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Metabolically healthy but obese individuals: relationship with hepatic enzymes

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Abstract

The purpose of this study was to investigate the level of plasma hepatic enzymes in obese women displaying the metabolically healthy but obese (MHO) phenotype. We studied 104 obese, sedentary, postmenopausal women. Subjects were classified as MHO or at risk based on insulin sensitivity as assessed with the oral glucose tolerance test–derived Matsuda index. Subjects were divided into quartiles according to insulin sensitivity values. Subjects in the upper quartile were categorized as MHO, whereas subjects in the lower 3 quartiles represented at-risk subjects. Outcome measures were hepatic enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and γ-glutamyltransferase [GGT]], high-density lipoprotein cholesterol, triglycerides, triglycerides to high-density lipoprotein cholesterol ratio, apolipoprotein B, fatty liver index, body composition (dual-energy x-ray absorptiometry), and visceral adipose tissue (computed tomography). The MHO individuals had significantly lower concentrations of ALT, AST, and GGT as well as a lower fatty liver index compared with at-risk subjects ($P < .05$). In addition, lean body mass index and visceral adipose tissue were significantly lower in MHO individuals ($P < .05$). Moreover, stepwise regression analysis showed that ALT explained 17.9% of the variation in insulin sensitivity in our cohort, which accounted for the greatest source of unique variance. Results of the present study indicate that postmenopausal women displaying the MHO phenotype present favorable levels of ALT, AST, and GGT. Lower concentrations of hepatic enzymes, in particular, lower circulating ALT levels, in MHO individuals may reflect lower hepatic insulin resistance and lower liver fat content; and this could be involved, at least in part, in the protective profile of MHO individuals.

1. Introduction

Obesity is associated with an increased risk of developing comorbidities such as cardiovascular disease, type 2 diabetes mellitus, and nonalcoholic fatty liver disease (NAFLD) [1,2]. However, a unique subset of obese individuals has been well described in the medical literature that appears to be protected or more resistant to the development of comorbidities associated with obesity [3-6]. These individuals, now known as *metabolically healthy but obese* (MHO), despite having excessive body fatness, display a favorable metabolic profile characterized by high levels of insulin sensitivity, no hypertension, a favorable immune profile, as well as normal lipid, inflammation, and hormonal profiles [3,7-10]. In addition, the MHO phenotype may be predominantly characterized by low hepatic steatosis [10]. Moreover, a recent longitudinal study

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reported that the protective metabolic profile observed in MHO individuals was associated with lower incidences of type 2 diabetes mellitus and cardiovascular diseases [11]. Furthermore, evidence suggests that MHO individuals may account for as much as 30% of the obese population [12-14]. Despite a general clinical awareness of the MHO individual, there is only a rudimentary understanding as to the constellation of factors or mechanisms underlying this "protective profile."

Recent studies have shown that higher plasma levels of hepatic enzymes such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) are associated with the metabolic syndrome, insulin resistance, and NAFLD, which could lead to an increase risk for the development of type 2 diabetes mellitus and cardiovascular diseases [15-18]. These studies provide tantalizing evidence that hepatic enzymes may be implicated in the favorable metabolic profile of MHO individuals. Therefore, the purpose of this study was to compare plasma levels of hepatic enzymes in MHO and at-risk subjects. We hypothesized that MHO individuals would present lower plasma concentrations of hepatic enzymes compared with at-risk subjects.

2. Methods

2.1. Subjects

The study sample consisted of 104 obese postmenopausal women aged between 46 and 69 years enrolled in 2 different weight loss studies (n = 41 and n = 63) with comparable inclusion criteria. These studies were approved by the *Université de Montréal* ethics committee. After reading and signing the consent form, each participant was invited to the Metabolic Unit for a series of tests. Methods for body composition, body fat distribution, blood samples, and oral glucose tolerance tests (OGTTs) were determined as previously described [19-21]. Women were included in the study if they met the following criteria: (1) body mass index (BMI) between 30 and 40 kg/m^2, (2) cessation of menstruation for more than 1 year and a follicle-stimulating hormone level of at least 30 U/L, and (3) free of known inflammatory disease. On physical examination or biological testing, all participants had no history or evidence of (1) cardiovascular disease, peripheral vascular disease, or stroke; (2) diabetes (fasting glucose <7.0 mmol/L and 2-hour post–75-g OGTT <11.0 mmol/L); and (3) medications that could affect cardiovascular function and/or metabolism.

2.2. Hepatic enzymes

Aspartate aminotransferase, ALT, ALP, and GGT were measured using the COBAS INTEGRA 400 analyzer (Roche Diagnostic, Montreal, Canada). In addition, the fatty liver index (FLI) was calculated as proposed by Bedogni et al [22]:

$$\mathrm{FLI} = [e^{0.953 * \log(\text{triglycerides}) + 0.139 * \mathrm{BMI} + 0.718 * \log(\mathrm{GGT}) + 0.053 * \text{waist circumference} - 15.745}]/[1 + e^{0.953 * \log(\text{triglycerides}) + 0.139 * \mathrm{BMI} + 0.718 * \log(\mathrm{GGT}) + 0.053 * \text{waist circumference} - 15.745}] * 100.$$

It should be noted that this index has been shown to be a simple and accurate predictor of hepatic steatosis in the general population.

2.3. Identification of MHO individuals

Stefan et al [10] identified MHO individuals using the OGTT-derived Matsuda index, a marker of insulin sensitivity [23], and reported that liver fat content was significantly lower in MHO individuals. Therefore, we will use the same method to identify MHO individuals in the present study. That is, subjects were divided into quartiles according to the Matsuda index values. Subjects in the upper quartile were categorized as MHO, whereas subjects in the lower 3 quartiles represented at-risk subjects.

2.4. Statistical analysis

Data are expressed as the mean ± standard deviation. We first verified the normality of the distribution of variables with a Kolmogorov-Smirnov test and found that the AST, ALT, GGT, triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C) ratio, and FLI were not normally distributed. Therefore, we used the log-transformed (base 10) for these variables in the analysis. An independent *t* test was performed to compare MHO and at-risk individuals. Moreover, a stepwise regression analysis was performed to identify predictors of insulin sensitivity. Independent variables considered in the final model for insulin sensitivity were lean BMI, visceral adipose tissue, TG/HDL-C ratio, high-sensitivity C-reactive protein (hs-CRP), apolipoprotein B (apo B), hepatic enzymes (ALT, AST, and GGT), and FLI. All variables included in the regression model are significantly correlated with insulin sensitivity. Significance was accepted at $P < .05$.

3. Results

Physical and metabolic characteristics of MHO and at-risk subjects are presented in Table 1. Both groups were comparable for age, BMI, fat mass, fat mass index, waist circumference, and hs-CRP. Lean body mass, lean BMI, visceral adipose tissue, TG, TG/HDL-C, and apo B were significantly different between the 2 groups ($P < .05$). By design, insulin sensitivity values were significantly higher in MHO subjects compared with at-risk individuals (4.8 ± 1.3 vs 2.3 ± 0.7, $P < .05$). In addition, homeostasis model assessment (HOMA) values were significantly lower in MHO individuals (2.4 ± 0.7 vs 4.2 ± 1.8, $P < .05$).

Hepatic enzymes are shown in Table 2. Plasma levels of ALT, AST, and GGT were significantly lower in MHO women compared with at-risk subjects ($P < .05$), whereas no differences were noted between groups for ALP concentra-

Table 1
Physical and metabolic characteristics of MHO and at-risk individuals

Variables	MHO n = 26	At risk n = 78
Age (y)	56.1 ± 4.5	57.9 ± 4.8
BMI (kg/m^2)	33.6 ± 2.7	34.2 ± 2.8
Lean body mass (kg)	42.1 ± 4.1*	44.8 ± 6.2
Lean BMI (kg/m^2)	16.2 ± 1.1*	17.1 ± 1.6
Fat mass (kg)	43.0 ± 6.7	42.1 ± 6.6
Fat mass index (kg/m^2)	16.5 ± 2.2	16.1 ± 2.2
Visceral adipose tissue (cm^2)	175.8 ± 43.9*	209.2 ± 47.8
Waist circumference (cm)	103.6 ± 7.0	107.2 ± 9.5
Insulin sensitivity	4.8 ± 1.3*	2.3 ± 0.7
HOMA	2.4 ± 0.7*	4.2 ± 1.8
HDL-C (mmol/L)	1.4 ± 0.3	1.4 ± 0.3
TG (mmol/L)	1.3 ± 0.5*	1.7 ± 0.9
TG/HDL-C	1.0 ± 0.5*	1.3 ± 0.9
hs-CRP (mg/L)	2.7 ± 1.9	3.6 ± 2.2
Apo B (g/L)	0.9 ± 0.2*	1.0 ± 0.2

* Significantly different from at-risk individuals ($P < .05$).

tions. Moreover, the FLI was significantly lower in MHO individuals (5.1 ± 3.0 vs 8.8 ± 7.9, $P < .05$). Furthermore, visceral adipose tissue was significantly associated with ALT ($r = 0.31$, $P < .05$), AST ($r = 0.20$, $P < .05$), and GGT ($r = 0.21$, $P < .05$).

Finally, we performed a stepwise regression analysis to identify independent predictors of insulin sensitivity. Table 3 illustrates the summary of the model. Our results show that the variables of ALT, apo B, visceral adipose tissue, and lean BMI were independent predictors of insulin sensitivity, collectively explaining 39.6% of the variance ($P < .05$).

4. Discussion

The concept of the MHO individual was first described in the 1980s [24,25], but little understanding has emerged to explain why MHO individuals seem to be protected from metabolic complications [6]. The MHO individuals display high levels of insulin sensitivity, are normotensive, and have normal lipid and inflammation profiles, despite excessive body fatness [3,8]. To add to the body of literature, we attempted to provide new information on metabolic factors that characterize the profile of MHO postmenopausal women. We hypothesized that MHO individuals would present lower plasma concentrations of hepatic enzymes

Table 2
Hepatic enzymes of MHO and at-risk individuals

Variables	MHO n = 26	At risk n = 78
ALP (U/L)	82.3 ± 20.7	83.2 ± 22.5
ALT (U/L)	18.4 ± 6.4*	27.4 ± 14.7
AST (U/L)	17.6 ± 3.7*	21.0 ± 6.7
GGT (U/L)	18.7 ± 8.4*	30.3 ± 26.9
FLI	5.1 ± 3.0*	8.8 ± 7.9

* Significantly different from at-risk individuals ($P < .05$).

Table 3
Stepwise regression analysis

Dependant variable	Step	Independent variable	Partial r^2	r^2 cumulative	P value
Insulin sensitivity	1	ALT	0.179	0.179	<.01
	2	Apo B	0.122	0.301	<.01
	3	VAT	0.065	0.366	<.05
	4	LBM index	0.030	0.396	<.05

VAT indicates visceral adipose tissue; LBM, lean body mass.

compared with at-risk subjects. Results from the present study support our hypothesis. That is, we found that ALT, AST, and GGT levels were significantly lower by 32.8%, 16.2%, and 38.3%, respectively, in MHO women compared with at-risk obese women. This suggests that lower levels of hepatic enzymes, despite high levels of body fat, could contribute to the favorable metabolic profile observed in MHO individuals. In support of this idea, we showed that ALT levels explained 17.9% of the variation in insulin sensitivity in our cohort, which accounted for the greatest source of unique variance. These findings are in line with previous studies that show that hepatic enzymes may be negatively associated with insulin sensitivity [15,16,18,26]. In addition, similar results have been observed in subjects with severe obesity (BMI ≥40 kg/m^2) that fit the description of the MHO phenotype [27].

What are the potential mechanisms that could explain the lower levels of hepatic enzymes in MHO individuals? Several studies have shown that AST, ALT, and GGT could be independently associated with type 2 diabetes mellitus [16,28-31]. In addition, it has been suggested that the association between hepatic markers and the risk of diabetes could be mediated by insulin resistance [16]. Accordingly, we observed that insulin resistance, assessed with the HOMA index, was significantly lower by 42.9% in MHO individuals compared with at-risk subjects.

Moreover, it has been reported that higher levels of AST, ALT, and GGT likely reflect NAFLD [2,32], a condition that is characterized by excessive lipid deposition in the liver [2]. Interestingly, Stefan et al [10] showed that MHO individuals had 54% less fat accumulation in the liver than at-risk obese subjects. Accordingly, we found that MHO individuals have a lower risk of developing NAFLD, as assessed with the FLI, compared with at-risk subjects. The lower liver fat content in MHO individuals could be due to higher free fatty acid oxidation rates as well as a lower production of lipogenesis and lipid infiltration in the liver, and this could be explained by the better ability of MHO individuals to “trap” free fatty acids in the adipose tissue [33]. Finally, ectopic fat accumulation in the liver may be indicative of more generalized susceptibility to fatty infiltration in other organs, such as the skeletal muscle, visceral adipose tissue, and myocardium [32]. In support of this hypothesis, we showed that visceral fat content was significantly lower in MHO

subjects compared with at-risk individuals. Collectively, lower concentrations of hepatic enzymes in MHO individuals may be explained by lesser hepatic insulin resistance and lower liver fat content.

The present study has several limitations. First, our cohort is only composed of nondiabetic, sedentary, obese, postmenopausal women. Therefore, our findings are limited to this population. Second, we used a cross-sectional approach, which does not allow us to conclude any causal associations between insulin sensitivity and hepatic enzymes in our cohort. Third, we used an estimate of liver fat content [22]. Despite these limitations, our results are strengthened by studying a well-characterized cohort in a relatively large sample size.

In conclusion, results of the present study indicate that postmenopausal women displaying the MHO phenotype present favorable levels of ALT, AST, and GGT. Lower concentrations of hepatic enzymes, in particular, lower circulating ALT levels, in MHO individuals may reflect lower hepatic insulin resistance and lower liver fat content; and this could be involved, at least in part, in the protective profile of MHO individuals and in turn may be associated metabolically to a lower risk for the development of type 2 diabetes mellitus and cardiovascular disease. Finally, hepatic enzymes could be proposed as simple clinical metabolic markers that identify MHO individuals.

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