Relationship of Insulin Resistance to Weight Gain in Nondiabetic Asian Indian, Creole, and Chinese Mauritians

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There is evidence from animal models that postprandial insulin hypersecretion may precede the development of obesity and insulin resistance, but it is not clear if this is the case in humans. Recently, two longitudinal studies have suggested that insulin resistance acts to limit further weight gain rather than to promote it. The relationship of markers of insulin sensitivity and secretion to changes in weight and the waist to hip ratio (WHR) was therefore examined in nondiabetic Asian Indian (n = 2,169), Creole (n = 798), and Chinese (n = 189) Mauritians over a 5-year follow-up period. Younger age and lower initial body mass index (BMI) were consistent independent predictors of increase in weight in all sex-ethnic subgroups, and older age, higher BMI, and lower WHR were associated with change in WHR. Insulin sensitivity was assessed by homeostatic model assessment (HOMAS), as well as by fasting insulin and the ratio of fasting insulin to glucose. Insulin resistance predicted weight gain in Chinese men independently of baseline age and BMI. In Asian Indian and Creole men and women, these correlations were in the opposite direction (ie, insulin sensitivity predicted weight gain) but became nonsignificant when age and BMI were controlled. There was little relationship of insulin resistance/sensitivity to the change in WHR once baseline BMI was controlled. These data provide suggestive but not convincing evidence that insulin resistance may limit weight gain, and contradictory evidence in one ethnic group that insulin resistance promotes weight gain.

WHEN NEEL[1] FIRST PROPOSED the existence of a "thrifty" genotype as the basis for the high prevalence of diabetes observed in some populations, he hypothesized that individuals who were predisposed to diabetes had a "greater-than-normal" circulating insulin level that enabled them to use and/or consume available food more efficiently. Fat accumulation would be enhanced by insulin-sensitive adipose tissue and relative resistance to glucose uptake in skeletal muscle in an environment of hyperinsulinemia (or at least increased insulin responsiveness to alimentation), coupled with hepatic glucose output resistant to suppression by insulin and hepatic lipogenesis sensitive to stimulation by insulin.[2,3] Hyperinsulinemia and/or insulin resistance have been observed in populations with a high prevalence of non–insulin-dependent diabetes mellitus (NIDDM),[4-6] and one or both may be the basis for obesity and the vicious cycle of increasing insulin resistance and compensatory hyperinsulinemia that eventually leads to β-cell decompensation and NIDDM under conditions of readily available energy-dense food, limited physical activity, and a genetic predisposition to impaired β-cell function.[3,7]

However, recent studies in Pima Indians and both Mexican-Americans and non-Hispanic whites in San Antonio and San Luis Valley have suggested that relatively increased insulin sensitivity and lower fasting insulin concentrations (a surrogate for insulin sensitivity) are associated with weight gain.[8-10] It has been proposed that as weight increases, insulin resistance and hyperinsulinemia develop and eventually limit further weight gain by negative feedback.[8] However, in combination with β-cell failure, insulin resistance/hyperinsulinemia may lead to NIDDM. The observation that insulin sensitivity and low insulin levels predict weight gain is contrary to Neel's original hypothesis that hyperinsulinemia/insulin resistance drive obesity.[2,3] It is nonetheless possible that in other populations, hyperinsulinemia and/or insulin resistance could predict weight gain. An understanding of these mechanisms is of great importance to efforts to prevent obesity and NIDDM. We have therefore examined the association over a 5-year follow-up period in the multiethnic population of Mauritius. In addition, we examined the association of insulin and markers of insulin resistance with changes in fat distribution, which has not been reported previously.

SUBJECTS AND METHODS

Background and Study Population

Mauritius is a subtropical island located in the southwestern Indian Ocean approximately 800 km east of Madagascar. The population of just over 1 million is of predominantly Asian Indian origin (53.6% Hindu and 16.4% Muslim), 2.1% are Chinese, and 27.9% are of the general population, which is mainly people of mixed African, Malagasy, and European ancestry (Creoles).

All adults aged 25 to 74 years living within 11 geographically defined clusters were eligible for the 1987 baseline survey, as described previously.[11] Overall response (N = 5,080) was 83% in men and 89% in women.[11] All subjects still alive and living in Mauritius were eligible for the 1992 follow-up survey,[12] and longitudinal data were available for 3,752 individuals. Subjects were excluded from the analyses if there were inconsistencies between measurements taken at the two surveys that suggested an error in identity linkage or measurement (n = 28). Women who were pregnant at either survey were also excluded (n = 57), and analysis was limited to nondiabetic subjects (ie, normal or impaired glucose tolerance) at baseline, leaving a final study population of 1,486 men and 1,670 women. Subjects who developed NIDDM

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over the study period were retained in the analyses, since their exclusion did not alter the nature of the results.

Survey Procedure

Similar methods were used in the 1987 and 1992 surveys.[11,12] Subjects had a fasting 75-g (dextrose monohydrate) oral glucose tolerance test, and glucose tolerance was classified according to current World Health Organization criteria modified for epidemiological studies.[13] Plasma glucose level was measured immediately with a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Fasting and 2-hour insulin level was measured in serum transported on dry ice to Newcastle-upon-Tyne, using a modification of the method of Soeldner and Slone.[14] Interassay and intraassay coefficients of variation were 4% and 6%, respectively. Cross-reactivity with intact proinsulin and 32,33-split proinsulin was 27% and 16%, respectively. There was less than 5% difference between results obtained with this assay and a highly specific enzyme-linked immunosorbent assay.

Subjects were weighed and height was measured without shoes and in light clothing only, using a standard lever balance with attached height device. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist and hip circumferences were measured in duplicate, with subjects standing relaxed and in underclothes (1987) or light clothing (1992). Waist circumference was measured at the midpoint between the lower costal margin and the iliac crest, and hip circumference was measured at the horizontal level around the buttocks posteriorly that yielded the maximum measurement. If duplicate measurements differed by more than 2 cm, a third was taken. The mean of duplicate (or closest two) measurements was used to calculate the waist to hip ratio (WHR).

HOMA Model

The homeostatic model approach (HOMA) was used to estimate insulin sensitivity and β-cell function from fasting insulin and glucose values. For any combination of insulin resistance and β-cell function, this model predicts unique values of basal insulin and glucose or vice versa.[15,16] Results from HOMA correlate well with estimates obtained by clamp techniques and intravenous glucose tolerance tests.[15] Imprecision limits clinical use in classifying individuals, but the approach appears useful in analysis of epidemiologic data. Although the model was developed using data from whites, Dowse et al[17] tested the model in the Mauritian population and found that HOMA estimates were more strongly and consistently associated with other correlates of insulin resistance than were fasting insulin or the fasting insulin to glucose ratio.

Statistical Analyses

All analyses were performed using SPSS/PC+ statistical software.[18] Weight change over the 5-year follow-up period was calculated, and subjects were classified as gainers if weight had increased by at least 1 kg, maintainers if weight had remained within 1 kg of initial weight, and losers if weight had decreased by at least 1 kg. Pancreatic β-cell function (HOMAB) and insulin sensitivity (HOMAS) were estimated, and the ratio of fasting insulin to fasting glucose was also calculated as a measure of insulin sensitivity.

All glucose, insulin, and HOMA variables were transformed logarithmically (base e) to normalize distributions before analysis. Geometric means of fasting and 2-hour serum insulin and plasma glucose plus HOMAB, HOMAS, and the fasting insulin to glucose ratio were calculated for categories of weight change for men and women of each ethnic group. Multivariate ANOVA was used to examine the independent effects of weight change category, ethnic group, and sex on baseline metabolic and anthropometric parameters.

Crude and partial correlations (adjusting for baseline age, or age and BMI) were calculated for change in weight or WHR versus metabolic parameters with two-sided tests of significance. Age-adjusted mean changes in weight and WHR were calculated by sex/ethnic-specific quintiles of fasting insulin, fasting insulin to glucose ratio, and HOMAS by covariance analysis. This analysis was also performed with each sex/ethnic group stratified on the basis of sex/ethnic-specific median BMI into fat and lean subgroups. BMI by insulin sensitivity marker interaction terms were also tested. Linear regression analyses were computed for each sex/ethnic group to examine the independent effects of baseline age, BMI, WHR, HOMAB, and HOMAS on changes in weight and WHR with all variables forced into the model.

RESULTS

Table 1 shows baseline characteristics of gainers, maintainers, and losers for each sex and ethnic group. In each group, the majority of subjects gained weight between the two surveys, with the proportion of gainers varying from 46% in Chinese men to 70% in Creole men. Chinese men and women had smaller weight changes (positive or negative) than Asian Indians or Creoles. Gainers were younger and leaner (by both BMI and WHR) than those who lost weight, and maintainers generally had intermediate values. Weight change category was associated with baseline age, BMI, and WHR independently of ethnicity and sex.

Weight change, sex, and ethnic group contributed significantly to variations in all glucose, insulin, and HOMA variables, except that 2-hour glucose did not vary across ethnic groups (Table 2). There was a consistent trend for higher geometric-mean fasting and 2-hour insulin and glucose concentrations and fasting insulin to glucose ratio in losers than in gainers among each sex and ethnic group except Chinese men. Among women of each ethnic group, HOMAB (an estimate of β-cell function) was also greater in losers than in gainers, but results were inconsistent in men. Geometric-mean insulin sensitivity (HOMAS) was higher in subjects who gained weight in all subgroups except Chinese men.

To assess further the relationships of change in weight and WHR with markers of glucose-insulin metabolism, crude and partial correlation coefficients (adjusted for baseline age and BMI) were calculated within each sex/ethnic group (Tables 3 and 4). Crude correlations of fasting and 2-hour insulin and glucose, fasting insulin to glucose ratio, and HOMAB were invariably negative for all subgroups except Chinese men, although only correlations with fasting or 2-hour glucose were consistently significant. Crude correlations of HOMAS with weight change were positive for all groups except Chinese men, but were significant only for Asian Indian and Creole women. Adjustment for baseline age and BMI weakened associations between weight gain and metabolic parameters, and relationships tended to lose significance (Table 3). By contrast, in Chinese men, controlling for age and BMI resulted in stronger and opposing correlations with markers of insulin resistance and β-cell function.

Similar patterns were observed when correlations of

Table 1. Baseline Characteristics (mean) of Weight Gainers, Maintainers, and Losers by Ethnic Group and Sex: Mauritius 1987 to 1992

	Indian			Creole			Chinese			*P* (ANOVA)*		
Characteristic	Gain	Maintain	Lose	Gain	Maintain	Lose	Gain	Maintain	Lose	Change	Ethnic	Sex
Men												
No.	635	161	215	264	52	59	46	20	34			
%	62.8	15.9	21.3	70.4	13.9	15.7	46.0	20.0	34.0			
Age (yr)	37.4	44.4	44.7	40.6	47.3	48.2	42.3	45.9	49.2			
	(10.2)	(12.0)	(12.4)	(12.7)	(13.0)	(12.2)	(11.7)	(11.5)	(11.0)	<.001	<.001	.015
BMI (kg/m²)	22.7	22.4	23.3	22.8	22.9	24.0	22.8	23.7	25.8			
	(3.4)	(3.6)	(3.5)	(3.5)	(3.8)	(3.4)	(3.0)	(3.0)	(3.0)	<.001	<.001	<.001
WHR	0.882	0.890	0.901	0.873	0.879	0.892	0.877	0.875	0.919			
	(0.06)	(0.06)	(0.06)	(0.06)	(0.05)	(0.05)	(0.06)	(0.06)	(0.05)	<.001	.023	<.001
Weight change (kg)	4.82	0.05	−3.55	5.35	0.11	−4.32	4.24	0.21	−3.10			
	(3.1)	(0.5)	(3.1)	(3.1)	(0.6)	(4.2)	(3.6)	(0.5)	(1.9)		.037	.036
Women												
No.	763	172	223	283	60	80	47	19	23			
%	65.9	14.9	19.3	66.9	14.2	18.9	52.8	21.3	25.8			
Age (yr)	38.7	43.2	47.3	42.1	46.1	49.3	41.2	43.7	49.7			
	(11.0)	(12.8)	(13.8)	(12.8)	(13.6)	(13.4)	(10.8)	(43.4)	(10.7)			
BMI (kg/m²)	23.4	23.8	24.6	24.4	24.9	27.1	22.8	23.7	23.4			
	(4.6)	(4.2)	(4.6)	(4.8)	(4.6)	(5.4)	(3.3)	(3.3)	(3.1)			
WHR	0.795	0.804	0.816	0.812	0.820	0.841	0.783	0.780	0.808			
	(0.06)	(0.07)	(0.07)	(0.06)	(0.07)	(0.07)	(0.04)	(0.05)	(0.05)			
Weight change (kg)	5.28	0.03	−3.69	5.67	−0.05	−3.81	3.66	0.10	−3.01			
	(3.3)	(0.5)	(3.0)	(3.7)	(0.5)	(2.4)	(2.5)	(0.6)	(1.9)			

NOTE. Numbers in parentheses are standard deviations.

*ANOVA for independent effects of weight change category, ethnicity, and sex on various baseline characteristics.

markers of insulin sensitivity with change in WHR were examined (Table 4). Adjustment for age and BMI dramatically diminished correlations in most groups. Results in Chinese subjects were inconsistent.

Age- and BMI-adjusted means of change in weight and WHR were computed for sex- and ethnic-specific quintiles of metabolic markers of insulin sensitivity: fasting insulin, fasting insulin to glucose ratio, and HOMAS. There were no significant differences in weight change across quintiles of metabolic variables in Asian Indian or Creole men, but among Indian men weight gain tended to be lowest in subjects who were most insulin-resistant as reflected by the upper quintile of fasting insulin and the fasting insulin to glucose ratio and the lower quintiles of HOMAS (Table 5). Among Chinese men, a different pattern emerged: weight gain varied significantly across quintiles of fasting insulin, fasting insulin to glucose ratio, and HOMAS, with the greatest gains occurring in the most insulin-resistant sub-

Table 2. Baseline Levels of Metabolic Factors by Weight Change Category, Sex, and Ethnic Group: Mauritius 1987 to 1992

	Indian			Creole			Chinese			*P* (ANOVA)†		
Factor	Gain	Maintain	Lose	Gain	Maintain	Lose	Gain	Maintain	Lose	Change	Ethnic	Sex
Men												
Fasting insulin (μU/mL)	4.9	4.3	5.3	3.9	4.0	5.0	5.7	6.2	4.8	<.001	.008	<.001
2-hour insulin (μU/mL)	27.2	29.1	30.1	18.9	21.2	24.16	26.0	30.1	26.7	.001	<.001	.001
Fasting glucose (mmol/L)	5.1	5.2	5.3	5.3	5.5	5.5	5.6	5.6	5.5	<.001	<.001	<.001
2-hour glucose (mmol/L)	5.6	6.0	6.0	5.6	5.8	6.2	6.0	6.2	6.3	<.001	.270	<.001
Fasting I/G	0.96	0.82	1.00	0.74	0.73	0.90	1.02	1.10	0.90	.001	<.001	<.001
HOMAB (%)	82.7	73.4	82.1	66.2	63.0	72.1	76.1	80.2	71.2	.021	<.001	<.001
HOMAS (%)	77.3	88.0	71.8	95.9	92.6	75.0	65.4	60.3	74.8	<.001	.019	<.001
Women												
Fasting insulin (μU/mL)	5.9	6.1	7.1	5.4	6.1	7.4	5.0	6.0	6.2			
2-hour insulin (μU/mL)	40.4	41.1	47.0	33.6	40.6	40.3	32.3	35.9	42.2			
Fasting glucose (mmol/L)	5.0	5.1	5.2	5.3	5.4	5.6	5.2	5.5	5.4			
2-hour glucose (mmol/L)	6.4	6.6	6.8	6.3	7.0	7.0	6.5	7.0	6.7			
Fasting I/G	1.17	1.18	1.37	1.02	1.12	1.34	0.96	1.10	1.14			
HOMAB (%)	97.0	94.4	102.7	83.1	84.4	92.4	79.6	82.5	86.6			
HOMAS (%)	65.4	63.0	54.0	70.9	61.8	50.3	75.4	62.2	60.9			

NOTE. All values are geometric means.

Abbreviation: I/G, insulin to glucose ratio.

*ANOVA for independent effects of weight change category, ethnic group, and sex on various metabolic parameters associated with insulin resistance and β-cell function.

Table 3. Crude and Partial Correlation Coefficients for Weight Change With Metabolic Factors in Mauritians

Factor	Men		Women	
	Crude	Adjusted for Age and BMI	Crude	Adjusted for Age and BMI
Indian				
BMI	−.1014†		−.1261‡	
Fasting insulin	−.0466	−.0067	−.0831†	−.0495
2-hour insulin	−.0960†	−.0474	−.0987‡	−.0649*
Fasting glucose	−.0945†	−.0232	−.1684‡	−.0703*
2-hour glucose	−.1425‡	−.0666*	−.1530‡	−.0914†
Fasting I/G	−.0356	−.0035	−.0622*	−.0391
HOMAB	−.0119	.0034	−.0165	−.0174
HOMAS	.0489	.0074	.0889†	.0519
Creole				
BMI	−.1161*		−.1561†	
Fasting insulin	−.0906	−.0522	−.1263†	−.0939
2-hour insulin	−.0919	.0063	−.1097*	−.0722
Fasting glucose	−.1925‡	−.1427†	−.1650‡	−.0903
2-hour glucose	−.2060‡	−.1035*	−.1774‡	−.1175*
Fasting I/G	−.0680	−.0320	−.1043*	−.0812
HOMAB	−.0149	.0156	−.0517	−.0492
HOMAS	.0971	.0584	.1326†	.0974*
Chinese				
BMI	−.3210†		−.1282	
Fasting insulin	.1494	.3065†	−.1311	.0108
2-hour insulin	.0134	.1199	−.1999	−.1602
Fasting glucose	−.0092	.0519	−.2139*	−.0974
2-hour glucose	−.0695	−.0138	−.1161	−.1213
Fasting I/G	.1501	−.0812	−.1123	.0023
HOMAB	.1408	.2583*	−.0690	.0402
HOMAS	−.1507	−.3095†	.1359	−.0074

NOTE. All significance tests are two-sided.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

jects and mean weight losses in the most insulin-sensitive subjects. Among women, there were no significant differences in weight change across quintiles of insulin sensitivity markers except for fasting insulin in Chinese women, in whom the greatest weight gain occurred in the second and third quintiles. In general, more insulin-sensitive women gained more weight. The overall trend of greater weight gain in the more insulin-sensitive subjects, except in Chinese men, for whom the reverse was true, was consistent with earlier analyses.

The above analyses were repeated for each sex and ethnic group after stratification by BMI into lean (<median) and fat (≥median) subgroups. After stratification, the tendency for greater weight gain in more insulin-sensitive subjects, although still not significant, was more pronounced in the upper half of the BMI distribution in Asian Indians and Creole women. Conversely, the effect appeared greater in lean Creole men (results not shown), and the greater weight gain associated with insulin resistance in Chinese men was particularly marked in the lean subgroup. However, further investigation revealed that statistical interaction terms between baseline BMI and markers of insulin sensitivity were uniformly nonsignificant.

Similar analyses indicated no significant differences and little consistency in the relationships of change in WHR with quintiles of insulin sensitivity for Asian Indian or Creole men or women (data not shown). Among Chinese men, P values were significant for each metabolic parameter tested, and in general, a mean increase in WHR was greater in the more insulin-resistant quintiles.

Linear regression models were computed within each sex/ethnic group to assess the independent contributions of age, BMI, WHR, HOMAB, and HOMAS at baseline to variations in change in weight and WHR (Tables 6 and 7). Age was negatively associated with weight gain in each group and significantly independent in all but Chinese men. By contrast, age was positively associated with an increase in WHR and independently significant in all groups. Baseline BMI was also inversely related to increased weight and positively related to a change in WHR. Baseline WHR was negatively and independently associated with changes in WHR, but not weight. HOMAS was not independently related to change in WHR in any sex/ethnic group, but coefficients were negative for all. Among Chinese men, there was an independent inverse association between HOMAS and change in weight, but in other groups, the direction of the association was inconsistent and nonsignificant.

Table 4. Crude and Partial Correlation Coefficients for WHR Change in Mauritians

Factor	Men		Women	
	Crude	Adjusted for Age and BMI	Crude	Adjusted for Age and BMI
Indian				
BMI	−.2274‡		−.2936‡	
Fasting insulin	−.1311‡	.0012	−.2003‡	−.0502
2-hour insulin	−.1009†	.0007	−.1237‡	−.0222
Fasting glucose	−.0321	.0240	−.0988‡	−.0509
2-hour glucose	−.0568	.0214	−.1520‡	−.0821†
Fasting I/G	−.1302‡	−.0026	−.1927‡	−.0446
HOMAB	−.1202‡	−.0079	−.1638‡	−.0272
HOMAS	.1312‡	−.0016	.2036‡	.0531
Creole				
BMI	−.1977‡		−.3963‡	
Fasting insulin	−.1193*	−.0149	−.2220‡	−.0536
2-hour insulin	.0407	.1145*	−.0989*	.0218
Fasting glucose	.0333	.0335	−.1426†	−.0723
2-hour glucose	.1191*	.1474†	−.1017*	.0050
Fasting I/G	−.1250*	−.0198	−.2067‡	−.0436
HOMAB	−.1304*	−.0282	−.1646‡	−.0232
HOMAS	.1175*	.0139	.2249‡	.0556*
Chinese				
BMI	−.3774‡		−.0268	
Fasting insulin	−.1123	.1142	−.0073	−.0738
2-hour insulin	−.1617	−.0664	−.0179	−.0329
Fasting glucose	.02662	.0304	−.0292	−.1059
2-hour glucose	−.0853	−.1563	.0076	.0188
Fasting I/G	−.1155	.1092	−.0042	−.0629
HOMAB	−.1181	.0905	.0018	−.0372
HOMAS	.1104	−.1151	.0083	.0768

NOTE. All significance tests are two-sided.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table 5. Age- and BMI-Adjusted Mean Change in Weight (kg) by Quintiles of Metabolic Parameters Associated With Insulin Resistance

	Men			Women		
Quintile	Fasting Insulin	Fasting I/G	HOMAS	Fasting Insulin	Fasting I/G	HOMAS
Indians						
1	2.29	2.18	1.87	3.21	3.24	2.45
2	2.25	2.39	2.46	2.98	2.86	2.42
3	2.79	2.64	2.58	2.93	2.97	2.67
4	2.38	2.42	2.23	2.38	2.29	3.17
5	1.78	1.84	2.27	2.33	2.47	3.18
P	.260	.431	.548	.286	.269	.294
Creoles						
1	3.81	3.49	3.00	4.12	4.00	2.60
2	2.97	3.12	2.69	3.03	3.85	2.37
3	3.16	2.88	2.87	3.08	3.10	3.23
4	2.70	2.79	3.20	2.60	2.41	3.06
5	3.12	3.44	3.87	2.43	2.88	4.07
P	.708	.850	.638	.271	.357	.258
Chinese						
1	−1.61	−1.52	2.99	0.65	0.77	0.35
2	−0.24	0.17	0.99	2.71	2.64	0.14
3	2.87	1.60	2.59	2.79	1.00	1.91
4	1.21	1.64	−0.21	−0.16	1.26	2.63
5	2.47	2.80	−1.60	0.34	0.55	0.99
P	.004	.020	.002	.022	.425	.202

DISCUSSION

We have examined the association of several markers of baseline insulin sensitivity with weight gain and changes in fat distribution in three ethnic groups with a high prevalence of NIDDM. On the basis of fasting and 2-hour insulin and glucose, the fasting insulin to glucose ratio, and insulin sensitivity estimated by the HOMA model, subjects who gained weight appeared more insulin-sensitive than those who lost weight among Asian Indian and Creole men and women and Chinese women. By contrast, among Chinese men, the gainers appeared more insulin-resistant than the losers, a trend maintained throughout other analyses. However, after controlling for baseline obesity, these relationships were markedly attenuated in all subgroups except Chinese men. We are unable to explain the uniqueness of Chinese men in these analyses, although the relatively lower proportion of weight gainers in Chinese as compared with other subgroups may have some importance.

The results from sex/ethnic groups other than Chinese men lend some but not convincing support to findings in Mexican-Americans and non-Hispanic whites, in whom weight gainers had lower fasting insulin concentrations.[9,10] However, in the San Antonio Heart Study,[9] the relation of fasting insulin to weight gain only occurred in the most obese tertile of baseline BMI. It is not clear whether the relationship would have held if BMI was controlled within the obese subgroup, and therefore, the findings could be due to residual confounding by relatively lower BMI, which predicted weight gain in the overall data and is associated with lower insulin levels. Among the relatively lean individuals of San Luis Valley,[10] there was also a greater effect of fasting insulin on weight change in more overweight subjects, but the interaction of BMI by insulin was not significant. We did not find any convincing evidence for an interaction between BMI and insulin sensitivity in Mauritian subjects.

In the only other prospective report to examine this issue, studies in Pima Indians have shown that insulin-sensitive subjects gained more weight than insulin-resistant subjects, and the percent weight change per year was correlated with total glucose disposal, but especially glucose oxidation, during a hyperinsulinemic-euglycemic clamp independently of sex, initial weight, and age.[8] In contrast to the findings of the San Antonio Heart and San Luis Valley Diabetes studies, the association between insulin sensitivity and weight gain was stronger in less obese Pima subjects. The reasons for this difference are not clear, but may relate to the different methods used to assess insulin sensitivity and weight change, or perhaps to lifestyle factors. It is noteworthy that Mauritians of each sex/ethnic group were slimmer than the Pimas or the San Antonio population, with mean BMIs less than 25 kg/m^2, and this may influence the strength of the relationships observed. However, even when stratified by BMI, the relationship with markers of insulin sensitivity in lean versus obese subjects was inconsistent between sex-ethnicity subgroups.

Younger age and lower initial BMI were associated with increased weight gain in all Mauritian sex/ethnic groups, and fatter, older Mauritians were at greater risk of increases in WHR. The younger, slimmer subjects would also be expected to be the most insulin-sensitive, and indeed, after adjusting for age and baseline BMI, insulin sensitivity estimates were no longer associated with change in weight or WHR in most groups, although the negative association

Table 6. Standardized Regression Coefficients (β) for Age, BMI, WHR, HOMAB, and HOMAS in Linear Regression Models With Change in Weight as the Dependent Variable

	Men						Women					
	Indian		Creole		Chinese		Indian		Creole		Chinese	
Factor	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Age	−.331	<.001	−.277	<.001	−.056	.129	−.296	<.001	−.232	<.001	−.381	<.001
BMI	−.113	.006	−.083	.218	−.485	<.001	−.065	.069	−.100	.085	−.032	.798
WHR	−.026	.505	.008	.899	.104	.421	−.045	.190	.013	.827	−.188	.162
HOMAB	.008	.803	−.007	.912	.048	.070	−.025	.447	−.086	.127	−.017	.928
HOMAS	−.000	.996	.079	.183	−.0271	.026	.012	.709	.063	.273	−.182	.186
Adjusted R^2	.121		.081		.182		.106		.066		.139	

NOTE. All variables were forced into the equation.

Table 7. Standardized Regression Coefficients (β) for Age, BMI, WHR, HOMAB, and HOMAS in Linear Regression Models With Change in WHR as the Dependent Variable

	Men						Women					
	Indian		Creole		Chinese		Indian		Creole		Chinese	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Age	.128	<.001	.253	<.001	.377	<.001	.168	<.001	.222	<.001	.335	.003
BMI	.222	<.001	.198	<.001	.057	.594	.014	.647	−.119	.011	.135	.294
WHR	−.805	<.001	−.743	<.001	−.808	<.001	−.666	<.001	−.653	<.001	−.413	.003
HOMAB	.029	.368	.011	.828	.066	.510	.014	.618	.062	.170	.045	.727
HOMAS	−.024	.368	−.052	.287	−.090	.350	−.046	.104	−.035	.442	−.016	.910
Adjusted R^2	.443		.375		.473		.375		.406		.121	

NOTE. All variables were forced into the equation.

between markers of insulin sensitivity and change in weight in Chinese men was independent of age and baseline BMI.

The fact that younger, slimmer people gain the most weight is consistent with the theory that metabolic factors eventually limit further weight gain in obese subjects.[8,9,19] Prospective studies in Pima Indians have shown that higher insulin sensitivity, low basal metabolic rate, low spontaneous energy expenditure, and high 24-hour respiratory quotient predict weight gain.[20] However, in cross-sectional studies, these factors were all inversely related to fatness, and as weight was gained they all tended toward "normal" values, hence providing less stimulus for weight gain.

In a small study of 137 second-generation Japanese-American men, no significant correlations were seen between fasting or stimulated insulin or C-peptide levels and changes in BMI or weight, whereas basal and stimulated C-peptide but not insulin predicted visceral fat accumulation as measured by computed tomography.[21] Although the indicators of insulin secretion and visceral fat are clearly different, this contrasts with our failure to discern a relationship between β-cell function (HOMAB) and increases in WHR in Mauritians, regardless of ethnicity.

We have estimated relative insulin sensitivity in Mauritians using indicators derived from fasting insulin and/or glucose rather than actually measuring insulin-mediated glucose uptake, and this may weaken the reliability of our findings. Nevertheless, in the Mexican-Americans and non-Hispanic whites of San Antonio and San Luis Valley, fasting insulin was associated with weight gain in obese subjects.[9,10] Laakso[22] concluded that for population studies fasting insulin level could be used as a marker of insulin resistance, being more accurate in subjects with normal glucose tolerance. Although the HOMA model[15,16] has not been validated directly in Mauritians, a previous study in this population found that HOMA estimates of insulin sensitivity were more strongly associated with known modulating factors, including obesity and physical activity, than were fasting insulin levels or fasting insulin/glucose.[17] Thus, although our indicators of insulin sensitivity are indirect, our failure to find significant independent associations with weight change calls into question the hypothesis that insulin resistance limits further weight gain.

The reported results include all Mauritians who were nondiabetic at the baseline survey irrespective of their glucose tolerance status in the follow-up survey. It could be argued that including incident diabetics might confound the results, since subjects who were more insulin-resistant initially would be at greater risk of developing NIDDM,[23-25] which is in turn associated with increased risk of weight loss.[26] However, when analyses were repeated excluding incident diabetic subjects, the nature of results was not altered.

Studies in rodent models of obesity suggest that hyperinsulinemia, perhaps due to central nervous system abnormalities, leads to obesity and tissue insulin resistance.[27] Careful longitudinal studies in rhesus monkeys also suggest that increased insulin responsiveness and increasing body fat precede the development of insulin resistance, after which point body fat stabilizes or declines slightly.[28]

The observations in Pimas, San Antonio Mexican-Americans, and Mauritians are not necessarily inconsistent with the animal data or with the notion that hyperinsulinemia (or perhaps, more correctly, increased insulin responsiveness) with or without selective insulin resistance leads to obesity. Although these three studies were longitudinal, adult humans were studied and many individuals were already obese at baseline. Hence, by the time of the baseline examination, the negative-feedback loop may have already come into effect in many individuals, whereby the prevailing picture was that insulin resistance was limiting further weight gain.[8] However, as the animal studies suggest, hyperinsulinemia may precede the development of significant insulin resistance, and it seems likely that longitudinal changes in tissue selectivity of resistance further complicate the picture.

Although difficult to perform, longitudinal studies in humans are needed that follow individuals from youth and examine relative changes in basal insulin, insulin responsiveness, body fat, and insulin sensitivity in adipose tissue, muscle, and liver. As Hansen and Bodkin[28] have suggested, longitudinal studies that rely on only two observations and group individuals together may obscure critical phases of the pathogenetic pathway leading to obesity and glucose intolerance. Presumptive evidence for the primacy of insulin hypersecretion is provided by the observation of hyperinsulinemia in lean, normal children and adolescents of populations at high risk for obesity and NIDDM.[29] Moreover, a recent study of children at varying stages of obesity found that insulin hypersecretion in response to a meal

preceded the development of fasting hyperinsulinemia and insulin resistance,[30] in agreement with the rat and monkey models.[27,28]

Our findings and those of others[8-10] are not inconsistent with the thrifty genotype hypothesis, whereby an exaggerated insulin responsiveness may lead to increased fat deposition in the context of selective changes in insulin sensitivity in target tissues,[2,3] even if overall insulin sensitivity is somewhat reduced. Overly simplistic use of such terms as hyperinsulinemia and insulin resistance in part explains different interpretations of what the thrifty genotype hypothesis involves. Moreover, Neel[2] himself suggested three hypotheses, and he and others[7] have recognized that there may be many variants of the genotype between and within populations. Certainly, there is good evidence that obesity causes or exacerbates insulin resistance, and insulin resistance may indeed limit further weight gain.[8,19] It remains unclear whether insulin resistance per se leads to obesity, but in the context of insulin hyperresponsiveness, selective insulin resistance in muscle with preservation of sensitivity to lipogenic pathways in liver and adipose tissue may be important.

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