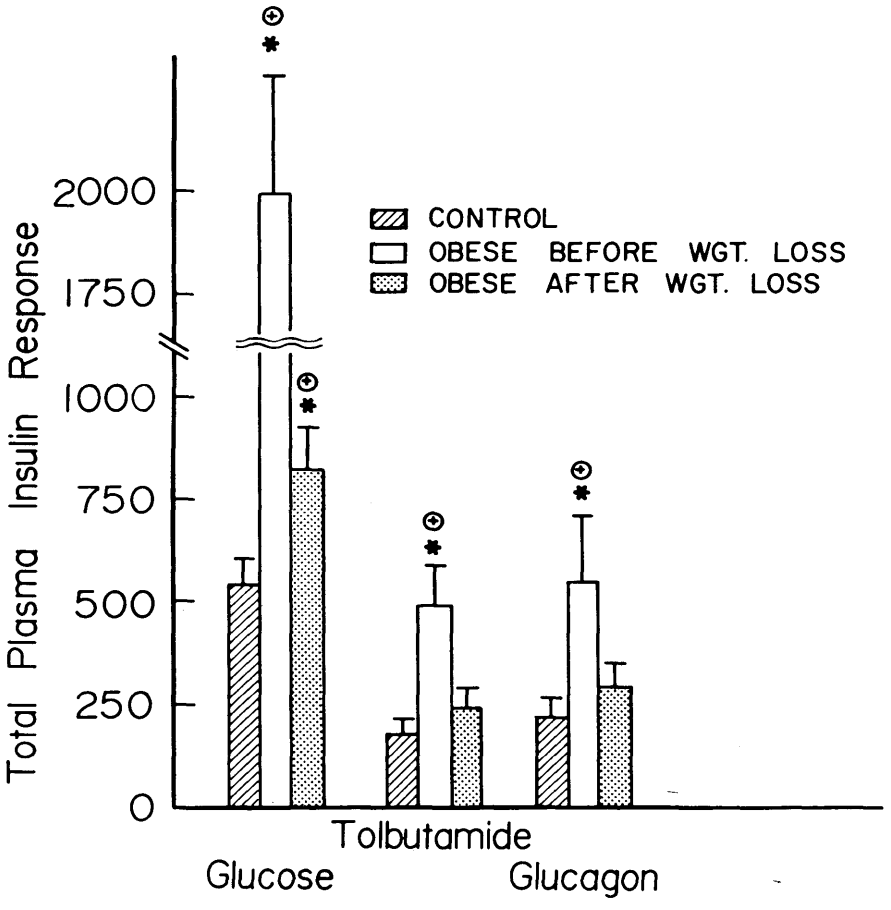

FIG. 4.

Total plasma insulin responses during glucose, tolbutamide and glucagon tolerance tests in six obese and ten control subjects. Values are expressed in planimetry units. See legend in figure 1 for explanation of asterisks (*) and plus signs (+).

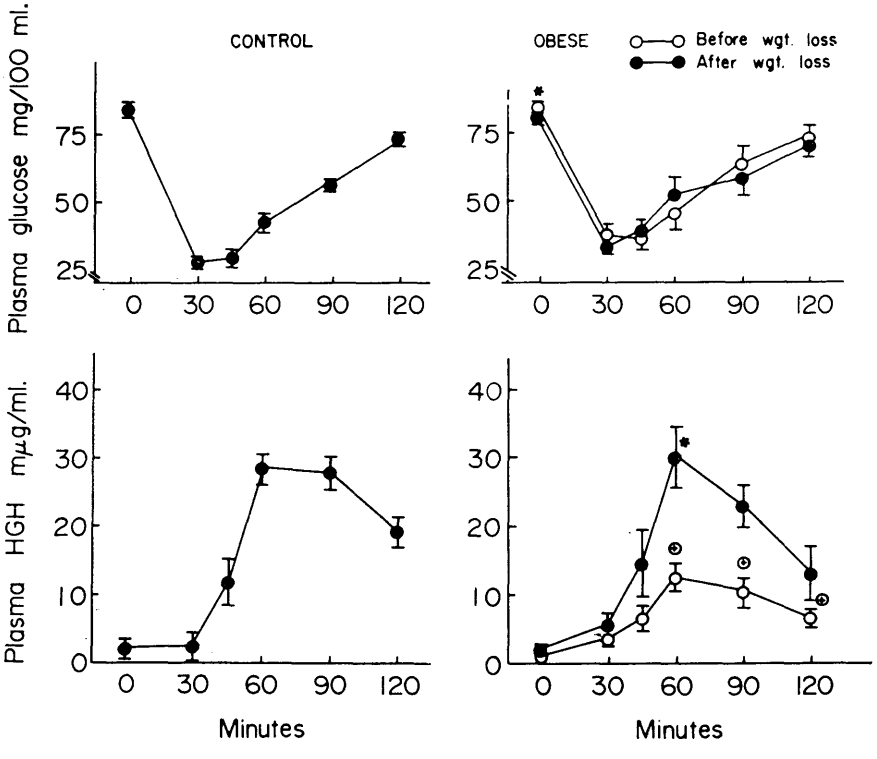

FIG. 5.

Plasma glucose and growth hormone responses (HGH) during insulin tolerance tests in six obese and ten control subjects. Asterisks (*) and plus signs (+) are explained in figure 1.

improved, and there were slight reductions in glucose levels during glucagon tolerance as well. These results suggest that insulin antagonism is an acquired defect and with weight loss, the glucose-lowering action of the hormone becomes more effective at a given plasma concentration. This finding has been documented by others with respect to glucose tolerance alone.[15-17] Sims and co-workers also have reversed the sequence of this kind of study and have shown that hyperinsulinemia appears during glucose tolerance tests in normal men following prolonged forced feeding and weight gain.[18]

Examination of tissues of obese patients has revealed changes that correlate with results of clinical investigations. Salans and co-workers demonstrated that fat cells isolated from biopsied tissue of overweight subjects have decreased responsiveness to the effects of insulin on glucose utilization.[16] This resistance was associated with the increased triglyceride content and size of adipocytes. After weight loss and reduction of cell size, normal hormonal sensitivity was restored, suggesting that accumulation of body fat may require adaptive hyperinsulinemia to maintain normal glucose utilization in this tissue.

Similar forms of resistance to insulin in skeletal muscle have been reported by Rabinowitz and Zierler in their studies of forearm metabolism in obese patients.[19] Moreover, there is additional evidence that experimental obesity is attended by hepatic glucose overproduction which undoubtedly reflects another instance of antagonism to the glucose-lowering effects of this hormone.[20] Combinations of enhanced hepatic release of glucose into the circulation and its impaired utilization by peripheral tissues including fat and muscle very likely account for the changes observed in this and previous studies. This had led to a search for possible substrate and hormonal abnormalities that might explain these effects.

Randle and co-workers have suggested that metabolic conditions that promote tissue accumulation of free fatty acids (FFA) in insulin-sensitive tissues such as skeletal muscle will impair the positive effects of insulin on glucose utilization in that tissue.[21] Substrate-induced insulin antagonism may have some relevance to the observed changes in overweight individuals. In stable obesity, plasma FFA concentrations are elevated above normal levels frequently.[22] According to the recent review of Bortz, this may indicate increased adipose tissue turn-over and release of FFA into the circulation, and evidence was cited to suggest increased preferential oxidation of this substrate as opposed to glucose by peripheral tissues as well.[23] While it is true that insulin antagonism may be evident in obese patients with normal plasma FFA levels,[24] Schonfeld and Kipnis have reported that extracellular concentrations of this substrate do not necessarily correlate with tissue levels.[25] In six overweight patients reported in this study, FFA concentrations decreased to a normal range concomitant with weight reduction and improvement of plasma insulin abnormalities, but the relationship of multicentric metabolic effects of FFA to insulin antagonism in obesity remains uncertain.

Although there was no alteration of fasting plasma alpha-amino nitrogen observed in obese patients before or after treatment, samples were not fractionated to measure individual amino acids, and more subtle changes may have been undetected.

Recently, Felig and associates reported that plasma levels of valine, leucine, isoleucine, tyrosine and phenylalanine were significantly elevated above normal concentrations in obese patients, and the change was proportional to the degree of elevation of basal plasma insulin levels.[26] They concluded that this change is a consequence of depressed responsiveness of skeletal muscle to insulin, and that accumulation of these substrates in blood could lead to a chronic stimulation of pancreatic beta cells to secrete more insulin. This does not exclude the primary importance of plasma glucose disturbances in the initiation of islet insulin hypersecretion in the obese, since depressed insulin effects on tissue glucose utilization would necessitate additional hormonal output to maintain euglycemia. Slight to moderate elevations of glucose levels in middle-aged overweight subjects reported in this study very likely indicate incomplete hormonal compensation.

Among hormonal insulin antagonists that have been studied frequently in overweight subjects are glucocorticoids and growth hormone. The metabolic properties of the latter hormone have been reviewed recently.[27] Several groups have demonstrated that growth hormone cannot be implicated in the development of contra-insulin effects in obesity since basal levels are usually in a normal range and responses during the fourth and fifth hours of oral glucose tolerance or following insulin-induced hypoglycemia or arginine infusion frequently are blunted.[6-8] This subnormal response, observed in the present study during insulin tolerance tests, was corrected by weight loss. Two laboratories have reported similar findings,[28,29] while the results of two other investigations have not confirmed these data.[30,31] In one instance, however, the failure to improve plasma growth hormone responses after weight loss in obese patients was observed after a relatively

brief period of caloric deprivation.[30]

The cause and physiologic significance of growth hormone defects in overweight subjects are unknown. Four of six patients in our study remained significantly obese after treatment, but growth hormone responses were still considerably improved. In the prospective study of Sims, et al., a gain in body weight of only 15 per cent was associated with a 75 per cent reduction in growth hormone increments at the fourth hour of oral glucose tolerance tests.[18] These two findings may indicate that the hormonal abnormality may be just as dependent upon whether an overweight patient has been in a recent prolonged phase of active weight gain as it is upon the degree of obesity.

Clinical similarities between obese patients and individuals with Cushing's Syndrome have been emphasized in the past, but laboratory evidence for abnormal endogenous glucocorticoid effects in the obese patient is not conclusive.[23] It should be mentioned, however, that peripheral insulin antagonism, hepatic over-production of glucose, elevated fasting and post-prandial glucose levels, increased free fatty acid levels and subnormal growth hormone responses observed in obesity can be reproduced in normal animals or man after glucocorticoid administration.[32-36] Efforts to delineate other hormonal changes among obese individuals that might explain an anti-insulin effect have not been successful.[23]

Factors directly related to weight gain and which specifically promote the development of plasma substrate changes, insulin antagonism and plasma growth hormone disturbances in the overweight subject are not clearly defined and require more investigation. Results of the present study suggest that these defects are improved when appropriate weight reduction is achieved.

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REFERENCES

[1] Newburgh, L. H., and Conn, J. W.: A new interpretation of hyperglycemia in obese middle-aged persons. JAMA *112*: 7-11, 1939.

[2] Karam, J. H., Grodsky, G. M., and Forsham, P. H.: Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. Diabetes *12*:197-204, 1963.

[3] Perley, M., and Kipnis, D. M.: Plasma insulin responses to glucose and tolbutamide of normal weight and obese diabetic and non-diabetic subjects. Diabetes *15*:867-74, 1966.

[4] Seltzer, H. S., Allen, E. W., Herron, A. L., and Brennan, M. T.: Insulin secretion in response to a glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J. Clin. Invest. *46*:323-35, 1967.

[5] Benedetti, A., Simpson, R. G., Grodsky, G.M., and Forsham, P. H.: Exaggerated insulin response to glucagon in simple obesity. Diabetes *16*:666-69, 1967.

[6] Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Secretion of human growth hormone: physiologic and experimental modification. Metabolism *12*:577-79, 1963.

[7] Beck, P., Koumans, J. H. T., Winterling, C., Stein, M., Daughaday, W. H., and Kipnis, D. M.: Studies of insulin and growth hormone secretion in human obesity. J. Lab. Clin. Med. *64*:654-67, 1964.

[8] Copinschi, G., Wegienka, L. C., Hane, S., and Forsham, P. H.: Effect of arginine on serum levels of insulin and growth hormone in obese subjects. Metabolism *16*:485-91, 1967.

[9] Hill, J. B., and Kessler, G.: An automated determination of glucose utilizing a glucose oxidase-peroxidase system. J. Lab. Clin. Med. *57*:970-80, 1961.

[10] Itaya, K., and Ui, M.: Colorimetric determination of free fatty acids in biological fluids. J. Lip Res. *6*:16-20, 1965.

[11] Frame, E. G., Russell, J. A., and Wilhelmi, A. E.: The colorimetric estimation of amino nitrogen in the blood. J. Biol. Chem. *149*:255-70, 1943.

[12] Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: two antibody system. Diabetes *12*:115-26, 1963.

[13] Schalch, D. S., and Parker, M. L.: A sensitive double antibody immunoassay for human growth hormone in plasma. Nature *203*:1141-47, 1964.

[14] Ogilvie, R. F.: The islands of Langerhans in 19 cases of obesity. J. Path. Bact. *37*:473-51, 1933.

[15] Karam, J. H., Pavlatos, F. C., Grodsky, G. M., and Forsham, P. H.: Critical factors in excessive serum-insulin response to glucose. Lancet *I*:286-89, 1965.

[16] Salans, L. B., Knittle, J. L., and Kirsch, J.: The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. J. Clin. Invest. *47*: 153-65, 1968.

[17] Farrant, P. C., Neville, R. W. J., and Stewart, G. A.: Insulin release in response to oral glucose in obesity: the effect of reduction of body weight. Diabetologia *5*:198-200, 1969.

[18] Sims, E. A. H., Goldman, R. F., Gluck, C. M., Horton, E. S., Kelleher, P. C., and Rowe, D. W.: Experimental obesity in man. Trans. Ass. Amer. Physicians *81*:153-70, 1968.

[19] Rabinowitz, D., and Zierler, K. L.: Forearm metabolism in obesity and its response to intra-arterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. J. Clin. Invest. *41*:2173-81, 1962.

[20] Sandler, R., Herrera, E., and Freinkel, N.: Glucose overproduction in obese-hyperglycemic mice. Clin. Res. *16*:351, 1968.

[21] Randle, P. J., Garland, P. B., Newsholme, E. A., and Hales, C. N.: The glucose fatty acid cycle in obesity and maturity onset diabetes mellitus. Ann. N. Y. Acad. Sci. *131*: 324-33, 1965.

[22] Dole, V. P.: A relation between non-esterified fatty acids in plasma and the metabolism of glucose. J. Clin. Invest. *35*: 150-54, 1956.

[23] Bortz, W. M.: Metabolic consequences of obesity. Ann. Int. Med. *71*:833-43, 1969.

[24] Bagdade, J. D., Porte, D. Jr., and Bierman, E. L.: The interaction of diabetes and obesity on the regulation of basal lipolysis in man. Diabetes *18*:759-72, 1969.

[25] Schonfeld, G., and Kipnis, D. M.: Glucose-fatty acid interactions in the rat diaphragm in vivo. Diabetes *17*:422-26, 1968.

[26] Felig, P., Marliss, E., and Cahill, G., Jr.: Plasma amino acid levels and insulin secretion in obesity. New Eng. J. Med. *281*:811-16, 1969.

[27] Daughaday, W. H., and Kipnis, D. M.: The growth-promoting and anti-insulin actions of somatotropin. *In* Recent Progress in Hormone Research, edited by G. Pincus, New York, Academic Press, 1966, pp. 49-99.

[28] Lessof, M. H., Young, M. S., and Greenwood, F. C.: Growth hormone secretion in obese subjects. Guy's Hosp. Rept. *115*:65-71, 1966.

[29] Londono, J. H., Gallagher, T. E., Jr., and Bray, G.: Effect of weight reduction, triiodothyronine, and diethylstilbesterol on growth hormone in obesity. Metabolism *18*:986-92, 1969.

[30] Tchobroutsky, G., Rosselin, G., Assan, R., Freychet, P., and Derot, M.: Growth hormone secretion in subjects with and without obesity. Physiopathology of Adipose Tissue, edited by J. Vague, Amsterdam, Excerpta Medica Foundation, 1969, pp. 279-88.

[31] El-Khodary, A. Z., Ball, M. F., Krop, T. M., and Canary, J. J. (abstract): Inappropriate growth hormone response to hypoglycemia in obesity regardless of body weight. Program of the 52nd Meeting of the Endocrine Society, St. Louis, Mo., June 11, 1970, p. 115.

[32] Riddick, F. A., Riesler, D. M., and Kipnis, D. M.: The sugar transport system in striated muscle. Diabetes *11*:171-78, 1962.

[33] Welt, M. H., Stetten, D., Jr., Ingle, D. J., and Morley, E. H.: Effects of cortisone on rates of glucose production and oxidation in the rat. J. Biol. Chem. *197*:57-66, 1952.

[34] Perley, M., and Kipnis, D. M.: Effect of glucocorticoids on plasma insulin. New Eng. J. Med. *274*:1237-41, 1966.

[35] Kalkhoff, R. D., Richardson, B. L., and Beck, P.: Relative effects of pregnancy, human placental lactogen and prednisolone on carbohydrate tolerance in normal and subclinical diabetic subjects. Diabetes *18*:152-75, 1969.

[36] Frantz, A. G., and Rabkin, M. T.: Human growth hormone. Clinical measurement, response to hypoglycemia and suppression by glucocorticoids. New Eng. J. Med. *271*:1375-81, 1964.