The effect of insulin on net lipid oxidation predicts worsening of insulin resistance and development of type 2 diabetes mellitus

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Koska J, Ortega E, Bogardus C, Krakoff J, Bunt JC. The effect of insulin on net lipid oxidation predicts worsening of insulin resistance and development of type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 293: E264–E269, 2007; doi:10.1152/ajpendo.00662.2006.—Suppression of lipid oxidation (LOX) by insulin is impaired in obesity and type 2 diabetes mellitus (T2DM). Here we tested whether high LOX represents a primary or acquired characteristic in the pathogenesis of T2DM. Hood-indirect calorimetry was performed under postabsorptive conditions and during a two-step hyperinsulinemic euglycemic clamp (insulin infusion rates in mU·m⁻²·min⁻¹: 40 low and 400 high) in 465 Pima Indians: 317 with normal glucose tolerance (NGT), 117 with impaired glucose tolerance (IGT), and 31 with T2DM. The predictive effect of net lipid oxidation (LOX) on development of T2DM was assessed in 296 subjects (51 of whom developed T2DM), whereas the predictive effect of LOX on followup changes in insulin-mediated glucose disposal (M) and acute insulin response (AIR) was studied in 190 subjects with NGT at baseline. Cross-sectionally, after adjustment for age, sex, body fat (BF), and M, LOX low was increased in T2DM compared with NGT and IGT subjects (P < 0.05). Prospectively, after adjustment for followup duration, age, sex, BF, M, and AIR, increased clamp LOX predicted T2DM [hazard ratio (95% CI): LOX low, 1.5 (1.1, 2.0), P < 0.01; LOX high, 1.3 (1.0, 1.8), P = 0.05]. High LOX low at baseline was also associated with subsequent worsening of M (P = 0.04). These data indicate that the inability of insulin to suppress LOX may represent an early risk marker for insulin resistance and T2DM that is independent of adiposity, acute insulin secretion, and insulin action on glucose uptake.

Diabetes mellitus; euglycemic clamp; indirect calorimetry

GLUCOSE AND FATTY ACIDS ARE major substrates for oxidation in mammals. Utilization of both is regulated by insulin, although in a reciprocal fashion: insulin increases glucose oxidation while decreasing lipid oxidation (LOX) (31, 34). Insulin also stimulates fatty acid uptake and triglyceride synthesis in adipose tissue (17). Therefore, during fasting, when insulin levels are low and glycogen stores are depleted, energy is provided mainly by oxidation of fatty acids, whereas in the postprandial state, when insulin levels are high, glucose that is not used for glycogen synthesis becomes the prevalent substrate for oxidation. However, this postprandial decrease in LOX is absent in type 1 diabetes mellitus (29) and in states characterized by decreased insulin-mediated glucose disposal such as nondiabetic obesity or type 2 diabetes mellitus (T2DM) (13, 15, 18, 23, 28).

Experimental evidence indicates that relatively less suppression of LOX by insulin is not just a secondary marker of decreased glucose oxidation in the insulin-resistant state but represents a primary condition in the pathogenesis of T2DM (19, 30). In fact, increased LOX is inversely associated with nonoxidative glucose disposal and suppression of endogenous glucose production during hyperinsulinemia (13, 15). Moreover, increased LOX is associated with inhibition of insulin-signaling pathways that are upstream of glucose oxidation in humans (35) and with reduced glucose-induced insulin secretion in animals (36). On the other hand, variability in the systemic glucose level itself has a significant impact on the rates of LOX in skeletal muscle (28), which may explain reduced rates of fasting lipid oxidation in individuals with overt diabetes mellitus (13).

The Pima Indians of Arizona have one of the highest documented incidence rates of T2DM in the world (20). Prospectively, decreased insulin-mediated glucose disposal and low acute insulin secretion predict T2DM in Pima Indians with normal glucose tolerance (NGT) (25). Longitudinally in this population, the natural history of T2DM is a progressive decline in insulin-mediated glucose disposal and insulin secretory capacity (41). In cross-sectional analyses in a small group of 18 nondiabetic Pima Indian women, decreased insulin-mediated glucose uptake was associated with high rates of LOX during insulin infusion (23).

To investigate whether changes in LOX represent a primary or acquired characteristic in the setting of insulin resistance and T2DM, we evaluated the relationship of LOX rates under basal and hyperinsulinemic conditions with risk for T2DM both cross-sectionally by comparing Pima Indians with NGT, impaired glucose tolerance (IGT), and T2DM and prospectively by assessing the risk for development of T2DM and worsening of insulin-mediated glucose disposal and acute insulin secretion in Pima Indians with NGT.

MATERIALS AND METHODS

Subjects in this study were participants in an ongoing longitudinal study of the pathogenesis of type 2 diabetes initiated in 1982 (4). All participants were at least three-quarters Pima or closely related Tohono O’Dham Indians from the Gila River Indian Community near Phoenix, AZ. A total of 465 subjects (Table 1) were admitted to the Clinical Research Unit of the National Institutes of Health (NIH) in Phoenix and underwent testing for body composition, oral glucose tolerance, insulin-mediated glucose disposal with hood-indirect calorimetry, and early-phase insulin secretion (see below). All subjects were healthy according to a comprehensive medical history, physical examination, and routine blood and laboratory tests, and none smoked or took medications known to alter glucose or insulin metabolism at the time of the study. The study protocol was approved.

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by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the Tribal Council of the Gila River Indian Community. All subjects gave written informed consent before participation.

Upon arrival to the unit, the subjects were placed on a weight-maintaining diet (containing 50% of calories as carbohydrates, 30% as fat, and 20% as protein) for 2–3 days before clinical testing. Body composition was estimated by underwater weighing, with simultaneous determination of residual lung volume by helium dilution or by total body dual-energy X-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI) with calculations of percentage of body fat (BF), fat mass, and fat-free mass as previously described (39). At least 3 days after admission and after a 12-h overnight fast, subjects underwent a 3-h, 75-g oral glucose tolerance test.

Insulin action was assessed at physiological and supraphysiological insulin concentrations during a two-step hyperinsulinemic euglycemic clamp as described (41). In brief, after an overnight fast, a primed, continuous intravenous insulin infusion was administered for 100 min at a rate of 40 μU·m²·body surface area⁻¹·min⁻¹ (low dose) followed by a second 100-min infusion at a rate of 400 μU·m²·body surface area⁻¹·min⁻¹ (high dose). The rate of total insulin-mediated glucose disposal (M) was calculated for the last 40 min of the insulin infusions. The M value during the low-dose insulin infusion was corrected for the rate of endogenous glucose production (EGP) calculated using average values for 40 min prior to and for the last 40 min during the insulin infusion, and net Lox values were determined from the equations of Lusk (27).

All measurements derived from the clamp were normalized to estimated metabolic body size (or fat-free mass + 17.7 kg) (22). The effects of variations in plasma glucose concentrations on total glucose disposal during the clamps were adjusted to 100 mg/dl, as suggested by Best et al. (2). Individual differences in insulin concentrations during the low-dose insulin infusion were taken into account in the calculation of the rate of glucose utilization (24). It was assumed that, during the high-dose insulin infusion, maximal effect of insulin was achieved in all subjects.

Insulin secretion was measured in response to a 25-g intravenous glucose tolerance test, with calculation of the acute insulin response (AIR) as the average increase in plasma insulin concentration from the 3rd to the 5th minute after the glucose bolus adjusted for fasting insulin concentration (26).

Statistical analyses were performed using the software of the SAS Institute (Cary, NC). The values for nonnormally distributed variables were logarithmically transformed before analysis to approximate normal distributions. To identify confounders, one-way ANOVA and Fisher’s exact text were performed to compare groups, whereas Pearson correlation was used to test for relationships between the variables. Multiple linear regression models were used to allow adjustment for covariates. The metabolic predictors of diabetes were assessed using the Cox proportional hazard analyses using variables standardized to mean = 0 and SD = 1. Followup time was determined as the time from baseline examination until the event (i.e., diagnosis of T2DM) or the final examination attended if diabetes had not occurred. After each variable was tested by including a time-dependent interaction term, followup time was truncated to 12 yr to satisfy the assumption of proportionality. The effect of baseline net Lox on change (followup adjusted for baseline) in M low and AIR was evaluated using general linear regression models. Models were adjusted for sex, age at baseline, time of followup, percent body fat at baseline, and change in percent body fat. The change in AIR was additionally adjusted for M low at followup.

RESULTS

Cross-sectional analyses. Of the 465 subjects studied, 31 had T2DM and 117 had IGT. The proportion of women significantly increased with worsened glucose tolerance status (P < 0.0001). Subjects with IGT and T2DM were older and had higher BF than those with NGT (P < 0.0001; Table 1). Fasting and 2-h plasma glucose levels by design progressively

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**Table 1. Anthropometric and metabolic characteristic of study population**

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>T2DM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (total/women)</td>
<td>317/102</td>
<td>117/68</td>
<td>31/26</td>
<td>&lt;0.0001+‡‡</td>
</tr>
<tr>
<td>Age, yr</td>
<td>27 (6)</td>
<td>30 (7)</td>
<td>30 (7)</td>
<td>&lt;0.0001+†</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>31 (8)</td>
<td>36 (6)</td>
<td>39 (5)</td>
<td>&lt;0.0001+†</td>
</tr>
<tr>
<td>FPG, mg/dl</td>
<td>87 (9)</td>
<td>94 (10)</td>
<td>114 (21)</td>
<td>&lt;0.0001+‡‡</td>
</tr>
<tr>
<td>2-h PG, mg/dl</td>
<td>107 (20)</td>
<td>161 (16)</td>
<td>245 (36)</td>
<td>&lt;0.0001+‡‡</td>
</tr>
<tr>
<td>FPI, mU/l</td>
<td>36 (17)</td>
<td>51 (20)</td>
<td>64 (27)</td>
<td>&lt;0.0001+‡‡</td>
</tr>
<tr>
<td>AIR, mU/I</td>
<td>266 (175)</td>
<td>202 (140)</td>
<td>66 (102)</td>
<td>&lt;0.0001+‡‡</td>
</tr>
<tr>
<td>M low, mg·kg·EMBS⁻¹·min⁻¹</td>
<td>2.9 (1.2)</td>
<td>2.2 (0.5)</td>
<td>2.0 (0.4)</td>
<td>&lt;0.0001+†</td>
</tr>
<tr>
<td>M high, mg·kg·EMBS⁻¹·min⁻¹</td>
<td>9.5 (2.1)</td>
<td>7.7 (2.1)</td>
<td>6.2 (2.1)</td>
<td>&lt;0.0001+‡‡</td>
</tr>
</tbody>
</table>

Data are means (SD). NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; 2-h PG, 2-h plasma glucose; FPI, fasting plasma insulin; AIR, acute insulin response; M, insulin-mediated glucose disposal; EMBS, estimated metabolic body size.

Post hoc comparison, *NGT vs. IGT; †NGT vs. T2DM; ‡IGT vs. T2DM.
increased from NGT to IGT to T2DM (all \( P < 0.0001 \); Table 1). As expected, fasting plasma insulin progressively increased, whereas AIR and M high progressively decreased with worsening of glucose tolerance status (\( P < 0.0001 \); Table 1). M low was reduced in IGT and T2DM compared with NGT (\( P < 0.0001 \)) but not in T2DM compared with IGT (\( P = 0.4 \); Table 1).

Fasting net \( \text{LOX} \) (\( \text{LOX} \) fasting) tended to be lower in subjects with NGT compared with those with IGT and T2DM (\( P = 0.06 \); Fig. 1). \( \text{LOX} \) low and \( \text{LOX} \) high progressively increased with worsening of glucose tolerance status (\( P = 0.001 \) and \( P = 0.0001 \), respectively; Fig. 1). After adjustment for age, sex, and BF, \( \text{LOX} \) fasting was similar between the three groups (\( P = 0.5 \); Fig. 1), whereas \( \text{LOX} \) during the clamp was higher in T2DM compared with IGT and NGT (\( P = 0.03 \) and \( P = 0.0003 \), respectively, \( \text{LOX} \) low; \( P = 0.01 \) and \( P < 0.0001 \), respectively, \( \text{LOX} \) high; Fig. 1) and in IGT compared with NGT (\( P = 0.03 \), \( \text{LOX} \) low; \( P = 0.006 \), \( \text{LOX} \) high; Fig. 1). After further adjustment for M low, \( \text{LOX} \) low remained higher in the T2DM than in the nondiabetic groups (\( P = 0.02 \), NGT; \( P = 0.05 \), IGT) but was not significantly different between the NGT and IGT subjects (\( P = 0.4 \); Fig. 1). There were no differences between the three groups in \( \text{LOX} \) high after adjustment for M high (\( P = 0.5 \); Fig. 1).

Fasting carbohydrate oxidation was similar between the three groups (\( P = 0.4 \)), whereas oxidative glucose disposal during insulin infusions was higher in NGT compared with IGT and T2DM (\( P < 0.0001 \) and \( P = 0.01 \), respectively, low dose; \( P = 0.001 \) and \( P = 0.0006 \), respectively, high dose) but not between IGT and T2DM (\( P = 0.8 \), low dose; \( P = 0.2 \), high dose) (Fig. 1). These differences between the groups remained significant after adjustment for age, sex, and BF (NGT vs. IGT and NGT vs. T2DM; \( P = 0.005 \) and \( P = 0.04 \), respectively, low dose; \( P = 0.004 \) and \( P < 0.0001 \), respectively, high dose) but not after further adjustment for M (\( P = 0.4 \), low dose; \( P = 0.9 \), high dose) (Fig. 1).

**Prospective analyses.** Of the 317 subjects who were NGT at baseline, 296 (99 females) had available followup data on glucose tolerance status [mean followup time 7.3 yr (SD 3.3)]. Fifty-one subjects (17%, 18 females) developed T2DM. At baseline, higher \( \text{LOX} \) fasting correlated with higher BF before (\( P = 0.0001 \)) and after adjustment for age and sex (\( P = 0.004 \)), with lower M low before (\( P = 0.01 \)) but not after adjustment for age, sex, and BF (\( P = 0.4 \)), and with lower AIR after adjustment for age, sex, BF, and M low (\( P = 0.03 \)), but not with M high (Table 2). Higher \( \text{LOX} \) low correlated with higher BF before (\( P = 0.002 \)) and after adjustment for age and sex (\( P < 0.0001 \)), with lower M low (\( P < 0.0001 \) both before and after adjustment for age, sex, and BF) and lower M high (\( P < 0.0001 \), before, and \( P = 0.005 \) after adjustment for age, sex, and BF) but not with AIR (Table 2). Higher \( \text{LOX} \) high correlated with higher BF only after adjustment for age and sex (\( P < 0.0001 \)), with lower M low (\( P < 0.0001 \) both before and after adjustment for age, sex, and BF) and with higher AIR before (\( P = 0.04 \)) but not after adjustment for age, sex, BF, and M low (Table 2).

In Cox proportional hazard analysis, \( \text{LOX} \) fasting predicted T2DM independently of age, sex, BF, and M low [hazard rate ratio per SD difference: 1.37 (95% confidence interval: 1.03, 1.81), \( P = 0.03 \); Fig. 2] but not after adjustment for AIR [1.20

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**Fig. 1.** Lipid and carbohydrate oxidation rates in Pima Indians with different levels of glucose tolerance prior to and during a 2-step hyperinsulinemia. Data are means (unadjusted plots) or least-square means (adjusted plots) ± SE. Fasting oxidation rates were not adjusted for insulin-mediated glucose disposal (M). *\( P < 0.01 \), **\( P < 0.001 \), ***\( P < 0.001 \), and ****\( P < 0.0001 \), multiple comparisons between the groups during each clamp stage: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; EMBS, estimated metabolic body size.
The present study supports the concept that the inability of insulin to suppress lipid oxidation is a significant independent characteristic of insulin action in deteriorating glucose tolerance and provides the first prospective evidence in humans for the primary role of this “metabolic inflexibility” in the pathogenesis of insulin resistance and T2DM (19). First, inhibitory action of insulin action on lipid oxidation was attenuated in subjects with T2DM compared with nondiabetic individuals, and this attenuation was independent of insulin action on glucose uptake. Second, it was observed in the prospective analyses of subjects with NGT that rates of lipid oxidation during hyperinsulinemic conditions predicted the development of T2DM independently of adiposity, insulin-mediated glucose disposal rates, and acute insulin secretion. Finally, higher baseline rates of net lipid oxidation at physiological hyperinsulinemia predicted greater future decline in insulin-mediated glucose disposal rate.

In the postabsorptive state, lipid moieties are the main substrates for oxidation in insulin-sensitive tissues (19). One mechanism by which hyperinsulinemia suppresses oxidation of lipids is decreased availability of fatty acids in both systemic and intracellular pools (7). The suppression of lipid oxidation has been shown to be necessary for normal insulin-mediated glucose uptake and utilization (35). At high physiological and supraphysiological insulin levels, intravenously infused glucose is almost exclusively disposed into skeletal muscle (12). An attenuated suppression of the lipid oxidation rate by hyperinsulinemia in the skeletal muscle and at the whole body level has been found in states of obesity, insulin resistance, and T2DM (13, 18, 28). Consistent with these data, we found less pronounced inhibition of whole body net lipid oxidation during hyperinsulinemia in subjects with T2DM compared with their nondiabetic counterparts.

In a previous study performed in a small group of Pima Indian women, Lillioja et al. (23) found no association between fasting lipid oxidation and adiposity or insulin-mediated glucose disposal. The present analysis performed in a larger group

Table 2. Simple and partial correlation of L_{ox} rates with body fat, M rate, and AIR in 296 Pima Indians who had NGT at baseline and had followup evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Body Fat</th>
<th>M Low</th>
<th>M High</th>
<th>AIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>L_{ox} fasting</td>
<td>Simple</td>
<td>Partial*</td>
<td>Simple</td>
<td>Partial*</td>
</tr>
<tr>
<td>L_{ox} low</td>
<td>0.18*</td>
<td>0.16*</td>
<td>-0.14*</td>
<td>-0.05</td>
</tr>
<tr>
<td>L_{ox} high</td>
<td>0.06</td>
<td>0.17*</td>
<td>-0.33‡</td>
<td>-0.30‡</td>
</tr>
</tbody>
</table>

*P < 0.05, †P < 0.01, and ‡P < 0.0001; partial variables: *age and sex; †age, sex, and body fat; ‡age, sex, body fat, and M low.

(0.89, 1.61), P = 0.2; Fig. 2]. L_{ox} low and L_{ox} high predicted T2DM independently of all the covariates [1.49 (1.11, 2.0), P = 0.008, and 1.33 (1.00, 1.77), P = 0.05, respectively; Fig. 2].

The predictive effect of L_{ox} at baseline on followup changes in M low and AIR was studied in 190 subjects (58 females) who were NGT at baseline and nondiabetic at followup [126 NGT, 64 IGT; mean followup time 4.8 yr (range 0.6–13.4)]. L_{ox} low at baseline predicted a lower M low at followup after adjustment for age at baseline, duration of followup, sex, BF at baseline, followup change in BF, and M low at baseline (P = 0.04; Table 3) but did not predict changes in AIR (P = 0.9). L_{ox} fasting and L_{ox} high at baseline did not predict followup changes in either M low or AIR (data not shown). The variance by which L_{ox} low at baseline contributed to M low at followup represented 1.4% of the total variance explained by the model (model R^2 = 0.63).

DISCUSSION

The present study supports the concept that the inability of insulin to suppress lipid oxidation is a significant independent characteristic of insulin resistance and T2DM (19). First, inhibitory
of Pima Indian men and women with NGT is in agreement with others (32) and shows that fasting lipid oxidation increases with adiposity but is not associated with insulin resistance after being adjusted for adiposity. A higher rate of fasting lipid oxidation, however, predicted risk of T2DM independently of adiposity and insulin-mediated glucose disposal. This observation might seem to contradict the concept that low oxidative capacity of skeletal muscle is associated with increased risk for insulin resistance and diabetes as indicated by cross-sectional findings in healthy offspring of T2DM subjects (33). However, reduced oxidative capacity of skeletal muscle in the latter study was not reflected by lower rates of fasting lipid oxidation (33).

In our study, higher fasting lipid oxidation was found in individuals with liver steatosis (8). Since increased liver fat content predicts T2DM independently of insulin-mediated glucose disposal (40), it is plausible that high fasting lipid oxidation is related to the risk of T2DM indirectly as a marker of increased lipid accumulation in liver. Alternatively, the negative correlation between fasting lipid oxidation and AIR as well as the attenuation of an independent predictive effect of fasting lipid oxidation on T2DM by AIR may suggest that chronically increased lipid oxidation alters glucose-induced insulin release, as proposed by some animal studies (36). Our prospective analyses did not show that higher fasting lipid oxidation predicted changes in AIR and thus do not support this hypothesis.

It must be noted that net lipid oxidation reflects the difference between lipid oxidation and lipid synthesis. If lipogenesis is stimulated, as occurs with insulin, this will be measured as an apparent decrease in lipid oxidation (7). Altered expression of lipogenic enzymes in adipose tissue of obese mice is associated with increased susceptibility to T2DM (21). Increased rates of net lipid oxidation during hyperinsulinemia were reported in patients with partial lipodystrophy (9), a syndrome characterized by dysfunctional subcutaneous adipose tissue, fatty liver, and T2DM (14). Altered postprandial suppression of net lipid oxidation was found in lipin-deficient fatty liver dystrophy mouse, a lipodystrophy model without adiposity but is not associated with insulin resistance after being adjusted for adiposity. A higher rate of fasting lipid oxidation, however, predicted risk of T2DM independently of adiposity and insulin-mediated glucose disposal (10), predicts T2DM independently of the degree of adiposity, insulin action on glucose metabolism, and insulin secretion (42). Our post hoc analyses in 79 subjects from that cohort do not show any significant association between adipocyte size and lipid oxidation that wouldn’t be explained by variance in adiposity (Lox fasting: r = 0.11, P = 0.3; Lox low: r = 0.14, P = 0.2; Lox high: r = 0.14, P = 0.2), indicating that the reduced lipogenic effect of insulin contributes to the increased risk for T2DM independently of the decreased adipogenic potential of subcutaneous adipose tissue.

Peroxisome proliferator-activated receptor-γ (PPARγ) agonists are drugs that affect glucose homeostasis via predominant action in subcutaneous adipose tissue (1). They increase its lipid storage potential by stimulating differentiation of adipocytes (11) and by stimulating expression of several genes related to fatty acid uptake and de novo lipogenesis (3). In nondiabetic humans, administration of PPARγ agonist increases fatty acid clearance during physiological hyperinsulinemia (37). Treatment with PPARγ agonist substantially reduced incidence of T2DM and increased the likelihood of regression to normoglycemia in individuals with impaired fasting glucose and/or IGT (12a). In parallel with this, our results indicate that individuals who naturally possess higher lipogenic response to insulin are protected against future development of T2DM.

In conclusion, lipid oxidation rates measured with indirect calorimetry during fasting and in response to increasing levels of insulin predicted development of T2DM independently from measures of insulin action on glucose uptake or glucose-induced insulin release. These results provide evidence that the inability to inhibit net lipid oxidation may represent part of a broader syndrome of insulin resistance, which further worsens the effect of insulin on glucose metabolism and increases the risk of developing diabetes.

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GRANTS

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