Association of Physical Activity and Serum Insulin Concentrations in Two Populations at High Risk for Type 2 Diabetes but Differing by BMI

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OBJECTIVE — Physical activity and insulin sensitivity are related in epidemiological studies, but the consistency of this finding among populations that greatly differ in body size is uncertain. The present multiethnic epidemiological study examined whether physical activity was related to insulin concentrations in two populations at high risk for diabetes that greatly differ by location, ethnic group, and BMI.

RESEARCH DESIGN AND METHODS — The study populations consisted of 2,321 nondiabetic Pima Indian men and women aged 15–59 years from Arizona and 2,716 nondiabetic men and women aged 35–54 years from Mauritius. Insulin sensitivity was estimated by mean insulin concentration (average of the fasting and postload insulin), and total (i.e., leisure and occupational) physical activity was assessed by questionnaire.

RESULTS — Pima men and women who were more active had significantly ($P < 0.05$) lower mean insulin concentrations than those less active (BMI and age-adjusted means were 179 vs. 200 and 237 vs. 268 pmol/l). Similar findings were noted in Mauritian men and women (94 vs. 122 and 127 vs. 148 pmol/l). In both populations, activity remained significantly associated with mean insulin concentration controlled for age, BMI, waist-to-thigh or waist-to-hip ratio, and mean glucose concentrations.

CONCLUSIONS — Physical activity was negatively associated with insulin concentrations both in the Pima Indians, who tend to be overweight, and in Mauritians, who are leaner. These findings suggest a beneficial role of activity on insulin sensitivity that is separate from any influence of activity on body composition.

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Insulin resistance both precedes and predicts type 2 diabetes (1) and is a strong risk factor for the disease. Both fasting and postload insulin concentrations are correlated with measures of insulin resistance from the insulin clamp and, therefore, are used to estimate insulin resistance in population studies of nondiabetic individuals (2–4).

Obesity and fat distribution are involved in the pathogenesis of type 2 diabetes (5). Both overall obesity and fat distribution are thought to be independently related to diabetes development primarily through their role in increasing insulin resistance (6).

Physical inactivity is also a major risk factor for the development of type 2 diabetes. Two of the key mechanisms underlying this relationship between physical activity and diabetes involve the influence of physical activity on improving insulin sensitivity (7) and on decreasing the deposition of total fat and intra-abdominal fat (8). Since physical activity is related to both insulin sensitivity and obesity, adjusting for obesity is crucial to examine the independent role of physical activity on insulin sensitivity.

In two separate studies, we have demonstrated that physical activity is associated with glucose concentrations in two unrelated populations at high risk for type 2 diabetes at opposite ends of the world: the Pima Indians of Arizona and residents of Mauritius, an island nation located in the southwest Indian Ocean (9,10). It was hypothesized that these associations between physical activity and glucose concentration were mediated, at least in part, by the effects of physical activity on insulin sensitivity.

The current study tests the hypothesis that physical activity is significantly related to fasting and postload insulin concentrations—both estimates of insulin sensitivity—in nondiabetic Pima Indians of Arizona and residents of Mauritius. In both studies, physical activity was assessed using a modified version of the same activity questionnaire that is being used in a number of epidemiological studies of diabetes worldwide (11,12). A significant relationship between physical activity and serum insulin concentrations or insulin sensitivity has already been demonstrated in laboratory training studies (13) and more recently in population-based studies (14–17). The present

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Abbreviations: ADA, American Diabetes Association; MET, relative metabolic cost; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; WHO, World Health Organization.

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

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analysis provides unique information regarding the relationship between physical activity and serum insulin concentrations in two populations at high risk for diabetes that differ not only by location and ethnic group, but also by the level of obesity.

RESEARCH DESIGN AND METHODS

Residents of the Gila River Indian Community in Arizona

Study description. Pima Indians of the Gila River Indian Community of Arizona have participated in a longitudinal population-based National Institutes of Health diabetes research study since 1965. They have the world's highest documented incidence rates of type 2 diabetes (18) and have a high prevalence of obesity (5). Pima individuals ≥5 years of age who live in the designated study area constitute the current study population.

At intervals of ~2 years, each subject is invited for a comprehensive examination conducted at the study clinic (18). At each examination, a 75-g oral glucose tolerance test is performed, in which venous serum insulin and plasma glucose concentrations are determined after an overnight fast and 2-h postload. Diabetes is diagnosed if the 2-h postload glucose concentration is ≥11.1 mmol/l at this examination or during the course of routine medical care (19). Serum insulin levels are determined by radioimmunoassay. The examination also includes a medical history, physical examination, and measurement of height and weight. Obesity is estimated by BMI (weight in kilograms divided by the square of height in meters). Body fat distribution is estimated by the ratio of waist circumference (at the level of the umbilicus with the subject supine) to thigh circumference (measured at the highest level of the right thigh with the subject standing).

Physical activity interview. Since September 1987, a physical activity questionnaire has been administered by trained interviewers to individuals between 15 and 59 years of age who take part in these examinations. The physical activity questionnaire assesses both leisure and occupational physical activity over the past year. The activity questionnaire, interviewer's instructions, and questionnaire calculations have been described previously (11,12). This questionnaire was previously shown to be both reliable and valid (11,12).

Estimates for leisure and occupational activity were calculated separately as hours per week (h/week) averaged over the past year. Total physical activity was calculated by summing the leisure and occupational estimates. Each activity was also weighted by its relative metabolic cost (MET), thereby deriving MET hours (MET-h) per week (MET-h/week) as the final unit of expression. One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure (11,12).

To determine the relationship between physical activity and insulin concentrations, all physical activities reported in the questionnaire were included in the activity estimate with the exception of walking for exercise. The reporting of walking for exercise had previously been shown to be relatively unreliable in the Pima population (11).

Interviews judged not reliable by the trained interviewer were eliminated from the analyses (11). In addition, pregnant women were excluded from all analyses. Individuals with known or newly diagnosed type 2 diabetes (determined at the time of the activity assessment) based on the World Health Organization (WHO) criteria (19) or the recent American Diabetes Association (ADA) criteria (20) were excluded from all current analyses along with individuals who had a missing insulin or physical activity measure.

Residents of the island nation of Mauritius

Study description. The island nation of Mauritius is a rapidly developing country located east of Madagascar in the southwest Indian Ocean. Its multiethnic population of just over one million persons includes Hindu and Muslim Indians, Creoles, and a small Chinese settlement (21). Population-based studies were conducted in 1987 and 1992 as part of a national prevention and control program.

The overall response rate in 1992 was 89.1%, resulting in a sample size of 6,616 adults 25–74 years of age. For the present analyses, we restricted the sample to those individuals who were administered the detailed physical activity questionnaire, which included nonpregnant individuals between 35 and 54 years of age.

Subjects were asked to fast overnight before the morning of the survey. A 75-g oral glucose (dextrose monohydrate) tolerance test was administered as described previously (21). Fasting and 2-h postload glucose concentrations were determined on-site with a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH) using a glucose oxidase method. For consistency, individuals were eliminated from the present analyses if they had known or newly diagnosed type 2 diabetes based on either WHO (19) or ADA (20) criteria. Serum fasting and 2-h postload insulin concentrations were analyzed in Newcastle Upon Tyne, England, using a modified method of Soeldner and Slone (22).

Height and weight were measured and used to calculate the BMI. Waist and hip circumferences were measured to the nearest 0.5 cm with a measuring tape while the individual was standing relaxed in one layer of light clothing.

Physical activity interview. The activity questionnaire used in the Pima Indian study was modified for use in Mauritius based on popular leisure and occupational activities in that population. Since the reliability of walking for exercise appears to be reasonable in this population, summary leisure physical activity estimates for Mauritian subjects were calculated from data that included walking for exercise. The questionnaire was administered by trained interviewers who spoke Creole, the national lingua franca of Mauritius, and had assisted in pilot testing.

Statistical analysis for both population studies

Mean insulin concentration was defined as the sum of the log of the fasting insulin plus the log of the 2-h insulin concentration divided by two. Similarly, the mean glucose concentration was defined as the sum of the log of the fasting glucose plus the log of the 2-h glucose concentration divided by two.

Analyses of covariance were computed to examine BMI- and age-adjusted means of mean insulin concentration between the two physical activity categories (low and high activity, split at the median). Multiple regression analyses were performed to examine the independent association of current physical activity to mean insulin concentrations, controlled for age, BMI, fat distribution (i.e., waist-to-thigh ratio in the Pima Indians and waist-to-hip ratio in Mauritians), and

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Table 1—*General characteristics of 2,321 nondiabetic Pima Indians and 2,716 nondiabetic Mauritian men and women*

				Glucose concentration		Insulin concentration	
Age-group (years)	*n*	BMI	WTR	Fasting (mmol/l) Median (Q_1, Q_3)*	2-h (mmol/l) Median (Q_1, Q_3)*	Fasting (pmol/l) Median (Q_1, Q_3)*	2-h (pmol/l) Median (Q_1, Q_3)*
Nondiabetic Pima men and women (ages 15–59 years)							
Men							
15–20	366	27.7	1.5	5.2 (4.9, 5.5)	5.6 (4.6, 6.6)	90 (54, 156)	321 (150, 684)
21–36	463	32.1	1.6	5.4 (5.1, 5.7)	5.9 (4.9, 7.1)	108 (60, 204)	408 (168, 798)
37–51	150	32.1	1.7	5.4 (5.1, 5.9)	6.1 (5.2, 7.3)	120 (66, 204)	459 (210, 828)
52–59	28	30.9	1.9	5.7 (5.3, 6.1)	6.9 (6.2, 8.0)	84 (54, 120)	549 (300, 897)
Women							
15–20	424	30.0	1.4	5.1 (4.8, 5.3)	6.1 (5.2, 6.9)	114 (72, 192)	636 (324, 1,209)
21–36	640	34.3	1.6	5.2 (4.9, 5.6)	6.4 (5.6, 7.4)	114 (66, 180)	651 (324, 1,110)
37–51	213	34.8	1.7	5.4 (5.1, 5.9)	6.8 (5.8, 8.2)	108 (72, 174)	690 (354, 1,092)
52–59	37	33.1	1.8	5.7 (5.1, 5.9)	7.0 (5.8, 8.5)	96 (72, 210)	624 (282, 1,692)
Nondiabetic Mauritian men and women (ages 35–54 years)							
Men			WHR				
42.9 ± 5.5	1,270	24.2	0.91	5.5 (5.2, 5.9)	6.0 (5.0, 7.1)	50 (31, 80)	273 (134, 479)
Women							
43.2 ± 5.6	1,446	25.8	0.84	5.3 (5.0, 5.7)	6.6 (5.7, 7.6)	56 (37, 89)	390 (247, 587)

*Median values. Those in parentheses represent the 25th and 75th percentiles. WHR, waist-hip ratio; WTR, waist-thigh ratio.

mean glucose concentrations. In these analyses, the logarithmic transformations of insulin and glucose concentrations and BMI were used to reduce skewness. Similarly, the square root of current (past year) physical activity was used to improve the fit of the models, according to analysis of the residuals.

RESULTS — From the time the activity questionnaire was incorporated into the clinical examinations in September 1987, physical activity interviews and insulin measurements were completed on 2,321 nondiabetic Pima men and women aged 15–59 years (Table 1). BMIs and waist-to-thigh ratios were extremely high compared with most other populations, in agreement with former studies (5). Physical activity levels have been reported previously in this population (9). In general, leisure physical activity was the largest contributor to total physical activity levels for most of the Pima men and women, although occupational activity was the largest contributor among the few individuals (mostly men) who had physically active jobs (data not shown).

Among the four ethnic groups in Mauritius, physical activity interviews and insulin measurements were completed in 2,716 nondiabetic men and women aged 35–54 years (Table 1). The Mauritius sample (35–54 years of age) had substantially lower BMI values than the most similarly aged group of Pima Indians (37–51 years). Physical activity levels have also been previously reported in this population (10). In contrast to the Pima Indians, occupational physical activity was the largest contributor to total physical activity levels for both men and women in Mauritius. In fact, >90% of the total physical activity was due to occupational activity in the men with little activity of any sort reported in the Mauritius women (data not shown).

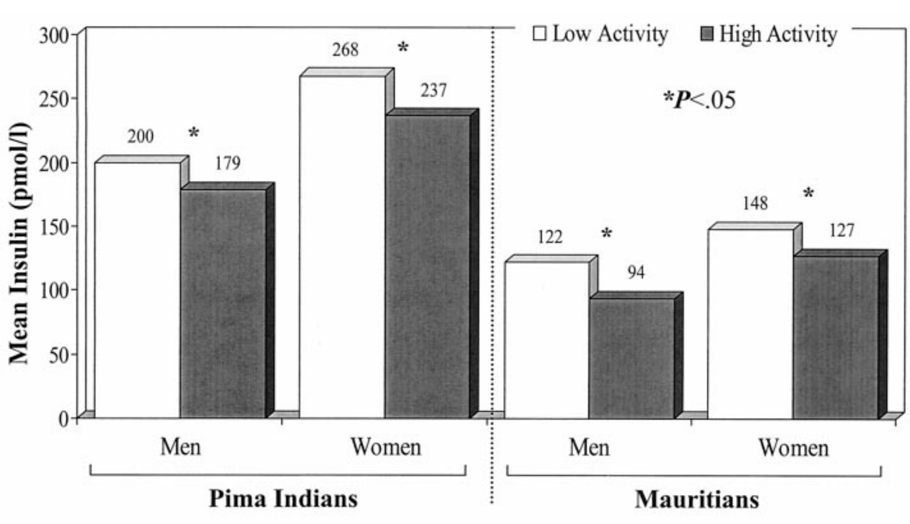

Figure 1—*Mean insulin concentration by physical activity level in Pima Indians (aged 15–60 years) and in residents of Mauritius (aged 35–54 years); geometric means adjusted for age and BMI.*

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Table 2—*Multiple linear regression analysis of mean insulin concentrations with reported past year total physical activity (leisure and occupational) in Pima Indians and Mauritius men and women without type 2 diabetes*

Variable	Dependent variable = Mean insulin* Nonstandardized regression coefficient	Standard error	P
Pima men and women			
Men			
Age (years)	–0.011	0.002	<0.001
BMI (kg/m²)*	1.573	0.120	<0.001
Waist-thigh ratio	0.012	0.144	0.934
Mean plasma glucose concentration (mmol/l)*	2.419	0.139	<0.001
Total activity (MET-h/week)	–0.017	0.004	<0.001
Women			
Age (years)	–0.017	0.002	<0.001
BMI (kg/m²)*	0.837	0.096	<0.001
Waist-to-thigh ratio	0.085	0.109	0.436
Mean plasma glucose concentration (mmol/l)*	2.678	0.137	<0.001
Total activity (MET-h/week)	–0.010	0.004	0.018
Mauritius men and women			
Men			
Age (years)	–0.011	0.003	<.001
BMI (kg/m²)*	0.080	0.005	<.001
Waist-hip ratio	2.288	0.396	<.001
Mean plasma glucose concentration (mmol/l)*	1.929	0.105	<.001
Total activity (MET-h/week)	–0.019	0.003	<.001
Women			
Age (years)	–0.011	0.002	<.001
BMI (kg/m²)*	0.046	0.003	<.001
Waist-hip ratio	1.040	0.250	<.001
Mean plasma glucose concentration (mmol/l)*	2.010	0.101	<.001
Total activity (MET-h/week)	–0.011	0.003	<.001

*The logarithm of the variable was used in the model. †The square root of physical activity was used in the model.

The BMI- and age-adjusted geometric means of mean insulin concentration are presented for the two activity categories (low and high) in Fig. 1. For both Pima and Mauritian men and women, those who were more physically active had significantly ($P < 0.05$) lower mean insulin concentrations than those in the low-activity group. Since the methods for measuring insulin differed between the Pima Indian study and the Mauritius study, comparisons of the absolute insulin values between the two studies are not justified.

Multiple regression analysis was used to determine whether physical activity was independently associated with the mean insulin concentration in nondiabetic Pima and Mauritian individuals (Table 2). In both men and women, current total physical activity (leisure and occupational), controlled for age, BMI, waist-to-thigh (or waist-to-hip) ratio, and mean glucose concentration, was significantly associated with mean insulin concentrations. The contribution of total physical activity to the model was higher if the dependent variable was 2-h postload insulin and lower if the dependent variable was fasting insulin. In addition, the contribution of total physical activity increased substantially when glucose concentration was removed from the model. Finally, if waist circumference is used in the model as an alternate measure of obesity, the results are similar (data not shown). The combined two-way interaction terms involving physical activity and the other independent variables did not significantly add to the model, so these interaction terms were not included in the models presented.

CONCLUSIONS — The independent relationships of total physical activity to mean insulin concentrations were similar in both populations, despite the fact that these two populations varied so greatly by obesity levels. Controlled for BMI and fat distribution, physical activity was significantly associated with mean insulin concentration (as well as with fasting and 2-h postload insulin concentrations separately; data not shown) both in the Pima Indians, who tend to be quite obese, and in the Mauritians, who are relatively leaner. Although these findings are cross-sectional and are limited by our estimate of insulin sensitivity, they suggest a beneficial effect of physical activity on insulin sensitivity that is separate from any influence of physical activity on body composition.

Early observations showed that both young and old athletes had lower glucose and insulin levels in response to a glucose load than age-matched nonathletes (23). Possible physiological mechanisms responsible for the beneficial influence of physical activity on insulin sensitivity include enhanced insulin receptor and postreceptor function, increased skeletal muscle insulin-sensitive glucose transporter proteins, increased skeletal muscle capillary density, and change in body composition (13,24). In fact, it appears that the enhanced insulin action in physically trained individuals involves not only muscle tissue but also liver and adipose tissue (25).

Physical activity training has been shown to enhance insulin sensitivity (7,13), and this effect appears to extend beyond that of body composition. Aerobic exercise training programs as brief as 7 days, in which no significant changes in body composition were noted, resulted in significant increases in whole-body insulin sensitivity (determined by a frequently sampled intravenous glucose tolerance test) in obese hypertensive African-American women (26). The beneficial effect of resistive exercise training on insulin sensitivity independent of weight loss is also starting to be recognized (27).

Likewise, epidemiological studies, including the current study, have identified a positive role of activity in insulin sensitivity. Many of the cross-sectional studies in nondiabetic individuals that have examined the association between physical activity and postload insulin concentrations (28,29) have found significantly

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higher insulin levels in less-active compared with more-active individuals. However, only a few cross-sectional studies have mirrored our findings of a significant relationship with activity and fasting insulin after adjusting for body size (14,16). Examining this question with a more valid measure of insulin sensitivity, the intravenous glucose tolerance test, Mayer-Davis et al. (17) demonstrated a positive association between both vigorous and nonvigorous physical activity and insulin sensitivity in a cross-sectional study of 1,467 men and women of African-American, Hispanic, and non-Hispanic white ethnicity who participated in the Insulin Resistance Atherosclerosis Study.

A few prospective studies have also examined this relationship, although not all of them adequately adjusted for body composition. In the Coronary Artery Risk Development in Young Adults Study, despite the fact that physical activity level was associated cross-sectionally with average fasting insulin in 18- to 30-year-old black and white men and women, change in activity over the 7-year study duration was not associated with a significant change in fasting insulin (16). In contrast, change in activity in Finnish adolescents and young adults was independently and inversely associated with changes in fasting insulin adjusted for subscapular skinfold thickness over a 6-year period in both sexes (15). Similarly, men who had the greatest reduction in activity over a 2.5-year period showed the largest increases in fasting insulin independent of changes in body weight (24).

Several reasons have been suggested to explain the failure of some of these studies to find a significant insulin-activity association independent of body size. Some of the differences in study results appear to be due to how insulin sensitivity was estimated. It appears that studies that have examined the relationship of physical activity and 2-h postload insulin concentration in nondiabetic individuals are more likely to find a significant relationship after controlling for obesity than those studies that used fasting insulin concentration as their estimate of insulin sensitivity (29,30). This result is consistent with our findings, in that the independent association of activity and 2-h postload insulin concentration adjusted for BMI and fat distribution was consistently stronger than that of fasting insulin in both sexes of both populations (data not shown). Although 2-h postload insulin concentration also partially reflects the insulin secretory response, it is still a good surrogate for insulin sensitivity. Previous research in Pima Indians had demonstrated that fasting insulin concentrations and insulin concentration determined 2 h after administration of an oral glucose load were both moderately correlated (approximately −0.60) with measures of insulin resistance from the insulin clamp in individuals with normal or impaired glucose tolerance (4).

In addition, some of the differences in study results may be due to the measurement of physical activity. Many of the existing studies found a significant relationship between insulin sensitivity and physical activity in men but not in women (14,15,31). Although the current study demonstrated a significant relation between mean insulin concentration and physical activity in both men and women, the association was relatively stronger in the men of both populations. Perhaps due to the historic tendency to conduct epidemiological research on men rather than women, physical activity questionnaires have been more oriented around the types of leisure-time and occupational activities typically performed by men. Women tend to engage in less intense activity and in child care and household activities, all of which are relatively more difficult to assess and less reproducible (12). Therefore, many of the currently used questionnaires may be less sensitive to differences in physical activity levels among women.

The independent association of physical activity with insulin sensitivity was much stronger when a direct measure of insulin sensitivity was used (e.g., a frequently sampled intravenous glucose tolerance test) than when fasting insulin concentration was used (17). Similarly, the relationship between physical activity and insulin sensitivity might be stronger if a more objective measure was used to assess physical activity level rather than an activity questionnaire. Thus, more valid measures of both insulin sensitivity and physical activity might strengthen the current findings.

In summary, physical activity and insulin concentrations were consistently and significantly correlated when controlled for obesity and fat distribution in two high-risk populations that differ not only by location and ethnic group, but also by level of obesity. The consistency of these results between populations—despite the limitations of the measures of insulin sensitivity and physical activity used—gives strong epidemiological support to the validity and potential importance of this association. The exact amount of physical activity that is needed to have a substantial impact on insulin levels goes beyond the limitations of a subjective activity questionnaire and must be answered by more objective measures. We turn to the clinical trials of diabetes prevention to provide insight into this issue.

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