Impaired Hepatic Ketogenesis in Moderately Obese Men With Hypertriglyceridemia

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Background: Several studies suggest that increased nonesterified fatty acid flux and increased de novo lipogenesis may contribute to hypertriglyceridemia, but few studies have examined fatty acid oxidation as a factor.

Rationale: Endogenous hypertriglyceridemia (increased very low density lipoprotein triglyceride) could result from (a) re-esterification of excess nonesterified fatty acids entering the liver, (b) activation of hepatic lipogenesis, and/or (c) defective oxidation of hepatic fatty acids leading to greater triglyceride synthesis. Therefore, this study used plasma levels of 3-hydroxybutyrate as a marker for fatty acid oxidation. The study was carried out in hypertriglyceridemic and normotriglyceridemic subjects under 3 conditions: (a) in the fasting state, (b) after a fatty meal that should enhance fatty acid oxidation, and (c) after an oxandrolone challenge, which we recently showed increases fatty acid oxidation.

Results: In the fasting state, 3-hydroxybutyrate concentrations in hypertriglyceridemic patients were only 53% of levels in normotriglyceridemic subjects. After a fatty meal, moderate increases in 3-hydroxybutyrate were observed, but values for patients with hypertriglyceridemia remained 62% of the levels in the normotriglyceridemic group. A similar pattern of response was observed with oxandrolone challenge. There were no significant changes in fasting or postprandial levels of nonesterified fatty acids, glycerol, or triglycerides before and during the oxandrolone challenge.

Conclusion: Patients with endogenous hypertriglyceridemia seem to have a defect in fatty acid oxidation as indicated by reduced levels of 3-hydroxybutyrate. This defect was observed during fasting, postprandially, and during oxandrolone challenge. We propose that this defect contributes to the development of hypertriglyceridemia.

Key Words: postprandial ketogenesis, hypertriglyceridemia, steroids

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Elevations of plasma triglyceride generally are of hepatic origin and are found mainly in very low density lipoproteins (VLDL).^{1,2} An excess of plasma triglyceride could originate in several ways: increased re-esterification of nonesterified fatty acids entering the liver, de novo lipogenesis, and/or defective fatty acid oxidation.^{3–11} In the current study, we examined fatty acid oxidation by measuring plasma 3-hydroxybutyrate as a

surrogate marker. Several studies have shown that levels of 3-hydroxybutyrate correlate with fatty acid oxidation.^{12–15} We hypothesized that higher levels of 3-hydroxybutyrate in hypertriglyceridemic patients would reflect increased influx of nonesterified fatty acids. Conversely, a reduction in 3-hydroxybutyrate would be indicative of a defect in fatty acid oxidation. To examine these alternatives, we measured 3-hydroxybutyrate levels under 3 circumstances: (a) after a 12-hour fast, (b) postprandially after a fatty meal, and (c) after an oxandrolone challenge. For the latter, we recently reported that oxandrolone treatment causes a marked increase in plasma levels of 3-hydroxybutyrate.¹⁶ At present, the mechanism whereby this occurs is unknown, but this effect presumably is indicative of increased fatty acid oxidation. The studies were carried out in moderately obese hypertriglyceridemic and overweight normotriglyceridemic adult men. Oxandrolone was used in the current study to determine whether its effects on fatty acid oxidation are retained in hypertriglyceridemic subjects.

METHODS

Forty-two men agreed to participate in metabolic studies of hepatic ketogenesis. They were recruited from the Dallas-Fort Worth area. Thirty-six were enrolled at the Lipid Clinic of the Dallas Veterans Affairs Medical Center, and 6 were recruited at the Clinical Translational Research Center of the University of Texas Southwestern Medical Center at Dallas. Four subjects withdrew from the study after consenting to participate. Of the remaining, 17 men were normotriglyceridemic (plasma triglycerides <150 mg/dL), and 20 had moderate hypertriglyceridemia (plasma triglycerides ≥150 mg/dL). Subsequently, 31 men at the Veterans Affairs Medical Center participated and completed a trial with 10 mg/d of oxandrolone that lasted 7 days. Subjects had a high-fat meal challenge at baseline and on the 7th day of oxandrolone treatment. Of the 42 subjects enrolled, 18 have had their results shown previously.¹⁶

None of the subjects were taking drugs known to affect lipid metabolism; 4 had history of smoking at the time of the study and none had chemical dependency.

The protocols were approved by the institutional review boards at the Dallas Veterans Affairs Medical Center and at the University of Texas Southwestern Medical Center. Each subject gave written informed consent to participate in the study.

Study subjects had anthropometry, measurement of fasting plasma lipids, lipoprotein cholesterol, and ketogenesis during an extended high-fat meal challenge. For the latter, after an overnight fast, subjects ingested a heavy whipping cream drink containing 75 g of fat (100% of calories from fat with 70% long-chain saturates). This meal composition was chosen to produce chylomicrons without eliciting an insulin response. During the fat meal challenge, subjects were allowed to drink water and sugar-free tea during the following 10 hours. Subjects kept their hand in an isothermal box ($T = 70^{\circ}\text{C}$) to obtain arterialized blood samples that were collected into tubes containing sodium-EDTA (2 mg/mL) before ($t = 0$) and

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TABLE 1. Subject Demography, Lipids, Lipoproteins, and Glucose

	Overweight Normotriglyceridemia		Moderate Obesity With Hypertriglyceridemia	
	n = 17		n = 20	
	Mean ± SE	Median	Mean ± SE	Median
Age, y	56 ± 3	62	56 ± 2	59
Body mass index, kg/m ²	27 ± 1	26	32 ± 1*	32
Waist circumference, cm	96 ± 3	95	107 ± 2†	105
Triglycerides, mg/dL	91 ± 7	84	244 ± 16‡,§	236
Non-HDL cholesterol, mg/dL	135 ± 8	143	178 ± 7¶	187
Total apo B, mg/dL	101 ± 7	101	141 ± 5¶	144
HDL cholesterol, mg/dL	44 ± 4	46	33 ± 1‡	34
Fasting plasma glucose, mg/dL	96 ± 2	94	103 ± 2†	103
Fasting plasma insulin, μU/mL	9.1 ± 1.7	7.7	18.0 ± 3.3*,§	13.2
HOMA-IR, %	2.2 ± .5	1.9	4.3 ± .9§,	2.9

*Significantly higher than normotriglyceridemia (NTG), $P < 0.009$.†Significantly higher than NTG, $P < 0.05$.‡Significantly different from NTG, $P < 0.0001$.¶Significantly higher than NTG, $P \leq 0.002$.

§Log transformed.

||Significantly higher than NTG, $P \leq 0.02$.

Apo B indicates apolipoprotein B; HDL, high-density lipoprotein.

every 2 hours until 10 hours after the meal. To avoid ongoing in vitro lipolysis by plasma lipoprotein lipase, blood samples were immediately placed on ice, centrifuged to separate plasma, that was subsequently frozen at -80°C . Analysis was carried out in less than 24 hours. In preliminary testing, we demonstrated that no significant lipolysis of triglycerides occurred before analysis under these conditions. 3-Hydroxybutyrate, nonesterified fatty acids, triglycerides, and glycerol were measured from plasma spectrophotometrically using enzymatic assays (Roche Diagnostics/Boehringer Mannheim Corp, Indianapolis, IN). Levels of plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured using standardized enzymatic assays. Levels of plasma apolipoprotein B were quantified chemically. All methods have been detailed previously.¹⁶

Data are summarized as means $\pm$ standard error of the mean. Wisker-box plots are used to describe the metabolic parameters including 3-hydroxybutyrate before and during the

7th day of treatment with oxandrolone. The Wisker-box plots show the data distribution (10th, 25th, 50th, 75th, and 90th percentiles) and the outliers (> 90 th and < 10 th percentiles). Analysis of variance is used to compare means of metabolic parameters between normotriglyceridemic and hypertriglyceridemic subjects. Log transformations were done for data not normally distributed before analyses. This included levels of plasma triglyceride, insulin, 3-hydroxybutyrate, and homeostasis model assessment of insulin resistance (HOMA-IR) index. Repeated measures analysis of variance with Bonferroni adjustment for multiplicity of testing was used to compare responses to oxandrolone for individuals in each study group. An $\alpha < 0.05$ was considered significant for the analyses. Area under the curve (AUC) was calculated by the trapezoid formula for the 10-hour interval of the high-fat meal challenge. Delta-AUCs were calculated as the difference between AUC minus level at zero time multiplied by 10 hours. Therefore, delta-AUC reflects the increment of metabolite above fasting levels attained during

FIGURE 1. Wisker-box plot showing the 10th, 25th, 50th, 75th, and 90th percentiles and outliers for fasting plasma levels of 3-hydroxybutyrate in normotriglyceridemic (NTG; $n = 17$) and hypertriglyceridemic (HTG; $n = 20$) men (A) and postprandial levels during a high-fat meal challenge (B). HTG men have lower hepatic ketogenesis than NTG men.

FIGURE 2. Effect of oxandrolone on fasting plasma levels (A) and postprandial levels (B) of 3-hydroxybutyrate in NTG (n = 11) and HTG (n = 19) men. Oxandrolone increases fasting levels and postprandial levels (B) of 3-hydroxybutyrate for NTG and HTG, respectively.

the fat meal challenge. Spearman correlation coefficients were calculated for insulin and HOMA-IR versus levels of 3-hydroxybutyrate. The StatView (version 5.0.1) program from SAS was used in the analyses of the data.

RESULTS

Baseline Characteristics of Subjects

The baseline characteristics of 20 moderately obese and 17 overweight men are shown in Table 1. Moderately obese men with hypertriglyceridemia had higher levels of fasting insulin and HOMA-IR index than normotriglyceridemic subjects (Table 1). They also had higher non-HDL cholesterol and apolipoprotein B and lower HDL cholesterol.

Fasting Levels of 3-Hydroxybutyrate

Fasting levels of 3-hydroxybutyrate were significantly lower in subjects with hypertriglyceridemia compared with the normotriglyceridemic group. The mean fasting levels were 203 ± 37 μmol/L in normotriglyceridemia and 108 ± 9 μmol/L in hypertriglyceridemia ($P = 0.003$). That is, hypertriglyceridemic subjects had a 46.8% lower fasting level of 3-hydroxybutyrate than normotriglyceridemic subjects. The distribution of fasting levels of the ketone body for each study group is shown in Figure 1A (see legend for detailed description).

Levels of 3-Hydroxybutyrate During an Oral Fat Meal Challenge

The levels of 3-hydroxybutyrate during the oral fat meal test calculated as delta-AUC during a 10-hour period were $18.4 \pm 2.3 \times 10^4$ μmol in normotriglyceridemia and $11.4 \pm$

1.9×10^4 μmol in hypertriglyceridemia; these levels were significantly different ($P = 0.009$) between the 2 study groups. Subjects with hypertriglyceridemia had 38% lower level of postprandial 3-hydroxybutyrate compared with normotriglyceridemic subjects. The Wisker-box plots for the delta-AUC levels are shown in Figure 1B for each study group.

Effects of Oxandrolone

Oxandrolone increased fasting levels of 3-hydroxybutyrate in normotriglyceridemic subjects by 67.9%. The baseline levels were 231 ± 49 μmol/L, and the levels during oxandrolone treatment were 388 ± 71 μmol/L. These mean levels were significantly different ($P = 0.03$). In hypertriglyceridemic subjects, the 3-hydroxybutyrate levels increased by 58.7%. The baseline levels were 109 ± 9 μmol/L, and during oxandrolone treatment, the levels were 173 ± 25 μmol/L. The treatment levels were significantly higher ($P = 0.03$) than the baseline. The distribution of the fasting before treatment and treatment levels are shown in Figure 2A for each study group.

Postprandial levels of 3-hydroxybutyrate also were increased on oxandrolone therapy by 30.6% ($P = 0.001$) in normotriglyceridemia. The baseline levels were $23.2 \pm 2.5 \times 10^4$ μmol versus oxandrolone levels of $30.3 \pm 4.7 \times 10^4$ μmol. In subjects with hypertriglyceridemia, the levels increased by 84% ($P = 0.001$). The baseline levels were $11.6 \pm 1.1 \times 10^4$ μmol versus oxandrolone treatment levels of $21.4 \pm 3.4 \times 10^4$ μmol. The distribution of the levels for each group is shown in Figure 2B.

Despite the increases in 3-hydroxybutyrate levels seen in both study groups during oxandrolone treatment, fasting and postprandial levels of the ketone body remained lower in

FIGURE 3. Levels of fasting plasma (A) and postprandial nonesterified fatty acids (NEFA) (B) in NTG (n = 11) and HTG (n = 19) men during administration of oxandrolone. There were no significant changes in levels or integrated (Δ-AUC), postprandial levels of NEFA during treatment. AUC indicates area under the curve.

FIGURE 4. Fasting (A) and postprandial (B) levels of triglyceride before and during administration of oxandrolone. The steroid does not affect triglyceride levels.

hypertriglyceridemic subjects compared with normotriglyceridemic subjects. The average fasting levels were 55% lower and the mean postprandial levels were 24% lower than the normotriglyceridemic group.

There were no significant correlations between levels of 3-hydroxybutyrate and fasting plasma insulin at baseline in either normotriglyceridemic ($r = -0.41$; $P = 0.21$) or hypertriglyceridemic subjects ($r = 0.03$; $P = 0.90$). There were also no significant correlations between the HOMA-IR and 3-hydroxybutyrate within each group.

Levels of fasting and postprandial nonesterified fatty acids (Figs. 3A, B), glycerol (not shown), and triglyceride (Figs. 4A, B) were unaffected by oxandrolone in both normotriglyceridemia and hypertriglyceridemic subjects.

DISCUSSION

Major Findings

In this study, we examined whether fatty acid oxidation as reflected by markers of hepatic ketogenesis was increased or decreased in moderately obese patients with hypertriglyceridemia. The major finding in this study was that hepatic fatty acid oxidation was significantly decreased in subjects with hypertriglyceridemia compared with moderately overweight normotriglyceridemic subjects. This finding points to a potential defect in fatty acid oxidation as a contributing factor to the development of hypertriglyceridemia.

Possible Mechanisms of Hypertriglyceridemia

Moderately obese patients with hypertriglyceridemia have been reported to have an overproduction of VLDL-triglyceride.^{1,2} Factors contributing to overproduction could include increased influx of nonesterified fatty acids, increased de novo lipogenesis, and decreased hepatic fatty acid oxidation.³⁻¹¹

In the first case, an increased influx of nonesterified fatty acids could induce fatty acid esterification and formation of VLDL-triglyceride.³⁻⁵ This in turn should raise serum triglyceride levels. Second, an increase in de novo lipogenesis likewise should enhance triglyceride accumulation and incorporation into VLDL-triglyceride.⁸⁻¹⁰ Third, a decrease in fatty acid oxidation should shunt excess fatty acids into VLDL-triglyceride production.

The possible causes of hypertriglyceridemia in the current patients can be considered. First, fasting or postprandial nonesterified fatty acids were not higher in the hypertriglyceridemic group compared with the normotriglyceridemic group. This may have been related to the relatively small differences in body mass index between the 2 groups of patients. Thus,

hypertriglyceridemia in one group cannot be explained by fasting or postprandial nonesterified fatty acid levels. Second, we have no evidence that in the hypertriglyceridemic group, there was increased lipogenesis. If de novo lipogenesis had been increased, we would expect increased ketogenesis which was not observed. Third, if the oxidation of fatty acids by the liver were to be decreased, fatty acids could be diverted to triglyceride formation. Our data are most consistent with this mechanism. Fourth, other studies have shown that hypertriglyceridemia is associated with insulin resistance. Reportedly, high insulin levels suppress ketogenesis^{12-15,17-20} and enhance VLDL-triglyceride secretion.^{5,5,21,22} Of interest, in the current study, hypertriglyceridemic patients were more insulin resistant than normotriglyceridemic controls. The mechanisms for insulin resistance in moderately obese subjects with hypertriglyceridemia are not apparent, but it seems that the degree of insulin resistance is not strictly a function of obesity.²³

Response to an Oral Fat Challenge

Increased ketogenesis has been reported after a high-fat meal.^{11,16} In the current study, we also observed increased ketogenesis after a high-fat challenge. However, in patients with hypertriglyceridemia, the response was blunted which supports the likelihood of a defect in fatty acid oxidation in hypertriglyceridemic subjects.

There are 3 possible mechanisms for an increase in ketogenesis after an oral fat challenge: (a) incomplete adipose tissue uptake of meal-derived fatty acid through the action of lipoprotein lipase, leading to "spill-over" of nonesterified fatty acids to the circulation and the liver; (b) direct uptake of postprandial lipoprotein triglyceride into the liver; and (c) uptake of fatty acid generated through the action of hepatic triglyceride lipase on postprandial lipoproteins. Our results cannot differentiate between these mechanisms.

Response to Oxandrolone Challenge

Previously, we showed that short-term oxandrolone therapy enhances fasting and postprandial fatty acid oxidation.¹⁶ In the current study, we show that hypertriglyceridemic subjects also have enhanced fatty acid oxidation during an oxandrolone challenge but the response is blunted; that is, subjects with hypertriglyceridemia did not have the same increase in fatty acid oxidation as normotriglyceridemic subjects during the oxandrolone challenge. This poor response is further evidence that patients with hypertriglyceridemia have reduced fatty acid oxidation compared with normotriglyceridemic subjects.

Another observation made in the current study is that short-term treatment with oxandrolone did not result in lower plasma triglyceride levels in contrast to the long-term treatment

reduction noted by others in hypertriglyceridemic subjects.^{24–26} One possible explanation for this lack of response is that it may take some time for oxandrolone to reduce the intrahepatic pool of triglyceride destined for secretion into VLDL.

In conclusion, this study suggests that defective oxidation for fatty acid can account for much of the hypertriglyceridemia found in some patients with elevated triglycerides. The presence of a defect in fatty acid oxidation was observed under 3 conditions: (1) in the fasting state, (2) after an oral fat meal, and (3) during treatment with oxandrolone. The consistency of this effect provides support for our contention that defective fatty acid oxidation is a common cause of hypertriglyceridemia.

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