Studies of the etiology of obesity in Pima Indians[1,2]

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ABSTRACT Studies have been conducted on various metabolic characteristics of lean and obese Pima Indians, including studies of fat-cell morphology, glucose transport, and lipolysis; lipoprotein lipase activities; sodium-potassium ATPase in red cells, adipocytes, and fibroblasts; lipids and lipoprotein metabolism; fatty acid metabolism; and sterol balance. Insulin concentrations, insulin binding, insulin action on glucose disposal, fatty acid metabolism, and islet function were compared in lean and obese individuals, and the relationship between insulin resistance and muscle morphology was explored. To explore potential abnormalities in energy balance, calorie intake and gastric emptying were compared in lean and obese Pimas and measurements of energy expenditure were performed. The data suggest that there are multiple metabolic differences that accompany obesity in Native Americans. A lower metabolic rate was a determinant of future weight gain, and abnormalities in use of free fatty acids and cell insulin action were suggested, which emphasize the need for further studies in these areas. *Am J Clin Nutr* 1991;53:1577S–85S.

KEY WORDS Obesity, fat cells, lipoprotein lipase, ATPase, lipoproteins, fatty acids, insulin resistance, calorie intake, energy expenditure

Introduction

The high prevalence of obesity occurring in Native Americans is of major importance because of the direct relationship of obesity with morbidity and the association of obesity with other diseases. The causes of obesity are poorly understood in all populations and, except for the obesity associated with a few rare metabolic diseases, its etiology is unknown. Many investigators believe that obesity has multiple possible determinants. The Pima, Tohono O'odham (Papago), and Maricopa Indians, who live southeast of Phoenix in a part of the Gila River Indian Community, have been participating in an ongoing longitudinal study of diabetes and its complications (1). In conjunction with this survey, a number of studies have been conducted on lean and obese Pima Indians that have yielded information on the metabolic characteristics of obesity in Native Americans and that have provided some insight into its possible etiology. In this review, we summarize information available from the studies of obesity in Pima Indians.

Studies of fat cells

Fat-cell morphology

To investigate how adipose cellularity relates to obesity, subcutaneous adipose tissue was obtained from the lower abdominal wall from Pima Indians who had been residing in a metabolic ward while on a constant diet for ≥ 3 d before the biopsy (2). Adipocytes were prepared by collagenase digestion, and cell size and number were determined on osmium fixed cells (3). With increasing body fat, the average adipocyte-cell size increased (**Fig 1,** top); however, in severely obese participants (above ~35% fat) cell size was highly variable but unrelated to body fat. On the other hand, the total-body number of adipocytes was directly related to obesity (Fig 1, bottom). These data suggest that fat cells in obese Native Americans are as large as those of other populations, but they also suggest that there is a maximum potential size for adipocytes and that with increasing obesity further adipocytes are recruited. An increased number of adipocytes was in fact observed in a group of overweight Pima Indians after overfeeding for 2 wk (4). Thus, obesity in Pimas is unlikely to be the result of a fixed or predetermined number of adipocytes.

Glucose transport and lipolysis

In vitro sensitivities of glucose transport and lipolysis to insulin were compared in adipocytes isolated from groups of lean, moderately obese, and severely obese nondiabetic Pima Indian men (5). The half-maximum concentrations of insulin (ED_{50}) for the stimulation of glucose transport and for the suppression of isoproterenol-stimulated lipolysis were significantly greater in moderately obese subjects than in lean subjects and were even greater in the severely obese group compared with the moderately obese group (**Fig 2**). Thus, the larger adipocytes in obese individuals were shown to be resistant to the action of insulin both in stimulating glucose transport and in inhibiting lipolysis. Further detailed studies established that these differences are not explained by decreased insulin binding (2). However, autophosphorylation studies suggested that there are possible ab-

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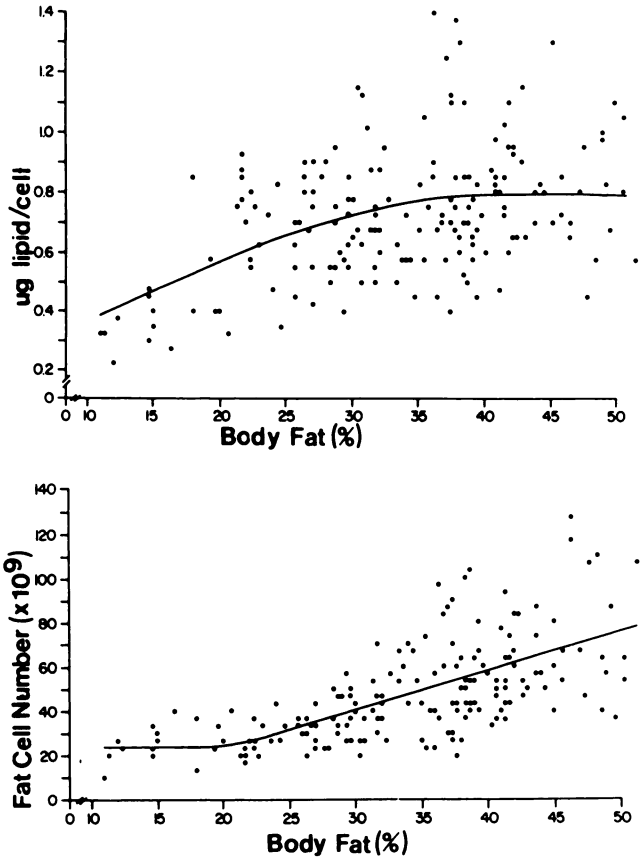

FIG 1. Mean adipocyte cell size (top) and estimated total body adipocyte number (bottom) in Pima Indians. Pima men and women (n = 156) with normal glucose tolerance followed a constant weight-maintaining diet for ≥ 3 d before biopsy. After ≥ 14 h fasting, subcutaneous adipose tissue was removed from the anterior abdomenal wall and isolated adipocytes were prepared by collagenase digestion and quantified by using osmium-fixed cells. The percentage of body fat was estimated by underwater weighing. From reference 3.

normalities in the postbinding steps of insulin action in the fat cells from obese subjects (6). Although the differences between the lean and moderately obese groups could be explained by differences in cell size, the differences between the moderately obese and severely obese could not. This suggests that these sensitivity changes may be important in the development of obesity. Longitudinal studies will be required to determine whether defects in adipocytes precede the development of obesity in Native Americans or other populations.

Lipoprotein lipase

To determine the relationship between obesity and lipase activities in Pima Indians, adipose-tissue lipoprotein lipase (LPL) and postheparin hepatic and LPL activities were measured in 21 obese and lean Pima Indian men and 18 age- and weight-matched Caucasian men (7). Values for adipose tissue LPL and postheparin LPL were found to be significantly lower in the Pimas (0.92 ± 0.08 vs 1.73 ± 0.26 $\mu mol \cdot h^{-1} \cdot g^{-1}$, $P < 0.009$). There was a significant positive correlation between adipose tissue LPLs and obesity in the Pima Indians (**Fig 3**). Neither postheparin LPLs nor hepatic lipase was related to degree of obesity.

Lipase activities were remeasured in eight participants after a period of weight reduction followed by several weeks of stabilization at reduced weights (7). After weight reduction adipose-tissue LPL activity declined in all participants (**Fig 4**). The data suggest that Pima Indians may have lower adipose-tissue LPL, although confirmation of this would require a population-based sample. The results also indicate that elevated LPL activity associated with obesity in Pimas returned to normal after weight reduction and, thus, were unlikely to precede the development of obesity.

Metabolic and endocrine studies

Sodium-potassium ATPase activity

Because one possible cause of obesity might be increased metabolic efficiency, considerable attention has been placed on the possibility that energy-generating metabolic processes such as sodium-pump activity might be lower in obese subjects. Sodium-potassium ATPase activity was measured in red blood cells from nondiabetic euthyroid male Pima Indians with various degrees of obesity (8). Sodium-potassium ATPase measured by both ^{86}Rb uptake in intact cells (**Fig 5**) and ATP hydrolysis in purified membranes was significantly negatively correlated with body mass index (BMI). Studies in isolated adipocytes showed no relation of basal-pump activity with obesity whereas insulin stimulation of ATPase was reduced (9). To determine to what extent these changes in sodium-pump activity in obese individuals is the result of inherent cellular defects in the regulation of this enzyme, sodium-pump activity was measured in diploid fibroblast cultures isolated from lean and obese donors (10) (**Fig 6**).

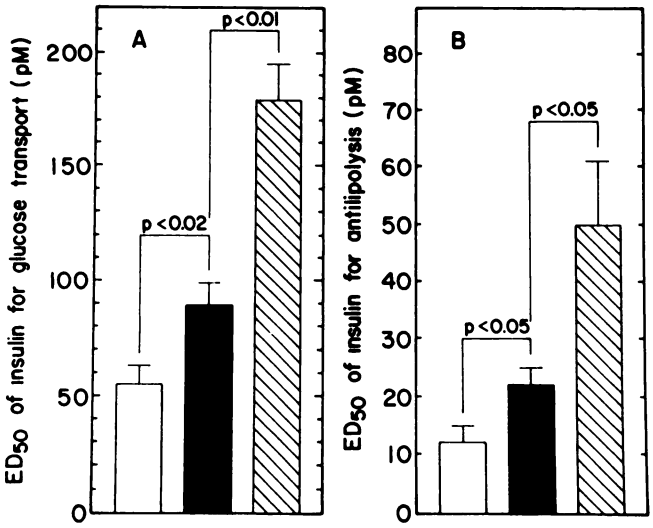

FIG 2. Half-maximum concentration of insulin (ED_{50}) for glucose transport (A) and antilipolysis (B) in 10 lean (11–22% body fat; □), 11 moderately obese (26–34% body fat; ■), and 7 severely obese (37–40% body fat; ▨) Pima Indian men. Abdominal adipocytes were isolated by collagenase digestion. Glucose transport was assessed by using [U^{14}C]D-glucose and lipolysis was measured as glycerol released in the presence of 25 nmol isoproterenol/L. ED_{50} was assessed from studies carried out on insulin concentrations ranging from 25 to 8000 pmol (3). From reference 5.

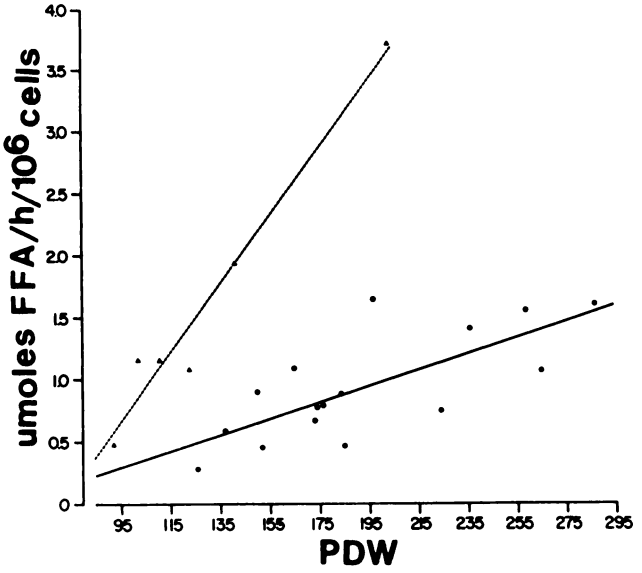

FIG 3. Relationship between adipose-tissue lipoprotein lipase (LPL) activity (vertical axis) and obesity (estimated as percentage of desirable weight, PDN; horizontal axis) in Pima Indians. Twenty-one Pima Indians (●), and 6 age- and weight-matched Caucasians (△) were placed on a weight-maintaining standard diet for ≥ 3 d, after which subcutaneous adipose tissue was aspirated from the gluteal region. LPL activity was measured from heparin eluates of tissue fractions by using radiolabeled triolen emulsions as substrate. Regression lines are for Pimas (—) and Caucasians (- - -). For the Pima group, $r = 0.76$, $P = 0.0001$. Data are shown only for the Caucasians measured in Phoenix. From reference 7.

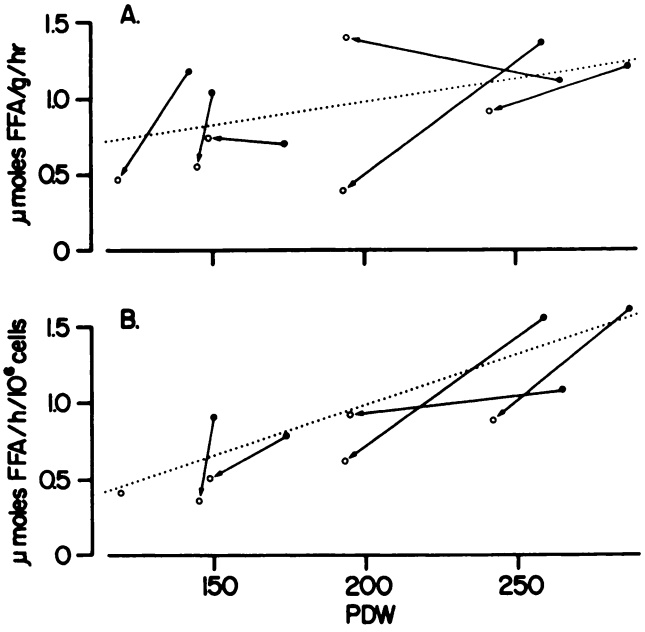

FIG 4. Response of adipose-tissue LPL activity (vertical axis) to weight reduction. The lines representing the relationships between adipose LPL per 10^6 cells and obesity (estimated as percentage desirable weight; horizontal axis) are superimposed and values shown before (●) and after (○) weight reduction. Two participants were measured only after weight reduction. From reference 7.

Although confluent cell density was found to be negatively correlated with basal and maximally stimulated sodium-potassium–pump activity, adjustment for this relationship showed that there was no evidence for an intrinsic cellular difference in basal-pump activity or in insulin regulation of the sodium-pump activity in fibroblasts from obese subjects. Thus, obese Native Americans may have lower sodium-pump activity, but there is no evidence that an intrinsic cellular defect in the sodium pump is responsible for the development of obesity.

Lipids and lipoproteins

Plasma lipoprotein cholesterol and triglyceride concentrations were measured in a population-based sample of 1400 Pima Indians > 15 y of age (11). In both younger and older Pimas of both sexes, obesity was associated with high concentrations of total and very-low-density-lipoprotein (VLDL) triglycerides (TGs) and low concentrations of high-density-lipoprotein (HDL) cholesterol (**Table 1**). When all the data from the population were examined by Duncan's multiple range test adjusted for age, the effect of obesity was significant in males on total and VLDL TG and HDL cholesterol. In females obesity had a significant effect on total and VLDL TG and HDL cholesterol. In a multivariate analysis adjusted for age, smoking, alcohol consumption, and plasma glucose, obesity was significantly positively associated with total and VLDL TG and inversely associated with HDL cholesterol in both men and women (**Table 2**). On the other hand, obesity had less of a relationship with total or low-density-lipoprotein (LDL) cholesterol. Metabolic studies of VLDL and LDL metabolism were performed to examine mechanisms for the differences in lipoproteins (12). The relatively high levels of VLDL in obese individuals appear to be the result of greatly increased rates of production of both VLDL TG and apolipoprotein B. There are, however, two compensatory mechanisms that result in maintenance of LDL at normal concen-

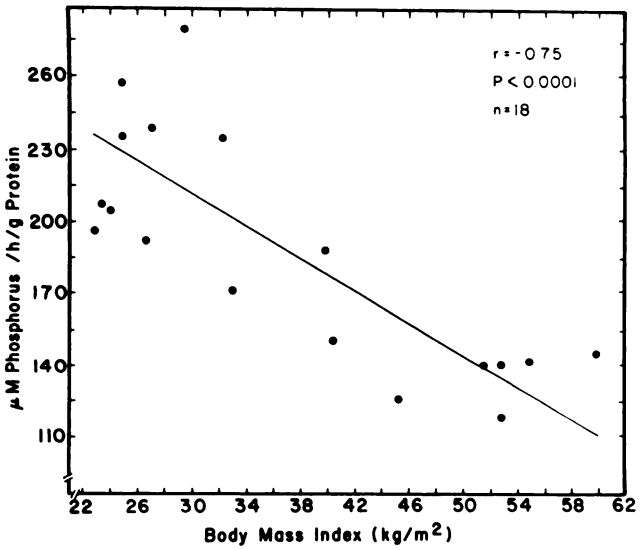

FIG 5. Relationship between sodium-potassium ATPase activity in isolated red blood cell membranes and the degree of obesity. Red blood cells were obtained from 19 nondiabetic Pima Indian men with a wide range of obesity. From reference 8.

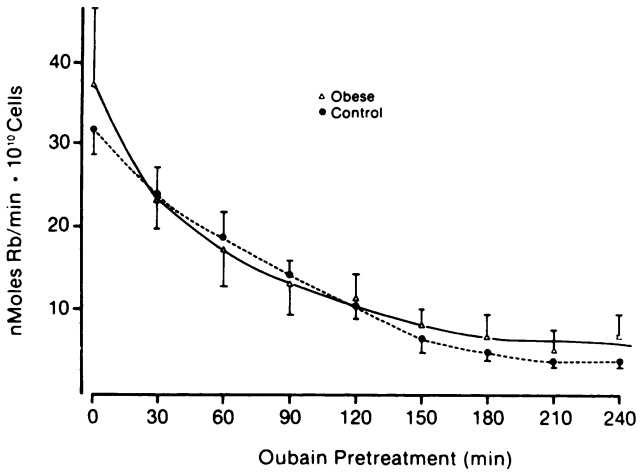

FIG 6. Sodium-potassium-ATPase activity in fibroblasts from nonobese and obese participants. Fibroblast cultures were obtained from skin biopsies from four Pima Indians with body mass index (BMI) < 30 and from five extremely obese hyperinsulinemic Pima Indians. Activity is assessed as the time course of ouabain action on the rate of ^{86}Rb uptake in fibroblasts. Monolayers were incubated with ouabain for the indicated period before the initiation of transport by the addition of $^{86}RbCl$. From reference 10.

trations. The first is an increase in direct removal of VLDL, which diminishes the amount converted to LDL. The second involves a concomitant increased fractional clearance of LDL.

Sterol balance studies indicate that there is an increase in total-body synthesis of cholesterol in obese Pimas and that the formation of supersaturated bile is principally because of an enhanced rate of cholesterol secretion in the bile (13). Thus, in obese Pimas virtually all pathways associated with cholesterol metabolism are augmented (14) (**Fig 7**). These changes may

TABLE 1
Plasma lipids and lipoproteins in lean [body mass index (BMI) < 27] vs obese (BMI > 35) Pima Indians*

	15–24 y of age		>35 y of age	
	Lean	Obese	Lean	Obese
	mmol/L			
Male subjects	[70]	[64]	[36]	[79]
Total cholesterol	4.3 ± 0.1	4.6 ± 0.1†	4.8 ± 0.1	4.6 ± 0.2
LDL cholesterol	2.8 ± 0.1	3.2 ± 0.1†	3.1 ± 0.1	3.2 ± 0.2
HDL cholesterol	1.2 ± 0.0	1.0 ± 0.0‡	1.3 ± 0.0	1.0 ± 0.0‡
Total TG	1.07 ± 0.07	1.66 ± 0.09‡	1.25 ± 0.09	1.70 ± 0.18†
VLDL TG	0.62 ± 0.06	1.15 ± 0.08‡	0.65 ± 0.07	1.03 ± 0.13†
Female subjects	[118]	[125]	[26]	[70]
Total cholesterol	4.2 ± 0.1	4.2 ± 0.1	4.6 ± 0.2	4.3 ± 0.1
LDL cholesterol	2.6 ± 0.0	2.8 ± 0.1§	3.0 ± 0.1	2.9 ± 0.1
HDL cholesterol	1.3 ± 0.0	1.1 ± 0.0‡	1.2 ± 0.1	1.1 ± 0.0§
Total TG	1.0 ± 0.04	1.35 ± 0.04‡	1.44 ± 0.15	1.33 ± 0.08
VLDL TG	0.52 ± 0.03	0.76 ± 0.03‡	0.79 ± 0.10	0.69 ± 0.06

* $\bar{x}$ ± SEM. *n* given in brackets. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.
†‡§ Significantly different from lean (Student's *t* test): †$P < 0.001$, ‡$P < 0.05$, §$P < 0.001$.

TABLE 2
Correlation coefficient between obesity and plasma lipoproteins in nondiabetic Pimas*

	Men (*n* = 392)		Women (*n* = 507)	
	r	Partial *r*†	*r*	Partial *r*†
Total cholesterol	—	—	—	—
LDL cholesterol	—	—	—	—
HDL cholesterol	−0.25 (0.0001)	−0.22 (0.0001)	−0.27 (0.0001)	−0.33 (0.0001)
Total TG	−0.17 (0.002)	—	−0.17 (0.0002)	—
VLDL TG	0.19 (0.0007)	0.19 (0.0007)	0.11 (0.01)	0.06 (NS)

* Obesity as measured by BMI. *P* given in parentheses.
† Controlled for age, smoking, alcohol consumption, and plasma glucose.

contribute to the increased prevalence of gallstones in obese Native Americans and may also be atherogenic. However, weight-reduction studies in Pimas (15, 16) suggest that all these changes in lipoproteins and sterol balance are potentially reversible; therefore, they are the result of and probably do not contribute to the etiology of obesity.

Fatty acid metabolism

Free-fatty acid metabolism was investigated in Pima Indian women over a wide range of obesity (17). Turnover rate was

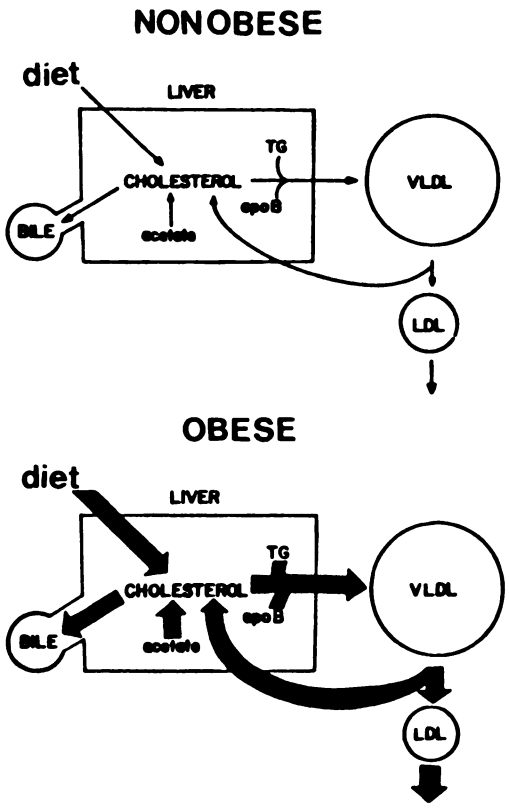

FIG 7. Summary of differences in lipoprotein metabolism and biliary cholesterol between lean and obese Pima Indians. From reference 11.

measured by using a [^{14}C]palmitate infusion, and fat-cell lipolytic rates were measured in vitro by using isolated adipocytes. Although fatty acid concentration and production were correlated with obesity (**Fig 8**), total-body fatty acid turnover (production), expressed per kilogram of body fat, was negatively correlated with degree of obesity (**Fig 9**, top). In contrast, the rate of lipolysis determined in vitro was positively correlated with degree of obesity (Fig 9, bottom). Thus, free fatty acid does not appear to be available in vivo in proportion to the size of the TG stores, suggesting an inability of fat cells from obese subjects to release their stored TG. The possible role this plays in the genesis of obesity requires further evaluation.

Insulin resistance

Because of the well-known association between insulin resistance and obesity observed in other populations, considerable attention has been placed on studies of insulin action in Pima Indians. In vivo insulin action, as measured by the hyperinsulinemic euglycemic-clamp technique, was quantified in a large number of Pima Indians over a wide range of obesity (18) (**Fig 10**). There was a significant negative relationship between insulin action and obesity until a percentage body fat of ~28–30% was reached; however, above this, greater degrees of obesity were not associated with differences in insulin action. Measurements of maximum insulin-stimulated glucose transport were available from isolated abdominal adipocytes of a number of these participants (19). Only a weak relationship was observed between insulin-mediated glucose disposal in vivo and insulin-stimulated glucose metabolism in isolated adipocytes ($r = 0.36$, $P < 0.02$).

The observations that insulin sensitivity was not associated with degree of obesity in those > 30% body fat and that there is only a weak relationship between in vivo glucose disposal and fat-cell metabolism suggest that the large adipose mass might not be the only cause of the insulin resistance observed in obese individuals and that the site of the insulin resistance may reside

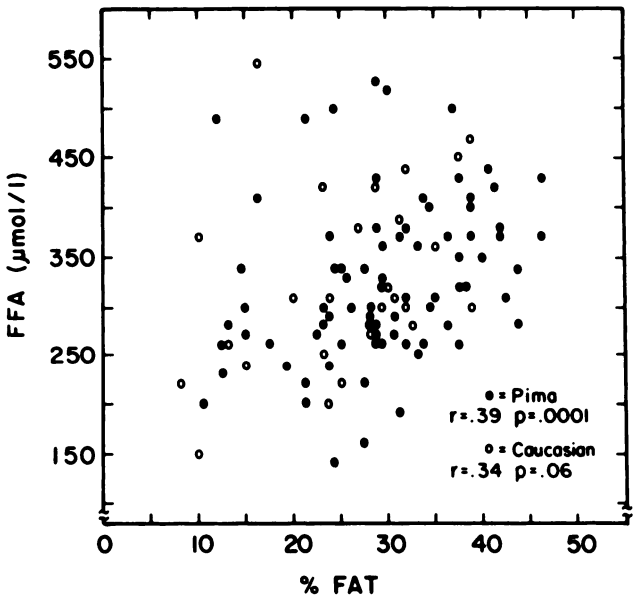

FIG 8. Relationships between plasma free fatty acids and obesity in Pimas and Caucasians.

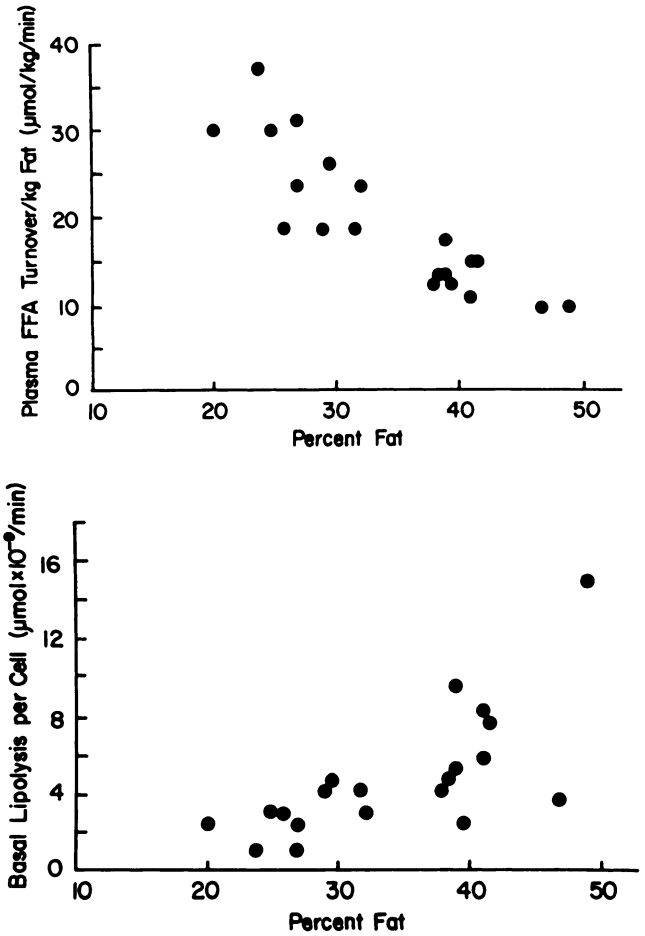

FIG 9. The relationship between free fatty acid production and obesity as measured by percentage of body fat. After at least 2 full days of consuming a standard diet in the metabolic ward, 20 Pima women, with a wide range of obesity, underwent measurements of free fatty acid using one [^{14}C]palmitate infusion (17). Lipolysis was measured in isolated adipocytes (3) and body fat was determined by underwater weighing. Top: The relationship between the absolute value of plasma free fatty acid turnover and obesity ($r = -0.90$, $P < 0.0001$). Bottom: The relationship between whole-body turnover (lipolysis) rate and obesity ($r = 0.92$, $P < 0.0001$). From reference 17.

in tissues other than adipose tissue. To explore the possibility that sites other than adipose tissue are responsible for mediating insulin resistance associated with obesity, studies of muscle-fiber type and capillary density were conducted and compared with in vivo insulin action (20). Morphologic examination of muscle fibers isolated from needle biopsies of the vastus lateralis in nondiabetic Pima Indian men indicated that there is a significant negative correlation between capillary density and degree of obesity as assessed by the percentage of body fat (**Fig 11**). Similarly, muscle-fiber cross-sectional area and degree of obesity were positively related ($r = 0.39$, $P < 0.002$). Insulin-mediated glucose disposal, as assessed by the hyperinsulinemic euglycemic clamp, was significantly correlated with capillary density ($r = 0.63$, $P < 0.0001$), percentage of type 1 fibers ($r = 0.20$, $P < 0.02$), and percentage of type 2B fibers ($r = -0.38$, $P < 0.003$); the percentage of type 1 or type 2B was correlated with both percentage of body fat ($r = -0.32$, $P < 0.01$ and $r = 0.32$, P

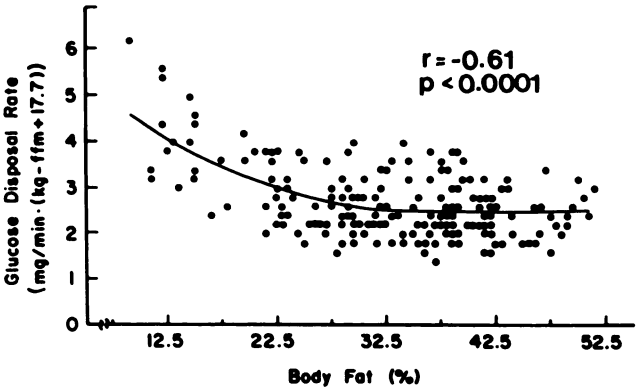

FIG 10. Relationship between insulin-mediated glucose disposal and percentage of body fat in 55 nondiabetic Pima Indian men. Glucose disposal rate was estimated by a hyperinsulinemic euglycemic clamp at an average insulin concentration of 834 ± 29 pmol/L. Body fat was determined by underwater weighing. From reference 18.

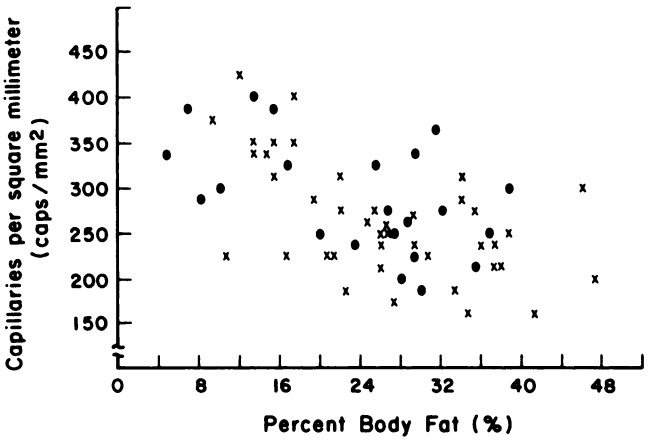

FIG 11. Relationship of muscle capillary density expressed as capillary/mm^2 and degree of obesity as expressed by percentage of fat determined by underwater weighing. Forty-one nondiabetic Pima Indian men (X) and 22 nondiabetic Caucasian men (O) were studied in a metabolic ward after ≥ 3 d on a standard diet. Capillary density and histochemical analyses were performed on biopsy specimens from the vastus lateralis ($r = -0.59$, $P < 0.0001$). From reference 20.

< 0.02, respectively) and waist-to-hip circumference ratio ($r = -0.39$, $P < 0.002$ and $r = 0.40$, $P < 0.002$, respectively). These results suggest that the volume of muscle supplied by each type, or some associated biochemical change in the muscle fibers, could play a role in determining in vivo insulin action. These results also indicate that muscle-fiber type is different in obese individuals. These data provide at least a partial explanation for the insulin resistance associated with obesity, although longitudinal studies will be required to assess whether these differences result from or precede the development of obesity.

A suggestion that insulin resistance may be an intrinsic property of obese individuals was made by studies of insulin binding in monocytes and cultured fibroblasts from lean and obese Pima Indians (21). Insulin binding in both cultured cells and monocytes correlated with the obesity of the cell donors. Additional evidence indicating that there may be an inherent defect in either insulin sensitivity or insulin secretion that may precede obesity in Pima Indians is derived from studies of 7–11-y-old lean, prepubertal Pima and Caucasian children who were matched for obesity, age, and sex (22). The Pima children had higher insulin ($P < 0.05$) and glucose ($P < 0.05$) concentrations than did the Caucasian children.

In addition to possible intrinsic cellular alterations in insulin action in obese subjects, it is also possible that because insulinemic response is directly related to size of meals, insulin resistance might be related to the increased caloric intake in obese individuals. To examine this possibility, 15 Southwestern American Indian men underwent 2 wk of overnutrition during which they consumed a 162% of weight-maintaining calorie intake (23). Insulin-mediated glucose disposal was evaluated both before and after this period. Overnutrition induced a marked decreased in insulin-mediated glucose disposal (**Fig 12**), specifically in the storage component; therefore, short-term overnutrition with only minimal weight gain (3 ± 0.2 kg) resulted in significant reduction in insulin action. These results suggest that overnutrition, independent of increased body mass, may contribute to the reduced insulin-mediated glucose disposal observed in obese individuals.

Despite this large body of evidence demonstrating impairment of insulin-mediated glucose disposal in obese Pima Indians, this insulin resistance may not extend to other actions of insulin.

The ability of insulin to regulate lipolysis was compared in lean and obese Pima Indians during hyperinsulinemic euglycemic clamps at various doses of insulin (24). Although insulin-me-

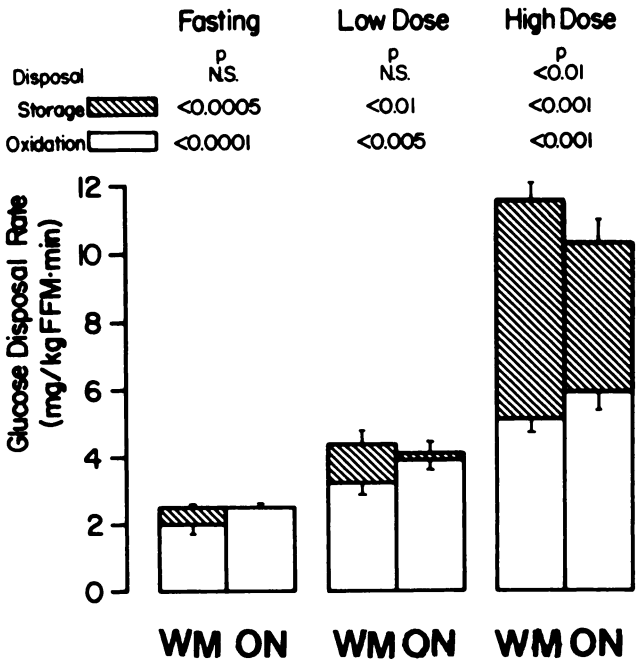

FIG 12. Effect of overnutrition on glucose disposal as measured during euglycemic clamp at basal low and high insulin concentrations at the end of weight maintenance (WM) and overfeeding (ON) periods. Mean basal and steady-state insulin concentrations are shown below the bars. Indirect calorimetry was used to measure glucose oxidation (unshaded area) and glucose storage (shaded area). Error bars are shown for glucose disposal and storage compared with weight-maintenance-insulin concentration. From reference 21.

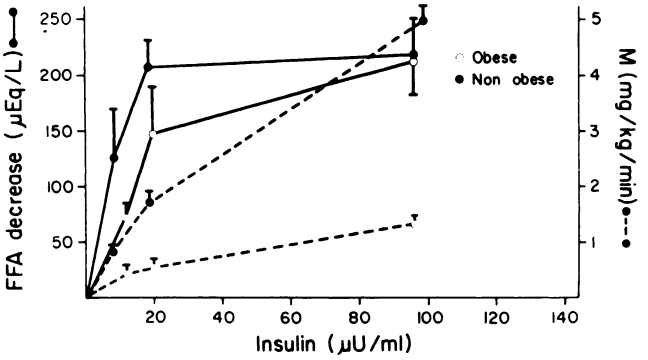

FIG 13. Antilipolytic and glucoregulatory actions of insulin in six obese and six nonobese, nondiabetic Pima Indian men. M represents glucose disposal in $mg \cdot kg^{-1} \cdot min^{-1}$ during 60–90 min of insulin infusion at the increment above basal level indicated. Free fatty acids were measured in plasma samples by a cupric-salt method. From reference 24.

diated glucose disposal at all insulin concentrations was much lower in the obese group, the mean decline in free fatty acids from basal concentration was only marginally reduced in the obese subjects (**Fig 13**). Thus, although the obese participants were significantly resistant to the glucoregulatory action of insulin, there were only small differences in the insulin's antilipolytic effects. Relative maintenance of sensitivity to the antilipolytic action of insulin, in the presence of resistance to insulin's glucoregulatory action, could maintain fat deposition in obese individuals.

There is also evidence that the islets of Langerhans in obese subjects also retain insulin sensitivity despite the glucoregulatory insulin resistance elsewhere (25). Suppression of C-peptide and plasma glucagon concentrations were examined in hyperinsulinemic euglycemic clamps by using multiple doses of insulin. C peptide and glucagon were suppressed to similar degrees in obese and lean participants, demonstrating that insulin inhibits to a comparable degree the alpha- and beta-cell secretion within the physiological range in both nonobese and obese individuals.

Energy balance

Individuals who are undergoing weight gain by definition have an energy imbalance in that there is an excess of energy intake compared with energy expenditure. This imbalance could be caused either by a problem in the regulation of food intake or by defective or diminished energy expenditure, resulting in a more efficient use of calories. Because only a small difference in either one of these areas over a sustained period could lead to significant calorie (fat) deposition in adipose tissue, the study of these areas is extremely difficult and requires precise measurements.

Calorie intake

Data on calories required for weight maintenance are available from a large number of Pima Indian men and women admitted to a metabolic ward. Because activity is necessarily restricted for all subjects, the opportunity is provided to assess calorie requirements in a situation of limited physical activity. Food-intake and body-weight records were kept for all participants admitted to the metabolic ward, and participants were fed a prescribed diet of equivalent calorie distribution. Over a wide range of adiposity, predictive equations for weight maintenance were derived for both men (intake = 7950 kJ (1889 kcal) + 43.1 kJ (10.3 kcal)/kg body wt) and women (intake = 6923 kJ (1654 kcal) + 43.1 kJ (10.3 kcal)/kg body wt) (26). Thus, calorie requirement increases with increasing weight equally in both lean and obese individuals. At any given body weight women require fewer calories for weight maintenance than do men, most likely because of their higher adiposity. Calorie requirement is high in obese individuals because increasing adiposity is accompanied by increases in fat-free mass (27). Thus, by this relatively crude assessment, no decrease in calorie requirements could be detected in obese individuals.

Although many aspects of feeding, behavioral, and gastrointestinal function remain to be explored, an extensive set of studies was conducted to evaluate gastric emptying to determine whether there might be abnormalities in gastrointestinal function associated with obesity (28). Obese Pima Indians were shown to have normal rates of gastric emptying, fractional gastric emptying, and gastric acid secretion both basally and after an acaloric liquid meal. Basal and postprandial plasma gastrin concentrations also did not differ significantly in obese and nonobese Pima Indians. Thus, abnormal gastric emptying rates do not appear to contribute to the pathogenesis of obesity in Pima Indians.

Energy expenditure

Recently, a method was developed for accurate measurement of energy expenditure over periods ≥ 24 h. A metabolic chamber was constructed in Phoenix to measure 24-h energy expenditure and its determinants in humans (29). Measurements of 177 Pima Indians over a wide range of body weight and body composition indicate that there is a close correlation between fat-free mass as estimated by densitometry and 24-h energy expenditure (29) (**Fig 14**). Obese individuals, because they have larger fat-free mass, have higher 24-h energy expenditure compared with lean

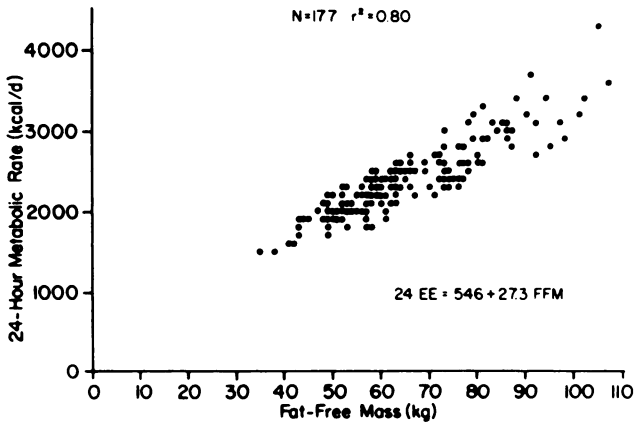

FIG 14. Relationship between 24-h energy expenditure and fat-free mass in 177 subjects ($r = 0.90$, $P < 0.0001$). Twenty-four-hour energy expenditure was estimated in the metabolic chamber after subjects were stabilized after 3 d on a weight-maintaining balanced diet. Estimated energy expenditure was calculated as the intercept between energy expenditure and activity as assessed by a radar detector. Fat-free mass was determined by underwater weighing. From reference 29.

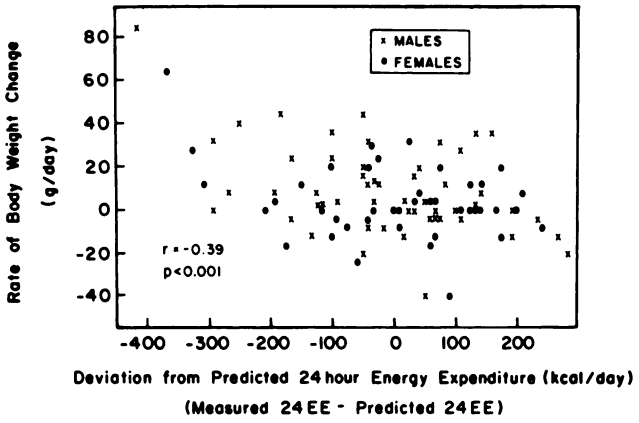

FIG 15. Relationship between the deviation from a predicted 24-h energy expenditure (EE), based on fat-free body mass, fat mass, age, sex, and the rate of change in body weight ($r = -0.39$, $P < 0.001$). The relationship remained statistically significant after the exclusion of two participants with the highest rates of weight gain. From reference 30.

individuals, and there was no significant difference between lean and obese participants in energy expenditure adjusted for differences in fat-free mass.

This technique was also used prospectively to determine the contribution of low energy expenditure to the development of obesity. The 24-h energy expenditure, adjusted for body weight and composition, was measured and correlated with the rate of change in body weight over a 2-y follow-up (30) (**Fig 15**). The estimated risk of gaining > 7.5 kg body wt was increased fourfold in Indians with a low, adjusted 24-h energy expenditure [837 kJ (200 kcal)/d below predicted values] compared with those with a high 24-h energy expenditure were familial (31). Thus, in American Indians, a low rate of energy expenditure may contribute to weight gain and low rates of energy expenditure may be familial and therefore have a genetic determinant.

Summary and conclusions

Studies of the causes and development of obesity are hampered by two major factors. First, cross-sectional comparisons of obese and lean individuals, which show differences, are unable to distinguish whether these differences are the cause or metabolic consequence of obesity. Second, because small metabolic differences can result over a long period in a large cumulative effect, studies require great precision and accuracy to identify significant causal factors. In fact, it is most likely that the most measurable differences between lean and obese participants are the results of obesity and that small subtle changes that tend to induce the gradual accumulation of adipose tissue have probably not yet been measured.

Studies to date in the Pima Indians suggest that there are multiple metabolic differences that accompany obesity in Native Americans. These differences are observed in adipose tissue and in other tissues and systems. A low metabolic rate is a determinant of future weight gain. Thus, in those persons destined to gain weight, there must be some metabolic difference or abnormality that results in a more efficient energy use. These recent observations bring us back to the need for a more careful examination of both adipose-tissue metabolism and metabolic and/or endocrine control mechanisms to understand the possible determinants. The studies summarized in this paper suggest that these differences may be in abnormalities in the mobilization of adipose free fatty acids or in fundamental differences in cell insulin action. It will also be important to determine whether the primary defect is genetic, environmental, or an interaction between the two.

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