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Serum Autotaxin/ENPP2 Correlates with Insulin Resistance in Older Humans with Obesity

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Abstract

Objective—Autotaxin (ATX) is an adipocyte-derived lysophospholipase D that generates the lipid signaling molecule lysophosphatidic acid (LPA). The ATX/LPA pathway in adipose tissue has recently been implicated in obesity and insulin resistance in animal models, but the role of circulating ATX in humans remains unclear. The aim of the present study was to determine the relationship between serum ATX and insulin resistance.

Methods—In this retrospective study, older (60–75 years), non-diabetic human participants with overweight or obesity (BMI 25–37 kg/m²), were characterized for metabolic phenotype including measures of energy, glucose, and lipid homeostasis. The relationship between serum ATX and metabolic parameters was then determined using correlative and predictive statistics.

Results—Serum ATX was higher in females than in males. After controlling for sex, serum ATX correlated with multiple measures of adiposity and glucose homeostasis/insulin action. Serum ATX and BMI also independently predicted glucose infusion rate during a hyperinsulinemic euglycemic clamp and homeostatic model assessment of insulin resistance after controlling for sex and medication use.

Conclusion—Serum ATX correlates with and predicts measures of glucose homeostasis and insulin sensitivity in older humans, suggesting that it may be a potential pathogenic factor and/or diagnostic/therapeutic target for insulin resistance in this population.

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Keywords

Autotaxin; adipokines; lysophosphatidic acid; obesity; insulin resistance; metabolic syndrome

Introduction

Obesity is a global public health problem that is linked to multiple metabolic abnormalities including insulin resistance, dyslipidemia, hypertension, and nonalcoholic fatty liver disease (NAFLD) (1, 2, 3). Adipose tissue is an essential endocrine organ (4) that secretes numerous adipocyte-derived bioactive substances (adipokines). Several of these adipokines such as adiponectin and leptin have been mechanistically linked to insulin resistance, the metabolic syndrome, and other cardiometabolic complications of obesity (5). Since adipokines are potential pathogenic factors and/or therapeutic targets for metabolic disease, understanding the function and physiological relevance of novel adipokines is of considerable biomedical importance.

Autotaxin (ATX; ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2)) (6, 7, 8) is an adipokine that is expressed by multiple tissues, but is primarily secreted by adipose tissue (9, 10) and cleared by the liver (11). It functions as the primary lysophospholipase responsible for converting extracellular lysophosphatidylcholine to the lipid signaling molecule lysophosphatidic acid (LPA) (12). As such, ATX regulates serum LPA concentrations. Additionally, serum ATX strongly correlates with LPA concentrations (13). LPA interacts with six known G-protein coupled receptors (LPAR₁₋₆), each with tissue-specific expression and unique down-stream signaling pathways by which it influences numerous biological processes (14, 15, 16). ATX has also been proposed to have LPA-independent biological activity through its non-catalytic C-terminal domain (8). The ATX-LPA signaling pathway has been implicated in a variety of disease processes including neuropsychiatric disorders, cardiovascular diseases, reproductive disorders, and cancer (14, 15, 16). As such, numerous pharmacological agents that target either ATX or LPA receptors have been or are being developed (16, 17, 18).

More recently, the ATX-LPA pathway has been implicated in obesity and impaired glucose homeostasis (19). Of particular relevance, administration of LPA impairs glucose tolerance whereas pharmacologic inhibition of the LPA receptor (LPAR₁) improves glucose tolerance in preclinical models (20). These data suggest that ATX, by increasing LPA, may also impair glucose homeostasis. Indeed, despite discrepancies among studies (21, 22, 23), modulation of ATX action also influences energy/glucose homeostasis as well as adipocyte biology in both cell and murine models (21, 24). These data support a potential role for pharmacological modulation of the ATX-LPA pathway in human obesity and/or diabetes, and yet only a few studies have examined the relationship between ATX and metabolic phenotypes in humans (21, 24, 25). Furthermore, although adipose tissue expression of ATX is higher in insulin resistant humans with obesity, the relationship between serum ATX and metabolic phenotypes in humans remains poorly understood.

The primary goal of the present study was to determine the relationship between serum ATX and measures of glucose homeostasis and insulin sensitivity in humans. We hypothesized that

serum ATX would positively correlate with obesity and insulin resistance. To test this hypothesis, we characterized the metabolic phenotype of sixty older, nondiabetic, human participants with overweight or obesity. Phenotypic analysis included measures of glucose homeostasis, energy homeostasis, lipid homeostasis, and blood pressure. We then determined serum ATX concentrations and evaluated the association between serum ATX and the aforementioned metabolic features.

Methods

Study design and population

The current analysis was performed in a subset of participants previously enrolled in randomized controlled trials of weight-loss interventions for obesity in older subjects (Skeletal Muscle Lipid and Insulin Resistance: Effect of Physical Activity and Weight Loss (SHELL), ClinicalTrials.gov Trial Registration Identifier: NCT00766298; Muscle Insulin Resistance in the Aged (MIRA), ClinicalTrials.gov Trial Registration Identifier: NCT00765505) (26, 27). The studies were approved by the University of Pittsburgh Institutional Review Board. All participants provided informed written consent to participate in the study. From June 2004 to December 2009, men and women aged 60–75 were enrolled if they were sedentary (exercise 1 day/week), weight stable (<3 kg weight loss or gain in the previous 6 months), non-diabetic, with overweight to moderate obesity [BMI 25.0–35.0 kg/m²], postmenopausal, and nonsmokers. All participants had either normal glucose homeostasis (fasting glucose of <100 mg/dL and 2-h 75g OGTT glucose of <140 mg/dL), impaired fasting glucose (IFG; fasting glucose of 100 but <126 mg/dL), or impaired glucose tolerance (IGT; 2-h 75g OGTT glucose of 140 but <200 mg/dL). Subjects were excluded if they had uncontrolled hypertension (SBP >150 mmHg and DBP >95 mmHg), anemia (Hct <34%), elevated liver enzymes (25% above normal), proteinuria, hypothyroidism (sensitive TSH >8 mIU/L).

Demographic and clinical evaluation

Study participants were phenotypically characterized for multiple measures of glucose homeostasis and insulin sensitivity including fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), HbA1c, 2-h 75g oral glucose tolerance test (OGTT), and glucose infusion rate (GIR) during a hyperinsulinemic euglycemic clamp. The latter is the gold standard for assessing insulin sensitivity reflected by GIR under insulin clamp conditions. Clamp studies were conducted as previously reported using a continuous infusion of insulin (Humulin; Eli Lilly) at a rate of 40 mULm²Lmin⁻¹ for 4 h and euglycemia (target 90 mg/dL) maintained using an adjustable infusion of 20% dextrose (26, 27). The HOMA-IR index was calculated as glucose (mg/dL) × insulin (mU/L)/405 (28).

Serum adipokine measurement

During the parent studies, blood was collected from all study participants at entrance into the study thus any degradation of serum proteins during storage would be the similar across groups. Blood was collected, processed and stored using consistent standard operating procedures. Briefly, blood was collected in serum separation tubes containing no added coagulants or platelet aggregation inhibitors and left at room temperature for 15 min to allow

clotting. Serum was isolated by centrifugation (1500 x *g* for 5 min), aliquoted into several 1mL vials, and immediately stored at -80° C for future use. Serum ATX is stable and activity is preserved after freezing and storage (29). One serum aliquot was thawed for this study. Serum ATX was determined by ELISA (R&D Systems, Minneapolis, MN). ATX protein expression strongly correlates with ATX's enzymatic activity for conversion of LPC to LPA (13, 30).

Statistical methods

Clinical and demographic characteristics were reported as absolute frequency, percentage, or mean with standard deviation as noted in the table legend. Data were assessed for normality using Shapiro-Wilk's normality test. Categorical data were analyzed using chi-square test. Continuous variables were analyzed using Student's t-test. Pearson's correlations were used to identify relationships between ATX and measures of insulin resistance. Since sex was significantly correlated with serum ATX, Pearson's partial correlation was used to control for sex interaction. Hypertensive and lipid medication use may alter glucose homeostasis, Pearson's partial correlation was used to also control for medication interaction. We controlled for sex, and hypertensive and lipid medication use in regression modeling. Multivariable linear regression models were used to determine if serum ATX was a predictor of GIR and HOMA-IR. Multivariable linear regression models used $p < 0.05$ as entry into the model and $p = 0.10$ as removal from the model. Statistical significance was assumed *a priori* at $p < 0.05$. SPSS version 21.0 (IBM, Armonk, NY) was used for statistical analyses.

Results

Clinical and Demographic Characteristics of Study Participants

Participant demographic and anthropometric data are presented in Table 1. The study was comprised of 20 older (mean 68.7 ± 3.8 years) males with overweight or obesity (mean 31.3 ± 3.7 kg/m²), and 40 older (mean 66.1 ± 4.2 years) postmenopausal females with overweight or obesity (mean 31.4 ± 3.4 kg/m²) of primarily Caucasian ethnicity. Of the 60 participants, 23 subjects (8 males, 15 females) were taking blood pressure medications including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and/or thiazide diuretics; 29 subjects (10 males, 19 females) were taking lipid medications including HMG-CoA reductase inhibitors and/or fish oil; and 14 subjects (5 males, 9 females) were taking both antihypertensive and lipid-lowering medications. Subsequent analyses controlled for antihypertensive and lipid-lowering medication use due to the potential impact of these medications on cardiometabolic variables.

The majority of subjects were in obesity class I (30 BMI < 35 kg/m², 42%) or class II (35 BMI < 40 kg/m², 20%) with the remaining subjects being classified as overweight (25 BMI < 30 kg/m², 38%). All subjects were non-diabetic, as indicated by all subjects having an HbA1c < 6.5 (5.9 ± 0.42 and 5.8 ± 0.5 in males and females, respectively). Females had lower weight ($p = 0.0001$) and waist circumference ($p < 0.004$) than males. Females also had higher GIRs ($p = 0.0003$), higher HDL cholesterol ($p < 0.001$), and lower diastolic blood pressure ($p = 0.039$) than males. Consistent with a prior study (30), serum ATX was also sexually dimorphic with higher serum concentrations in females (290.1 ± 16.7 ng/mL) than

males ($172.4.0 \pm 11.3$ ng/mL, $p=0.001$). For these reasons, subsequent analyses controlled for sex.

Serum ATX correlates with measures of glucose homeostasis and insulin sensitivity

The relationship between serum ATX and cardiometabolic phenotypes were assessed (Table 2). After controlling for sex, serum ATX correlated with BMI, waist circumference, fasting glucose, fasting insulin, 2h glucose following an OGTT, HOMA-IR, and GIR. Serum ATX also tended to correlate with HbA1c ($r=0.27$, $p=0.091$). Partial correlations were similar after additionally controlling for medication use. These findings demonstrate that serum ATX significantly correlates with multiple measures of glucose homeostasis and insulin sensitivity in this cohort of older, nondiabetic, humans with overweight or obesity.

Serum ATX is an independent predictor of insulin sensitivity (GIR)

Since serum ATX correlated with multiple measures of glucose homeostasis and insulin sensitivity, we next investigated the ability of serum ATX to predict GIR during a hyperinsulinemic euglycemic clamp, the gold standard measure of insulin sensitivity, using multivariate regression (Table 3). Multivariate linear regression revealed that sex, medication use, serum ATX, and BMI predict 39.8% of GIR. After controlling for the effects of sex and medication use, BMI and serum ATX accounted for 9% and 8.6% of GIR variance, respectively.

Serum ATX is an independent predictor of insulin resistance (HOMA-IR)

Serum ATX showed the strongest correlation with a measure of insulin resistance, HOMA-IR. Therefore, we investigated the predictive capacity of serum ATX in a multivariate regression model for HOMA-IR (Table 4). Multivariate linear regression revealed that sex, medication use, BMI, and serum ATX predict 36.8% of HOMA-IR. After controlling for sex and medication use, BMI and serum ATX accounted for 13.2% and 22.5% of HOMA-IR variance, respectively.

Discussion

The ATX-LPA system has been implicated in obesity and impaired glucose homeostasis in cell and animal models (¹⁹), but its role in human metabolic homeostasis remains poorly understood. This study sought to determine the relationship between serum ATX and measures of glucose homeostasis and insulin sensitivity in humans. In this cohort of older, non-diabetic humans with overweight or obesity, we identified several novel findings regarding the relationship between serum ATX and human metabolic disease. First, serum ATX was different in females and males; therefore, we used partial correlation to control for the effect of sex. After controlling for sex, serum ATX correlated with features of glucose homeostasis and insulin resistance, including HOMA-IR and GIR during a hyperinsulinemic euglycemic clamp, as well as fasting glucose, fasting insulin, and 2-h glucose following a 75g oral glucose tolerance test (OGTT). These effects persisted after additionally controlling for medication use that may affect glucose homeostasis. Second, serum ATX positively correlated with measures of energy homeostasis, including BMI and waist circumference, although only the former correlation remained significant after additionally controlling for

medication use. Third, serum ATX, along with BMI, was an independent predictor of both GIR and HOMA-IR. Together these findings support a potential role for serum ATX in glucose homeostasis and insulin sensitivity in humans.

Our study indicates that serum ATX increases with insulin resistance in older humans. Because we performed a detailed phenotypic evaluation of the participants prior to the development of overt diabetes or advanced metabolic syndrome, our data indicate that elevations in serum ATX are associated with early impairments in glucose homeostasis and insulin action. These conclusions are supported by identification of significant correlations between serum ATX and multiple different measures of glucose homeostasis and insulin sensitivity including fasting glucose, fasting insulin, HOMA-IR, 2-hour glucose following an OGTT, and GIR by hyperinsulinemic euglycemic clamp - the gold standard for assessing insulin resistance. These results are consistent with animal models demonstrating that increasing adipocyte-specific ATX and/or LPA (either genetically or pharmacologically) impairs glucose homeostasis and insulin sensitivity; whereas, decreasing adipocyte-specific ATX and/or LPA improves glucose homeostasis and insulin sensitivity (20, 21, 22). These results are also consistent with evidence in mice and humans demonstrating increased visceral adipose tissue expression of ATX is strongly associated with impaired glucose homeostasis and/or insulin resistance (24, 25). Together, these data support a potential role for serum ATX in the pathogenesis of insulin resistance in humans; however, reciprocal regulation of the ATX-LPA system by altered glucose homeostasis or insulin action cannot be excluded.

While our study was in preparation, another human study by Nishimura et al. was published with contradictory results to our own (21). Specifically, they found negative correlations between serum ATX and BMI, SBP, and DBP, positive correlation with HDL, and no significant relationship with HOMA-IR. There are several contributors to these contradictory findings. First, the Nishimura cohort was generally normal weight (BMI < 24.9; ~30% of participants) to overweight (BMI 25.0 – 29.9; ~70% of participants) rather than with obesity (BMI ≥ 30; less than 1% of participants). As animal and human studies have indicated, tissue and/or serum ATX increases with obesity (9, 23, 24), and hence a relationship between ATX and metabolic parameters may not be evident or relevant in a normal weight population. In contrast, our cohort was generally class 1 obese (BMI 30.0-34.9) with approximately 62% of the participants had a BMI ≥ 30 kg/m². Second, the Nishimura study did not control for sex. Previous studies in rodents and humans have shown that ATX is sexually dimorphic with females having higher ATX than males (30, 31). Furthermore, other demographic and/or anthropometric details, which were not clearly defined in that study, may contribute to these divergent results. In contrast, our study examined a specific study population with detailed metabolic profiling, particularly with regard to glucose homeostasis and insulin sensitivity. Hence, additional studies in humans are required to resolve these differences and to better define the relationship between serum ATX and metabolic outcomes in relevant study populations.

The present study had several strengths and limitations. Regarding the latter, our study had a relatively small sample size of mixed sex with the male group of more limited size. As noted above, our study population was also limited to a relatively narrow population of older,

nondiabetic participants. In addition, our study did not include adipose tissue biopsies or serum LPA measurements, thereby preventing simultaneous assessment of serum ATX, adipocyte ATX expression, and serum LPA. Finally, our study was not designed to provide mechanistic insight into how ATX might causally contribute to obesity or insulin resistance. Despite these shortcomings, our study includes many strengths. Specifically, our study is the first to use multiple measures of glucose homeostasis to assess the relationship between serum ATX and metabolic phenotypes. We revealed a relationship between the ATX-LPA system, obesity, and insulin resistance previously not demonstrated in humans. Furthermore, by limiting our study to a well-defined, highly relevant study population with mild to moderate obesity and early metabolic disease, we were able to detect early associations between ATX, glucose homeostasis, and energy homeostasis. Since this cohort was nondiabetic, these data suggest that changes in the ATX-LPA signaling system may precede insulin resistance and may serve as a potential disease predictor and/or therapeutic target. Our study supports further investigation into the complex relationship between the ATX-LPA system and metabolic disease.

The potential impact of our findings are several fold. First, given the major role of ATX in determining local and systemic LPA concentrations, understanding its biology and physiology in humans is important, not only for understanding metabolic disease, but other diseases as well. In particular, since pharmacological modulators of the ATX-LPA system already exist and/or are in development (¹⁶), understanding the potential effects these agents have on metabolic outcomes in humans would be useful (^{16, 17, 18}). Conversely, it would also be useful to know whether ATX biology in humans supports further investigation into the therapeutic use of these agents for treatment of human metabolic diseases such as obesity, insulin resistance, and overt diabetes. Finally, ATX may serve as a predictor for obesity-associated metabolic risk. Indeed, we have recently shown that ATX is an independent predictor of NAFLD in females with obesity (³²). Thus, use of serum ATX to predict metabolic outcomes and/or therapeutic modulation of ATX in susceptible individuals might be beneficial in treatment of metabolic disease.

In conclusion, our study reveals a relatively strong and consistent relationship between serum ATX and glucose homeostasis and insulin sensitivity in older, non-diabetic, humans with overweight or obesity. Our study further supports a possible association between serum ATX and measures of energy homeostasis. Additional studies are required to further clarify the specific relationship, including predictive potential and possible underlying causal mechanisms, between serum ATX and energy/glucose homeostasis in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

What is already known about this subject

- Autotaxin (ATX, ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2)) is an adipocyte secreted protein
- The ATX-LPA pathway was recently implicated in both adipocyte biology and glucose homeostasis in cell and animal models
- The relationship between serum ATX and metabolic phenotypes in humans remains poorly understood

What this study adds

- In older, people with overweight or obesity, serum ATX correlates with measures of glucose homeostasis and insulin sensitivity
- In older, people with overweight or obesity, serum ATX is an independent predictor of insulin sensitivity (GIR)
- In older, people with overweight or obesity, serum ATX is an independent predictor of insulin resistance (HOMA-IR)

Table 1
Demographic, anthropometric, and clinical characteristics of human participants

Baseline characteristics of study participants. All data are expressed as mean (standard deviation) for continuous variables and number (percent of total population) for categorical values. Categorical data were analyzed using chi-square test. Continuous variables were analyzed using Student's t-test. BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GIR, glucose infusion rate; HbA1c, glycated hemoglobin (A1c); HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SBP systolic blood pressure; TG, triglycerides; VLDL, very low-density lipoprotein.

Characteristics	All N = 60	Males N = 20	Females N = 40
Demographic Data			
Age (yr)	66.92 (4.24)	68.7 (3.8)	66.1 (4.2)
Caucasian, n (%)	57 (95)	18 (90)	39 (97.5)
BP meds., n (%)	23 (38)	8 (40)	15 (37.5)
Lipid meds., n (%)	29 (48)	10 (50)	19 (47.5)
BP and Lipid meds., n (%)	14 (23)	5 (25)	9 (22.5)
Energy Homeostasis			
Weight (kg)	86.7 (12.8)	95.3 (13.1)	82.5 (10.5)
BMI (kg/m ²)	31.4 (3.4)	31.3 (3.7)	31.4 (3.4)
Waist Circ. (cm)	105.6 (11.4)	111.5 (10.3)	102.4 (10.7)
Blood Pressure			
SBP (mmHg)	140 (13)	140 (8)	139 (15)
DBP (mmHg)	76 (9)	80 (5)	75 (10)
Glucose Homeostasis			
HbA1c	5.8 (0.5)	5.8 (0.4)	5.8 (0.5)
Glucose (mg/dL)	91.9 (11.5)	92.5 (9.0)	91.6 (12.6)
Insulin (μU/mL)	5.8 (3.9)	6.4 (3.6)	5.5 (4.1)
OGTT (mg/dL)	145.3 (42.7)	148.3 (40.4)	143.8 (44.2)
HOMA-IR	1.4 (1.1)	1.5 (0.9)	1.3 (1.2)
GIR (mg/kg/min)	7.0 (2.9)	5.2 (2.7)	8.0 (2.6)
Lipid Homeostasis			
Cholesterol (mg/dL)	191.3 (28.8)	181.1 (28.2)	196.4 (28.1)
HDL (mg/dL)	56.3 (15.4)	44.8 (10.3)	62.1 (14.2)
LDL (mg/dL)	113.6 (25.8)	115.0 (25.7)	112.9 (26.1)
VLDL (mg/dL)	21.4 (9.1)	21.4 (7.3)	21.4 (9.9)
TG (mg/dL)	131.1 (55.8)	130.5 (45.9)	131.4 (60.1)
Autotaxin (ng/mL)	250.0 (107.5)	172.4 (11.3)	290.1 (16.7)

Table 2

Partial correlations of serum ATX

Pearson's correlations and partial Pearson's correlations for serum ATX, after controlling for sex, and sex and medication use, with corresponding *p* values. Variables that significantly correlated (*p*<0.05) with serum ATX are in bold. Variables with *p* value <0.10 are considered a trend and are presented in italics.

Variable	Unadjusted Correlation		Partial Correlation Control: Sex		Partial Correlation Control: Sex and Meds	
	Pearson's <i>r</i>	<i>p</i>	Pearson's <i>r</i>	<i>p</i>	Pearson's <i>r</i>	<i>p</i>
Demographic Data						
Age	-0.02	0.885	0.15	0.353	0.14	0.392
Race	-0.17	0.209	-0.13	0.346	-0.16	0.347
Medication Use	0.02	0.873	0.06	0.708		
Sex	0.53	0.000				
Energy Homeostasis						
BMI	0.25	0.051	0.37	0.021	0.37	0.023
Waist Circ.	0.01	0.939	0.26	0.046	0.25	0.126
Glucose Homeostasis						
HbA1c	0.16	0.214	0.27	0.091	0.29	0.076
Glucose	0.32	0.013	0.52	0.001	0.52	0.001
Insulin	0.39	0.006	0.60	< 0.0001	0.61	< 0.0001
OGTT	0.24	0.070	0.35	0.028	0.36	0.024
HOMA-IR	0.44	0.002	0.62	< 0.0001	0.62	< 0.0001
GIR	-0.06	0.669	-0.55	0.002	-0.56	< 0.0001
Blood Pressure						
SBP	0.10	0.469	0.19	0.253	0.18	0.282
DBP	-0.14	0.286	0.01	0.961	0.01	0.961
Lipid Homeostasis						
Cholesterol	0.19	0.149	0.02	0.908	0.04	0.810
HDL	0.15	0.251	-0.22	0.187	-0.22	0.195
LDL	0.07	0.603	0.05	0.746	0.08	0.656
VLDL	0.15	0.253	0.21	0.191	0.22	0.177

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Variable	Unadjusted Correlation		Partial Correlation Control: Sex		Partial Correlation Control: Sex and Meds	
	Pearson's r	p	Pearson's r	p	Pearson's r	p
TG	0.14	0.282	0.26	0.190	0.22	0.176

Table 3
Multivariable linear regression models for predicting glucose infusion rate

Multivariable linear regression model for predictors of glucose infusion rate, after controlling for sex, medication use, and BMI. Data are presented as standardized coefficient beta, R^2 , R^2 change, and associated p values. BMI and serum ATX as predictors of GIR after controlling for sex and medication use.

Variable	Beta	p	R^2	p	R^2 change	p
Sex	0.668	0.000	0.222		0.221	0.000
BMI	-0.214	0.065	0.312	0.000	0.090	0.012
ATX	-0.361	0.010	0.398		0.086	0.010

Table 4

Multivariable linear regression models for predicting HOMA-IR

Multivariable linear regression model for predictors of HOMA-IR, after controlling for sex, medication use, and BMI. Data are presented as standardized coefficient beta, R^2 , R^2 change, and associated p values. BMI and serum ATX as predictors of HOMA-IR after controlling for sex and medication use.

Variable	Beta	p	R^2	p	R^2 change	p
Sex	-0.389	0.011	0.006	0.006	0.006	0.591
BMI	0.224	0.088	0.143	0.001	0.132	0.014
ATX	0.584	0.000	0.363	0.225	0.225	0.000