Features of the Metabolic Syndrome Predict Higher Risk of Diabetes and Impaired Glucose Tolerance

A prospective study in Mauritius

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OBJECTIVE — To assess the independent and joint effects of the components of the metabolic syndrome, including leptin, which is a recently proposed addition to this syndrome, in predicting the cumulative incidence of impaired glucose tolerance (IGT) and diabetes among individuals with normal glucose tolerance.

RESEARCH DESIGN AND METHODS — This prospective study involved 2,605 residents of Mauritius with normal glucose tolerance who were followed for 5 years for IGT or diabetes onset in relation to total and regional adiposity (BMI, waist-to-hip ratio [WHR]), fasting and 2-h 75-g oral glucose load glucose and insulin, total and HDL cholesterol, blood pressure, serum uric acid, triglyceride, and leptin levels.

RESULTS — A multivariate logistic regression model adjusted for age, sex, ethnicity, and diabetes family history showed a significantly higher linear increase in risk of IGT and diabetes in association with the following variables only: fasting glucose (odds ratio 1.89 [95% CI 1.51–2.34]), 2-h glucose (1.68 [1.50–1.88]), WHR (1.30 [1.10–1.52]), BMI (1.04 [1.00–1.08]), and serum uric acid (1.37 [1.20–1.57]). However, a nonlinear increase was seen with serum triglyceride and plasma leptin concentrations. No risk factors resulted in joint effects that were greater than expected from combining individual effects.

CONCLUSIONS — Metabolic syndrome features independently predict a higher risk of diabetes or IGT in normoglycemic subjects but in combination confer no higher-than-expected risk of these outcomes. At higher concentrations of triglycerides and leptin, risk plateaus and even declines slightly.

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The more frequent occurrence than expected by chance of multiple characteristics associated with poor cardiovascular and other health outcomes such as hyperglycemia, hypertension, and lipid abnormalities has given rise to the concept of the "metabolic syndrome" (1). A recent review of this syndrome identified 6 components that were included in most of the definitions (fasting or stimulated circulating insulin and glucose levels, triglyceride levels, HDL cholesterol levels, blood pressure levels, and overall or central obesity) (1). Also included in some definitions were serum uric acid (2–4) and total or LDL cholesterol (5) levels. Recent data from our group (6), the results of a factor analysis by others (7), and the demonstration of associations between leptin and both insulin sensitivity (8) and hyperinsulinemia (9) argue for leptin's involvement in the metabolic syndrome.

The significance of this syndrome regarding the development of cardiovascular disease is fairly well understood because many of its components are well-accepted cardiovascular disease risk factors, but this is less true regarding the prediction of deterioration in glucose tolerance. Although many studies have examined features of the metabolic syndrome in relation to risk of diabetes and impaired glucose tolerance (IGT), few have examined the effects of all 6 components. A 3.5-year follow-up of an elderly Finnish cohort that considered these 6 components revealed higher diabetes risk in association with presence of IGT or hypertension; higher fasting and 2-h plasma insulin levels, total triglyceride level, waist-to-hip ratio (WHR), and BMI; and lower HDL cholesterol levels (10). The independent effects of these correlated factors were not directly assessed in multivariate models. The importance of assessing whether metabolic syndrome components have independent effects on the risk of this outcome was demonstrated by an analysis conducted using San Antonio Heart Study data (11). A multivariate model developed to predict diabetes identified fasting and 2-h glucose levels, BMI, HDL cholesterol levels, and pulse pressure as having independent effects on the risk of diabetes during 8 years of follow-up (11). In this model, fasting insulin levels, triglyceride levels, subscapular-to-triceps skinfold ratio (a measure of central adiposity), and systolic and diastolic blood pressure did not have independent effects on diabetes risk, even though they were significantly related to higher risk in an age-, sex-, and ethnicity-adjusted analysis. Whether the effects of these independent variables in

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Abbreviations: HOMA %S, insulin sensitivity measured with homeostasis model assessment; IGT, impaired glucose tolerance; RR, relative risk; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

combination had effects on diabetes risk that were greater than expected from combining individual effects was not assessed.

Few studies have examined in a comprehensive fashion the effect of most metabolic syndrome components and leptin concentration on the risk of diabetes and IGT in a manner that permitted the assessment of the independent effects and testing for interaction between individual components. We therefore investigated this issue among residents of Mauritius with normal glucose tolerance at baseline who were followed for 5 years for the development of IGT or diabetes.

RESEARCH DESIGN AND METHODS

Background and subjects

Mauritius is a subtropical island located in the southwestern Indian Ocean about 800 km east of Madagascar. The multiethnic population consists of 70% individuals of Indian origin (54% Hindu and 16% Muslim), 2% individuals of Chinese origin, and the remaining 28% are Creoles predominantly of African and Malagasy ancestry with some European admixture.

All adults 25–74 years of age living within 11 geographically defined areas were eligible for the 1987 baseline survey as previously described (12,13). Overall response (n = 5,083) consisted of 83% of eligible men and 89% of eligible women. All subjects alive and willing to participate were eligible for the 1992 follow-up survey. Longitudinal 1987–1992 data were available for 3,793 subjects (74.6%). This analysis focuses on the development of diabetes and IGT among individuals who were initially normoglycemic (as defined below) in 1987 (n = 3,467), of whom 2,605 (75.1%) had longitudinal information available from both surveys. The survey protocol was reviewed and approved by the Alfred Healthcare Group Ethics Committee (Melbourne, Australia).

Survey procedures

The following procedures were carried out on all subjects in 1987 as previously described (12–15). Height was measured without shoes to the nearest centimeter. Weight was measured to the nearest 0.1 kg in light clothes and without shoes. BMI was calculated as weight in kilograms by height in meters squared. Waist and hip circumferences were measured in duplicate to the nearest 0.5 cm with a measuring tape while the subject was standing relaxed and wearing 1 layer of light clothing. A third measurement was taken if the first 2 were not within 2 cm of each another. The mean of the closest 2 measurements was used to calculate the WHR. The waist measurement was taken at the midpoint between the iliac crest and the lower rib margin, and the hip circumference was taken around the maximum circumference of the buttocks posteriorly and the symphysis pubis anteriorly. Participants were seated and rested for at least 5 min before systolic and fifth-phase diastolic blood pressure measurements were taken in duplicate using a standard mercury sphygmomanometer. Ethnicity was determined by self-report.

All subjects not taking diabetes medication had a 2-h 75-g (glucose monohydrate) oral glucose tolerance test after an overnight fast in 1987 and 1992. Diabetes was diagnosed if subjects reported a history of diabetes and were taking oral hypoglycemic medication or insulin or if the fasting plasma glucose level was $\geq$7.0 mmol/l or the 2-h value was $\geq$11.1 mmol/l (16). Subjects with a fasting plasma glucose level $<$7.0 mmol but a 2-h value from $\geq$7.7 to $<$11.1 were defined as having IGT. Subjects who did not meet the criteria for either IGT or diabetes were deemed normoglycemic (16).

Fasting and 2-h venous blood samples were centrifuged and separated immediately, and plasma glucose was measured on-site using Yellow Springs Instruments glucose analyzers (Yellow Springs, OH) within 3 h of collection. Serum samples were stored at −20°C and were transported on dry ice from Mauritius to Newcastle upon Tyne, U.K., in 1987 and later to Melbourne in 1996. Serum fasting and 2-h insulin measurements were analyzed in Newcastle upon Tyne using a modified method of Soeldner and Slone (17). The interassay and intra-assay coefficients of variation were 6 and 4%, respectively. Serum uric acid, fasting serum triglyceride, and HDL cholesterol levels in plasma were measured using manual enzymatic methods at the central laboratory in Mauritius. For quality assurance, every 10th sample was also analyzed in Newcastle upon Tyne. Triglyceride and total cholesterol values were consistently overestimated across the distribution and were adjusted downward using a calculated regression equation. Leptin was measured in 1996 by radioimmunoassay (Linco, St. Charles, MO). The limit of detection for the assay is 0.5 ng/ml in human serum or plasma with acceptable interassay (8.2%) and intra-assay (4.1%) coefficients of variation. A measure of insulin sensitivity was estimated using homeostasis model assessment (HOMA %S) (18).

Statistical analysis

All statistical analyses were performed using Stata Version 6.0 (College Station, TX). Logistic regression analysis was used to estimate odds ratios (95% CIs) and P values for the independent associations between metabolic syndrome components and the odds of developing diabetes or IGT coded as a dichotomous variable (0 = normoglycemia, 1 = IGT or diabetes) (19). A backwards selection algorithm was used to arrive at the best final model. To assess whether nonlinear effects were present between diabetes or IGT occurrence and metabolic syndrome components, the risk of the dependent variable was plotted against the independent variable divided into 20 quantiles, and visual inspection was used to assess departures from linearity, which were modelled with appropriate transformations. To assess whether effect modification existed when multiple components of the metabolic syndrome were present simultaneously, first-order interaction terms were tested for significance in logistic regression models with the threshold for rejection of the null hypothesis of no interaction set at $P < 0.05$. This analysis permitted formal assessment of whether joint effects of metabolic syndrome components exceeded the expected combination of individual effects on the incidence of the outcomes of interest. Relative risk (RR) of diabetes or IGT was calculated in crude and stratified analyses using standard methods (19).

RESULTS

— A total of 2,605 subjects with normal glucose tolerance in 1987 and follow-up data in 1992 were available for analysis. Mean age for study subjects was 40.4 years and ranged from a low of 25 years to a high of 74 years. Subjects included 48.9% men and 51.1% women. Among these individuals, 356 (13.7%) developed IGT and 159 (6.1%) developed diabetes during the 5-year follow-up, which gave annual incidence rates of 2.9 and 1.3%, respectively.

Characteristics of study subjects by whether diabetes or IGT developed during follow-up in univariate analyses are shown in Table 1. Sex, ethnicity, and diabetes family history were not significantly related to diabetes or IGT odds. Regarding features of

Table 1—*Baseline characteristics of study subjects in relation to the occurrence of IGT and diabetes at the end of the follow-up period*

Characteristic	Normal glucose tolerance	IGT	Diabetes	Diabetes or IGT vs. normal glucose tolerance
n	2,090	356	159	
Age (years)	39.5 ± 11.8	43.4 ± 12.1	45.3 ± 12.3	3.3 (2.4–4.5)
Sex				
Men	48.7	40.7	70.4	1.0 (referent)
Women	51.3	59.3	29.6	1.0 (0.8–1.2)
Ethnicity				
Indian (Hindu)	54.8	55.1	54.7	1.0 (referent)
Indian (Muslim)	14.9	17.4	11.3	1.0 (0.8–1.4)
African Creole	24.9	21.1	26.4	0.9 (0.7–1.2)
Chinese	5.4	6.5	7.6	1.3 (0.8–1.9)
Family history of diabetes	20.1	22.8	21.4	1.1 (0.9–1.4)
BMI (kg/m^2)	22.8 ± 3.8	24.6 ± 4.5	24.2 ± 4.3	1.5 (1.4–1.7)
WHR	0.83 ± 0.07	0.85 ± 0.07	0.88 ± 0.08	1.7 (1.5–1.9)
Systolic blood pressure (mmHg)	122.0 ± 16.8	127.4 ± 19.3	131.2 ± 19.1	1.3 (1.2–1.5)
Diastolic blood pressure (mmHg)	75.3 ± 11.2	78.5 ± 11.2	81.5 ± 12.7	1.4 (1.3–1.5)
Serum triglycerides (mmol/l)	1.35 ± 1.04	1.50 ± 0.93	1.83 ± 1.31	See triglycerides model below
Plasma HDL cholesterol (mmol/l)	1.30 ± 0.34	1.27 ± 0.30	1.22 ± 0.32	0.8 (0.8–0.9)
Serum uric acid (mmol/l)	0.34 ± 0.08	0.36 ± 0.09	0.40 ± 0.09	1.5 (1.4–1.7)
Fasting plasma insulin (μU/ml)	6.48 ± 5.53	8.60 ± 6.50	8.38 ± 7.88	1.4 (1.3–1.5)
2-h plasma insulin (μU/ml)	37.67 ± 34.62	54.05 ± 49.81	48.85 ± 50.23	1.4 (1.3–1.6)
HOMA %S	114.6 ± 108.8	85.6 ± 92.1	98.9 ± 101.3	0.7 (0.6–0.8)
Fasting plasma glucose (mmol/l)	5.10 ± 0.49	5.25 ± 0.54	5.51 ± 0.57	1.5 (1.4–1.7)
2-h plasma glucose (mmol/l)	5.61 ± 1.14	6.39 ± 0.98	6.20 ± 1.07	2.1 (1.9–2.4)
Fasting plasma leptin (ng/ml)	8.52 ± 9.69	10.56 ± 8.80	7.52 ± 6.86	See leptin model below
Leptin model (leptin + $\log_e$ plasma leptin, 25th vs. 1st percentile)				1.7 (1.4–2.1)
Leptin quintiles				
1 (lowest)				1.0 (referent)
2				1.0 (0.7–1.4)
3				1.9 (1.3–2.7)
4				2.2 (1.6–3.1)
5				2.6 (1.8–3.6)
Triglycerides model (triglycerides + $\log_e$ serum triglycerides, 25th vs. 1st percentile)				2.1 (1.6–2.8)
Triglyceride quintiles				
1 (lowest)				1.0 (referent)
2				1.3 (0.9–1.9)
3				1.8 (1.3–2.5)
4				1.7 (1.2–2.4)
5				2.8 (2.0–3.9)

Data are *n*, means ± SD, %, or odds ratios (95% CIs). Odds ratios for continuous variables reflect a 1-SD magnitude increase.

the metabolic syndrome, all measures were significantly related to diabetes or IGT odds in the expected directions. Higher plasma leptin was significantly related to higher odds of diabetes or IGT. By visual examination, plots of the risk of diabetes or IGT in relation to triglyceride quantiles appeared nonlinear with a plateau followed by a slight decline at higher levels (Fig. 1*A*). A similar association was seen for plasma leptin (Fig. 1*B*). Because leptin levels differ markedly by sex in this and other populations, this relationship was reexamined by sex, but similar associations were seen (Fig. 1*C* and *D*). Therefore, multivariate models were fit with $\log_e$ transformations of these variables in addition to the linear term (Table 1). Because both the linear and $\log_e$ transformations of these variables were significant in these models at $P < 0.05$, this finding rejects the hypothesis that a linear association exists between diabetes or IGT odds and leptin or triglyceride levels. The relative odds of diabetes or IGT in relation to quintiles of leptin and triglycerides inserted into each model shown in Table 1 as a set of dummy variables demonstrated the leveling off of risk with increasing level, more so for leptin than for triglycerides.

Analysis of leptin effects on diabetes or IGT risk was further examined by estimating the RR of diabetes or IGT in crude and stratified analyses. In crude analysis, the RR (95% CIs) of diabetes or IGT for leptin concentration above the median value was 1.7 (1.4–2.0). A higher RR was seen in men (2.0

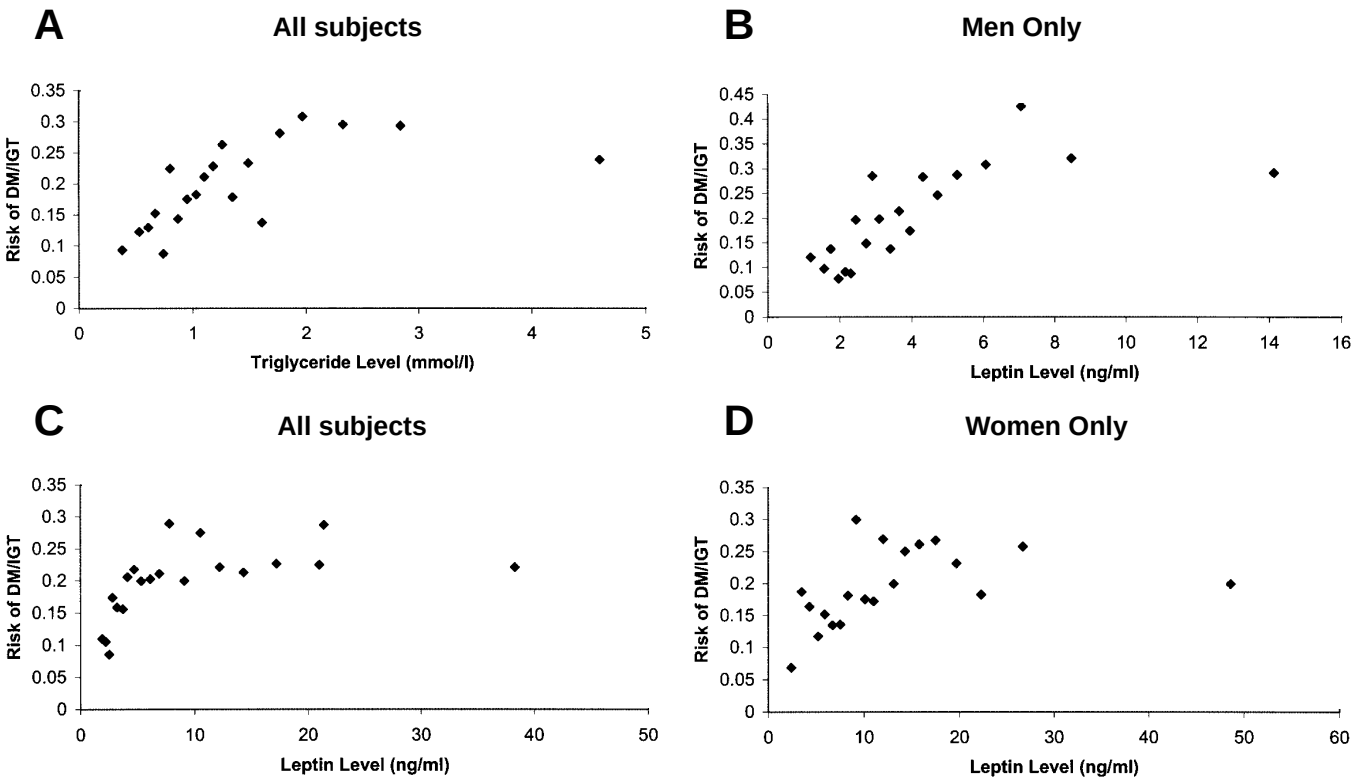

Figure 1—*Risk of the combined outcome in relation to quantiles (*n *= 20) of serum triglycerides (*A*) and plasma leptin levels (*B–D*). Mean triglyceride and leptin levels for each quantile are shown on the* x*-axis, and risk of diabetes or IGT (DM/IGT) is shown on the* y*-axis.*

[1.6–2.5]) than in women (1.5 [1.2–1.8]), but this difference was not significant by the heterogeneity χ^2 test ($P = 0.07$). In analyses stratified by BMI and WHR dichotomized at the median value (BMI: men 22.5 kg/m^2, women 23.0 kg/m^2; WHR: men 0.88, women 0.79), RRs associated with leptin concentration above the median value did not differ at higher versus lower levels of overall adiposity (BMI less than or equal to the median 1.3 [0.9–1.7]; BMI greater than the median 1.3 [1.0–1.7]) or at higher versus lower levels of WHR (WHR less than or equal to the median 1.5 [1.1–2.0]; WHR greater than the median 1.4 [1.1–1.7]).

All metabolic syndrome features were inserted into 2 logistic regression models (1 containing HOMA %S and the other containing insulin levels to avoid collinearity) for the prediction of diabetes or IGT that also contained age, sex, ethnicity, and diabetes family history (Table 2, full model). In these full models, the following variables were no longer significantly related to the outcome: BMI, HDL cholesterol level, HOMA %S, systolic and diastolic blood pressure, and fasting and 2-h insulin levels. Using backward stepwise logistical regression on these full models yielded 1 reduced model (Table 2) that contained variables that independently predict diabetes or IGT occurrence. Nonlinear associations between these continuous variables (except for leptin and triglycerides) and diabetes incidence were tested using exponential and logarithmic transformations, but none represented an improvement in fit compared with the model shown that used simple linear terms. This analysis showed that WHR, fasting and 2-h plasma glucose levels, serum uric acid levels, leptin concentrations, and triglyceride levels significantly predicted the occurrence of diabetes or IGT, whereas BMI was nearly significantly related to this outcome ($P = 0.053$).

The reduced model was repeated with diabetes only as the outcome (Table 2). Odds ratios of a similar magnitude were seen when compared with the diabetes or IGT reduced model except in several instances. The odds ratios for serum triglycerides and the log of this value were closer to 1, whereas the fasting glucose odds ratio was greater. Statistical significance of these associations differed as would be expected because of the smaller number of diabetes ($n = 159$) versus diabetes or IGT ($n = 515$) outcomes.

Interaction was tested by the insertion of first-order interaction terms between all possible pairs ($n = 35$) of independent variables in the reduced model predicting diabetes or IGT. None of these interactions was significant. The interaction between BMI and leptin came closest with a P value of 0.107, but P values for the remaining terms were generally much larger. Also, no significant difference in the effects of the variables in the reduced model predicting diabetes or IGT were seen according to age, sex, ethnicity, or diabetes family history. Relative odds were calculated using the reduced logistic model coefficients for different comparisons of leptin and triglyceride levels adjusted for all covariates (Table 2). These comparisons demonstrate an increase in the odds of diabetes or IGT when these levels increase from near the minimum value, with leveling off and eventually a small decline in the odds at higher values (Table 2).

CONCLUSIONS — This analysis demonstrates that all features of the metabolic syndrome that we considered were related in the univariate analysis to a higher risk of worsening of glucose tolerance among members of this multiethnic study

population with normal glucose tolerance at baseline. In multivariate models, however, several of these features did not contribute independently to this risk, including blood pressure, insulin levels, HOMA %S, and HDL cholesterol levels.

Insulin resistance and/or hyperinsulinemia have been proposed as the common underlying pathophysiological mechanism(s) for the features of the metabolic syndrome, which include hyperglycemia. That hyperinsulinemia and HOMA %S, which is an indirect measure of insulin sensitivity, are not independently related to higher diabetes or IGT risk was surprising. This result should not be interpreted as refuting a role for insulin resistance in the pathogenesis of diabetes because glucose level in the fasting and stimulated states is in part a function of insulin sensitivity, possibly more so for the stimulated value (20,21). Plasma glucose levels also depend on several other factors that may not be adequately captured by insulin level or HOMA %S, including the ability of glucose to promote its own disposal (glucose effectiveness) and counterregulatory hormones (20). These other phenomena may influence future risk of worsening of glucose tolerance. Our finding is supported by an analysis of San Antonio Heart Study data, which showed no independent effect of fasting insulin on diabetes risk in a stepwise logistic model that contained fasting and 2-h glucose levels (11). Further research would help to clarify these associations.

Leptin, a hormone secreted by adipose tissue and implicated in body weight regulation, has been reported to increase the risk of diabetes in a cohort of nondiabetic Japanese Americans followed prospectively (22). In that analysis, plasma leptin concentration was positively correlated with a higher odds of diabetes or IGT, although a nonlinear association best described this relationship. As can be seen in Fig. 1 and in the analysis of leptin quintiles (Table 1), diabetes or IGT risk appears to plateau with increasing leptin concentration. After adjustment for covariates, the odds ratio for diabetes or IGT initially increases and then diminishes with increasing leptin concentration. Leptin has been shown to inhibit insulin binding in isolated rat adipocytes (23), thereby possibly decreasing peripheral insulin sensitivity, although other investigators have shown enhanced glucose uptake in rat skeletal muscle because of leptin (24). Also, leptin may inhibit release of insulin by pancreatic islet cells, which has been demonstrated in

Table 2—*Multivariate logistic regression models of the odds of conversion to diabetes or IGT from normal glucose tolerance in relation to features of the metabolic syndrome adjusted for age, sex, ethnicity, and diabetes family history*

Model	Odds ratios (95% CIs)*	*P*
Full model		
BMI	1.1 (1.0–1.3)	0.119
WHR	1.3 (1.1–1.5)	0.004
Systolic blood pressure	1.1 (0.9–1.3)	0.398
Diastolic blood pressure	1.0 (0.8–1.2)	0.842
Fasting insulin level	1.1 (0.9–1.2)	0.441
2-h insulin level	1.0 (0.9–1.1)	0.820
Fasting plasma glucose level	1.4 (1.2–1.6)	<0.001
2-h plasma glucose level	1.8 (1.6–2.1)	<0.001
Serum uric acid	1.4 (1.2–1.6)	<0.001
Plasma HDL cholesterol	1.0 (0.9–1.1)	0.959
Serum triglycerides + $\log_e$ serum triglycerides (25th vs. 1st percentile)	1.5 (1.1–2.1)	0.030
Plasma leptin + $\log_e$ plasma leptin (25th vs. 1st percentile)	1.3 (1.0–1.7)	0.002
Reduced model (outcome = diabetes or IGT)		
BMI	1.2 (1.0–1.4)	0.053
WHR	1.3 (1.1–1.5)	0.002
Fasting glucose level	1.4 (1.2–1.6)	<0.001
2-h glucose level	1.8 (1.6–2.1)	<0.001
Serum uric acid	1.4 (1.2–1.6)	<0.001
Serum triglycerides + $\log_e$ serum triglycerides (25th vs. 1st percentile)	1.6 (1.2–2.1)	0.0159
Plasma leptin + $\log_e$ plasma leptin (25th vs. 1st percentile)	1.3 (1.0–1.7)	0.003
Reduced model (outcome = diabetes)		
BMI	1.1 (0.8–1.4)	0.710
WHR	1.2 (0.9–1.6)	0.160
Fasting glucose level	1.8 (1.5–2.1)	<0.001
2-h glucose level	1.4 (1.1–1.7)	0.002
Serum uric acid	1.4 (1.1–1.7)	0.001
Serum triglycerides + $\log_e$ serum triglycerides (25th vs. 1st percentile)	1.4 (0.9–2.1)	0.255
Plasma leptin + $\log_e$ plasma leptin (25th vs. 1st percentile)	1.3 (0.9–2.0)	0.171
Diabetes or IGT reduced model (adjusted for age, sex, ethnicity, family history of diabetes, BMI, WHR, fasting and 2-h glucose, and uric acid level)		
Leptin comparisons (ng/ml)		
5.4 vs. 0.4 ng/ml	2.06 (0.97–4.40)	
10.4 vs. 5.4	1.02 (0.87–1.18)	
15.4 vs. 10.4	0.92 (0.83–1.01)	
20.4 vs. 15.4	0.88 (0.81–0.97)	
25.4 vs. 20.4	0.86 (0.79–0.95)	
Triglyceride comparisons (mmol/l)		
1.1 vs. 0.1	3.61 (1.51–8.67)	
2.1 vs. 1.1	1.14 (1.00–1.31)	
3.1 vs. 2.1	0.96 (0.85–1.09)	
4.1 vs. 3.1	0.90 (0.77–1.04)	
5.1 vs. 4.1	0.86 (0.73–1.02)	

The full model contains all independent variables shown in Table 1, whereas the reduced model results from backwards removal of nonsignificant independent variables from the full model. *Odds ratios are shown for a 1-SD increase in the value of the independent variable except where indicated otherwise.

vitro in human cells (25), thereby contributing to inadequate insulin secretion. Although serum leptin and insulin concentrations have been shown to be positively correlated independent of obesity (26), differences have been noted in the associations between these hormones and insulin sensitivity. The association between insulin sensitivity and leptin depends on BMI, whereas the association between insulin concentration and insulin sensitivity does not (9,27). The conflicting effects of leptin on glucose metabolism may explain the nonlinear association between leptin and diabetes or IGT odds if these effects occur differentially depending on the serum leptin concentration. Also, leptin concentration may reflect other physiological processes not directly measured in this study that alter diabetes or IGT odds independent of BMI, insulin concentration, or insulin sensitivity.

Although significantly associated with the development of diabetes or IGT in univariate analyses, the odds ratios for systolic and diastolic blood pressure approached 1 with adjustment for other important covariates. The association between blood pressure and insulin resistance and its role in the insulin resistance syndrome is inconsistent and difficult to characterize (28). Given that the effects of blood pressure on diabetes or IGT odds diminished with adjustment for covariates, blood pressure likely acts as a marker for other factors associated with a higher risk of glucose intolerance. Central body fat distribution (as reflected by higher WHR) and BMI were related to higher risk of diabetes or IGT, which was expected (29), although the latter was at borderline statistical significance. Serum triglyceride level was related to diabetes or IGT odds, whereas HDL cholesterol level was not related after adjustment for covariates. The association between triglyceride level and the outcome appeared similar to that of leptin, with leveling off of risk at higher levels and even a diminished effect as seen in the multivariate model. This nonlinear association between serum triglycerides and diabetes or IGT was unexpected and will require further investigation. A possible explanation may be that the mechanism driving very high serum triglyceride levels is not as strongly related to glucose metabolism as it is at lower levels and therefore would not be expected to confer the same elevation in risk of progression to diabetes or IGT. Other prospective research has yielded mixed results on the association between concentration of triglyceride or HDL cholesterol levels and diabetes risk in multivariate models (10,11,30–33). Serum uric acid was strongly associated with diabetes or IGT occurrence (Table 2). Uric acid has been proposed as a feature of the metabolic syndrome by several authors (3,4) but has not gained universal acceptance (1). Several other prospective or cross-sectional studies have revealed a high or borderline-high risk of diabetes and IGT in relation to increasing uric acid levels (31,32,34,35).

Features of the metabolic syndrome in combination had effects that can easily be calculated from the individual effects. Because logistic regression analysis was used to model the odds of these outcomes, the independent variables are expected to have multiplicative effects on the odds ratio. For example, the odds ratio for diabetes in relation to both a 1-SD increase in uric acid and a 1-SD increase in 2-h glucose would be $1.4 \times 1.8 = 2.5$. One definition of the presence of interaction, alternately referred to as "effect modification" or "synergism," is deviation from the multiplicative combination of individual effects and is in fact the test of interaction used in logistic regression models (19). We did not find any pairs of metabolic syndrome variables that resulted in a significantly greater- or lesser-than-expected odds ratio for diabetes or IGT. Therefore, this analysis did not support the theory that metabolic features act synergistically in combination to result in a higher (or lower) odds ratio than would be expected from combining the odds ratios for effects estimated individually.

The independent variables from the reduced model for the occurrence of diabetes or IGT were used to predict the development of diabetes only (Table 2). In general, the odds ratios for this outcome were of a similar magnitude to those in the diabetes or IGT model. *P* values were in general larger and in some cases became nonsignificant, although this may reflect the reduced power because of the smaller number of diabetes compared with diabetes or IGT outcomes. The nonlinear association between leptin and diabetes was still apparent in this analysis.

This study has several limitations. No direct measure of insulin sensitivity or body fat mass was available. Surrogate measures that imperfectly classify these variables were used instead. Bias associated with this probable nondifferential misclassification is likely to have resulted in underestimates of odds ratios. In accepting these assumptions, significant differences are therefore likely to represent underestimates of unknown magnitude. Follow-up glucose tolerance could not be assessed for ~25% of subjects. Whether these results can be generalized to ethnic groups not included in this study sample is not clear.

In conclusion, features of the metabolic syndrome were related in a nonsyngergistic manner to deterioration in glucose tolerance of Mauritian subjects during a 5-year follow-up period. Explaining a common pathway or mechanism through which all of these factors contribute to the development of glucose intolerance is difficult, which raises the possibility that multiple mechanisms may lead to this outcome. The unexpected nonlinear associations between worsening glucose tolerance and serum triglyceride or plasma leptin concentrations will require further investigation.

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References

1. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 20:157–172, 1998
2. Zimmet PZ, Collins VR, Dowse GK, Alberti KGMM, Tuomilehto J, Knight LT, Gareeboo H, Chitson P, Fareed D: Is hyperinsulinaemia a central characteristic of a chronic cardiovascular risk factor clustering syndrome? Mixed findings in Asian Indian, Creole and Chinese Mauritians: Mauritius Noncommunicable Disease Study Group. *Diabet Med* 11:388–396, 1994
3. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G: A metabolic syndrome in whites and African-Americans: the Atherosclerosis Risk in Communities Baseline Study. *Diabetes Care* 19:414–418, 1996
4. Cigolini M, Targher G, Tonoli M, Manara F, Muggeo M, De Sandre G: Hyperuricaemia: relationships to body fat distribution and other components of the insulin resistance syndrome in 38-year-old healthy men and women. *Int J Obes Relat Metab Disord* 19: 92–96, 1995
5. Howard BV, Mayer-Davis EJ, Goff D, Zaccaro DJ, Laws A, Robbins DC, Saad MF, Selby J, Hamman RF, Krauss RM, Haffner SM: Relationships between insulin resistance and lipoproteins in nondiabetic African Americans, Hispanics, and non-Hispanic whites: the Insulin Resistance

Atherosclerosis Study. *Metabolism* 47:1174–1179, 1998
6. de Courten M, Zimmet P, Hodge A, Collins V, Nicolson M, Staten M, Dowse G, Alberti KGMM: Hyperleptinaemia: the missing link in the metabolic syndrome? *Diabet Med* 14:200–208, 1997
7. Leyva F, Godsland IF, Ghatei M, Proudler AJ, Aldis S, Walton C, Bloom S, Stevenson JC: Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. *Arterioscler Thromb Vasc Biol* 18:928–933, 1998
8. Haffner SM, Miettinen H, Mykkanen L, Karhapaa P, Rainwater DL, Laakso M: Leptin concentrations and insulin sensitivity in normoglycemic men. *Int J Obes Relat Metab Disord* 21:393–399, 1997
9. Schwartz MW, Prigeon RL, Kahn SE, Nicolson M, Moore J, Morawiecki A, Boyko EJ, Porte D Jr: Evidence that plasma leptin and insulin levels are associated with body adiposity via different mechanisms. *Diabetes Care* 20:1476–1481, 1997
10. Mykkanen L, Kuusisto J, Pyorala K, Laakso M: Cardiovascular disease risk factors as predictors of type 2 (non-insulin-dependent) diabetes mellitus in elderly subjects. *Diabetologia* 36:553–559, 1993
11. Stern MP, Morales PA, Valdez RA, Monterrosa A, Haffner SM, Mitchell BD, Hazuda HP: Predicting diabetes: moving beyond impaired glucose tolerance. *Diabetes* 42: 706–714, 1993
12. Dowse GK, Gareeboo H, Zimmet PZ, Alberti KGMM, Tuomilehto J, Fareed D, Brissonnette LG, Finch CF: High prevalence of NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians: Mauritius Noncommunicable Disease Study Group. *Diabetes* 39:390–396, 1990
13. Dowse GK, Zimmet PZ, Gareeboo H, George K, Alberti KGMM, Tuomilehto J, Finch CF, Chitson P, Tulsidas H: Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. *Diabetes Care* 14:271–282, 1991
14. Dowse GK, Gareeboo H, Alberti KGMM, Zimmet P, Tuomilehto J, Purran A, Fareed D, Chitson P, Collins VR: Changes in population cholesterol concentrations and other cardiovascular risk factor levels after five years of the non-communicable disease intervention programme in Mauritius: Mauritius Non-Communicable Disease Study Group. *BMJ* 311:1255–1259, 1995
15. Nan L, Tuomilehto J, Dowse G, Zimmet P, Gareeboo H, Chitson P, Korhonen HJ, Alberti KGMM, Fareed D: Prevalence and medical care of hypertension in four ethnic groups in the newly-industrialized nation of Mauritius. *J Hypertens* 9:859–866, 1991
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
17. Soeldner JS, Slone D: Critical values in radioimmunoassay of serum insulin using the double antibody technique. *Diabetes* 14:771–779, 1965
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
19. Rothman KJ, Greenland S: *Modern Epidemiology.* Philadelphia, Lippincott-Raven, 1998
20. Bergman RN: Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 38:1512–1527, 1989
21. O'Rahilly S, Hattersley A, Vaag A, Gray H: Insulin resistance as the major cause of impaired glucose tolerance: a self-fulfilling prophesy? *Lancet* 344:585–589, 1994
22. McNeely MJ, Boyko EJ, Weigle DS, Shofer JB, Chessler SD, Leonetti DL, Fujimoto WY: Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. *Diabetes Care* 22:65–70, 1999
23. Walder K, Filippis A, Clark S, Zimmet P, Collier GR: Leptin inhibits insulin binding in isolated rat adipocytes. *J Endocrinol* 155: R5–R7, 1997
24. Ceddia RB, William WN Jr, Curi R: Leptin increases glucose transport and utilization in skeletal muscle in vitro. *Gen Pharmacol* 31:799–801, 1998
25. Kulkarni RN, Wang ZL, Wang RM, Hurley JD, Smith DM, Ghatei MA, Withers DJ, Gardiner JV, Bailey CJ, Bloom SR: Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. *J Clin Invest* 100:2729–2736, 1997
26. Zimmet P, Hodge A, Nicolson M, Staten M, de Courten M, Moore J, Morawiecki A, Lubina J, Collier G, Alberti G, Dowse G: Serum leptin concentration, obesity, and insulin resistance in western Samoans: cross sectional study. *BMJ* 313:965–969, 1996
27. Mohamed-Ali V, Pinkney JH, Panahloo A, Goodrick S, Coppack SW, Yudkin JS: Relationships between plasma leptin and insulin concentrations, but not insulin resistance, in non-insulin-dependent (type 2) diabetes mellitus. *Diabet Med* 14:376–380, 1997
28. Saad M, Lillioja S, Nyomba B, Castillo C, Ferraro R, De Gregorio M, Ravussin E, Knowler W, Bennett P, Howard B, Bogardus C: Racial differences in the relation between blood pressure and insulin resistance. *N Engl J Med* 324:733–739, 1991
29. Fujimoto WY, Bergstrom RW, Boyko EJ, Kinyoun JL, Leonetti DL, Newell-Morris LL, Robinson LR, Shuman WP, Stolov WC, Tsunehara CH: Diabetes and diabetes risk factors in second- and third-generation Japanese Americans in Seattle, Washington. *Diabetes Res Clin Pract* 24 (Suppl.): S43–S52, 1994
30. Skarfors ET, Selinus KI, Lithell HO: Risk factors for developing non-insulin dependent diabetes: a 10 year follow up of men in Uppsala. *BMJ* 303:755–760, 1991
31. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ* 310:560–564, 1995
32. Ohlson LO, Larsson B, Bjorntorp P, Eriksson H, Svardsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus: thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798–805, 1988
33. Njolstad I, Arnesen E, Lund-Larsen PG: Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark Study. *Am J Epidemiol* 147:49–58, 1998
34. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H: Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am J Epidemiol* 127:321–336, 1988
35. Balkau B, King H, Zimmet P, Raper LR: Factors associated with the development of diabetes in the Micronesian population of Nauru. *Am J Epidemiol* 122:594–605, 1985