Association between serum transaminase levels and insulin resistance in euthyroid and non-diabetic adults

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ABSTRACT

Aim: To evaluate the association between elevated serum transaminase levels and insulin resistance (IR) in a population of healthy individuals.

Methods: We define IR with a cut-off point of homeostatic model assessment (HOMA-IR) ≥ 3.8 . For aspartate aminotransferase (AST), we consider elevated values >30 U/L in women and values >36 U/L in men. For alanine aminotransferase (ALT), we consider elevated values >30 U/L in women and values >40 U/L in men. We performed a crude and adjusted generalized linear model from Poisson family with robust variance, in order to evaluate the association between elevated serum transaminase levels and IR. The associations were presented as prevalence ratio (PR) with their respective 95% confidence intervals (95% CI).

Results: We included 261 participants in the study. The median age was 39 years (31–45) and 23.7% of the participants were men. The prevalence of elevated serum transaminase for AST and ALT were, 13.8% and 26.1%, respectively. The prevalence of IR was 34.1%. In the crude analysis we found statistical significance between elevated AST and ALT with IR (PR = 3.18; 95% CI: 2.33–4.34 and PR = 2.44; 95% CI: 1.88–3.30; respectively). However, in the multivariate analysis, the association only remained statistically significance with ALT, but lost its significance with AST, PR = 1.90; CI 95%: 1.31–2.77 and a PR = 1.23; CI 95%: 0.93–1.61; respectively.

Conclusion: Elevated serum levels of ALT were associated with insulin resistance. ALT could be used in clinical practice as an additional tool to assess IR in apparently healthy people.

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1. Introduction

Insulin resistance (IR) is defined as the decrease in the sensitivity of the tissues towards the insulin, which primary function is the facilitation of glucose uptake. According to its pathophysiology,

IR produces an increase in blood glucose, as well as an hyperinsulinism state and finally the development of type 2 diabetes mellitus (DM2) [1]. In 2015, 84.1 million US adult citizens had prediabetes [2]. It was shown that 45% of men and 42% of women in a heterogeneous population of Peru suffer from IR [3]. These numbers are alarming, since they indicate that approximately half of the population has a greater risk of developing diseases such as DM2 and metabolic syndrome.

On the other hand, it is known that IR plays an important role in the pathogenesis of various diseases such as neoplasms [4,5], hyperuricemia, cardiovascular and metabolic disorders [6–8]. IR also plays an important role in different liver diseases, among them are liver fibrosis, cirrhosis, cholelithiasis, cholecystitis and non-alcoholic hepatic steatosis (NASH) [9]. In addition, several studies

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Abbreviations

AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
IR	Insulin resistance
DM2	Type 2 Diabetes Mellitus
NASH	Non-Alcoholic Steatohepatitis
GGT	Gamma-Glutamyltransferase
HOMA	Homeostasis model assessment
FT3	Free Triiodothyronine
FT4	Free Thyroxine

show that patients with obesity, metabolic syndrome and insulin resistance have a higher prevalence of NASH as comorbidity [10–12]. This reflects the relationship between the liver and these metabolic diseases.

Several studies have been published that report the direct relationship of DM2 and the metabolic syndrome with elevated hepatic transaminases: aspartate aminotransferase (AST), alanine transaminase (ALT) and gamma glutamyl transpeptidase (GGT) [13]. A study carried out in Iran showed an elevation of AST and ALT in diabetic patients, independently of the presence or absence of any liver disease at the time of the study [14]. Furthermore, a case-control study conducted in China compared the levels of these enzymes in healthy patients and in patients with metabolic syndrome. It was found that the patients with metabolic syndrome had higher transaminase levels, especially GGT [15]. Another study involving 451 non-diabetic patients concluded that elevated ALT is a risk factor for type 2 diabetes [16]. These studies strengthen the idea that there is an association between the elevation of liver enzymes and DM2, IR and Metabolic Syndrome (MS). However, there is limited scientific evidence available regarding the association of elevated transaminases with insulin resistance in euthyroid people and without diabetes. The aim of our study is to evaluate the association between elevated serum transaminase levels and insulin resistance in non-diabetic and euthyroid patients who have been treated at a private clinic in Lima, Peru between January 2014 and December 2016.

2. Methods

2.1. Study design and population

We carry out an analytical cross-sectional study in adults of both sexes without a history of diabetes mellitus or another metabolic or endocrine disorder, who attend a private outpatient clinic in Lima-Peru between 2014 and 2016. The people who attend this clinic belong mainly in a high socioeconomic group. We included adults between ≥ 18 years and ≤ 60 years without diabetes mellitus, thyroid disorders or are pregnant. We excluded participants who had fasting glucose values ≥ 126 mg/dl, glycosylated hemoglobin $\geq 6.5\%$, glycemia > 200 mg/dl at 2 h of oral glucose overload, thyroid hormones out of range: Free T3: 2.3–4.2 pg/ml, free T4: 0.89–1.76 ng/dl and TSH: 0.35–5.5 μ U/ml [17], those with a chronic use of corticosteroids and those with missing value. The sample included all patients who attend private clinic in the study period and met our eligibility criteria.

2.2. Main variables

The main outcome variable in our research is insulin resistance. We calculated IR following the “Homeostasis Model Assessment for

Insulin Resistance” (HOMA-IR) [18]. The cut-off point to define the presence of IR was a HOMA-IR equal to or greater than 3.8. The formula used to calculate this value is: fasting blood glucose (mg/dl) x fasting insulin (mg/dl)/405.

The main independent variables are elevated serum transaminase levels for ALT and AST. The cut-off points for elevated AST and ALT levels were chosen in concordance to the study by Esteghamati et al. [14]. For AST, values > 30 U/L were considered in women and values > 36 U/L in men. For ALT, values > 30 U/L were considered in women and values > 40 U/L in men.

2.3. Data extraction

We reviewed the medical records of the participants during the study period. Fasting insulin and glucose values were only included if they were not more than 30 days old after the participants were attended in the ambulatory service. Only the first laboratory results of these analyzes were considered for inclusion in the database. All participants had a minimum period of 8 h of fasting before the collection of the samples for the laboratory tests. We also recollected data on age, sex, BMI, glycosylated hemoglobin, free T3 (Triiodothyronine), free T4 (Thyroxine) and TSH (Thyrotropin).

2.4. Statistical analysis

We reviewed the database and excluded those who did not meet the eligibility criteria or with incomplete data. We attempted to only include participants without any metabolic alteration.

The numerical variables were presented as mean and standard deviation, if they have a skewness distribution, the medians and interquartile range were also presented. Categorical variables were presented frequencies and percentages. Bivariate associations were assessed with the parametric T-Student test for normally distributed variables and with the Chi2 test for categorical variables. Numerical variables with skewness distributions were compared using the non-parametric Kruskal-Wallis test. Correlations between numerical variables were assessed with Pearson correlation coefficient.

To measure the strength of association between the elevated transaminase serum levels and insulin resistance we applied a crude and adjusted generalized linear model from Poisson family with robust standard errors. The prevalence ratio (PR) was established as the measure of association with their respective confidence interval of 95% (CI 95%).

The variables of age, sex, body mass index and T3L, were included in the adjusted model following epidemiological criteria. The data analysis was performed with the software STATA version 14.

2.5. Ethical aspects

The information analyzed was collected by an independent researcher for an epidemiological surveillance study. For this study, we sorted the data in Excel without identifying any of the participants, thus maintaining the anonymity and confidentiality of the participants. The study was designed in concordance to the declaration of Helsinki. The study was approved for Institutional Review Board of Universidad Peruana de Ciencias Aplicadas.

3. Results

3.1. General characteristics of the participants

In total, we reviewed 1133 medical records during the study period, 872 patients were excluded from the database due to

Table 1
Characteristics of study population (n = 261).

Variables	Median (Interquartile range)
Age (years)	39 (31–45)
Male sex	62 (23.7)*
BMI (kg/m ²)	28.3 (25.4–32)
Fasting glucose (mg/dL)	89 (82–96)
2 h GTT (mg/dL)	94 (79–111)
Fasting insulin (mU/ml)	12.18 (8.43–20.02)
Glycosylated hemoglobin (%)	5.43 (0.32) **
HOMA-IR index	2.84 (1.79–4.58)
Insulin resistance	89 (34.1)*
TSH (mIU/L)	2.27 (1.67–3.1)
FT3 (nmol/L)	3.18 (2.92–3.55)
FT4 (mcg/dL)	1.19 (1.1–1.31)
Elevated AST	36 (13.79)
Elevated ALT	68 (26.05)

*Frequency (percentage); **Mean (Standard deviation); BMI: Body mass index; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

alterations in thyroid hormone levels, abnormal glycemia values or because they didn't had the complete data required for the study. The exclusions were carried out in order to obtain a metabolically healthy population. Finally, we included and analyzed 261 participants for the study.

The median age of the participants was 39 years (31–45), 76.3% were female and the median BMI was 28.3 kg/m² (25.4–32). The median HOMA-IR in the study population was 2.84 (1.79–4.58). The median free triiodothyronine and free thyroxine were 3.18 (2.92–3.28) and 1.19 (1.1–1.31) respectively. The median serum value of AST was 21 U/L (17–26) and the median serum value of ALT was 21 U/L (16–35). 34.1% of the participants presented insulin resistance, according to the HOMA index. Table 1 shows the general characteristics of the study population.

3.2. Bivariate analysis according to elevated serum transaminase levels

There was no significant difference between age of participants with high levels of AST and ALT compared to participants with normal levels. Males had a higher prevalence of elevated ALT ($p < 0.01$) but not elevated AST ($p = 0.30$). Participants with elevated levels of ALT and AST had a higher median of BMI, fasting glucose, fasting insulin and 2-h glucose tolerance test levels compared to patients with normal levels ($p < 0.05$). The mean values of glycosylated hemoglobin were also higher in the group of participants with elevated transaminase levels. The HOMA-IR index

had a higher median in participants with elevated ALT [5.31 (3.31–8.22)] ($p < 0.01$) and in participants with elevated levels of AST [5.65 (4.55–7.80)] ($p < 0.01$). Participants with elevated transaminase levels presented a higher T3L levels compared to participants with normal levels ($p < 0.01$). Table 2 shows the characteristics of the study population according to elevated serum transaminase levels.

3.3. Bivariate analysis according to insulin resistance

There was a positive correlation between the logarithm of transaminases and logarithm of HOMA-IR, $r = 0.33$; $p < 0.01$ and $r = 0.56$; $p < 0.01$; respectively. (Fig. 1 and 2). It was found that 69.44% of patients with alterations of the AST values were also insulin-resistant. In the same way, 69.12% of patients with alterations in ALT values were insulin-resistant.

The bivariate analysis shows no differences between the median age of the insulin-resistant participants and the non-insulin-resistant patients. The median BMI was higher in the in IR group ($p < 0.01$), as well as the values of fasting glucose ($p < 0.01$) glucose at 2 h of GTT ($p < 0.01$) and fasting insulin ($p < 0.01$). The group of participants without IR had an average glycosylated hemoglobin of 5.38 (SD = 0.30, $p < 0.01$) versus 5.53 (SD = 0.33, $p < 0.01$) in the group with IR. Table 3 shows the characteristics of the study population according to insulin resistance.

3.3.1. Generalized linear model from Poisson family with robust standard errors to assess the association between elevated transaminases and insulin resistance

In the crude analysis between AST and IR, we found association between the two variables (PR = 2.44, 95% CI: 1.81–3.30). The same occurs between ALT and IR (PR = 3.18, 95% CI: 2.33–4.34). A multivariate analysis was performed adjusted for age, sex, BMI and T3L. In the adjusted analysis, the association between AST and IR lost statistical significance (aPR = 1.23, 95% CI: 0.93–1.63). Likewise, the magnitude of the association ALT and IR decreases, but it remains statistical significance (aPR = 1.90, 95% CI: 1.31–2.77). Table 4 shows crude and adjusted generalized linear model from Poisson family with robust standard errors.

4. Discussion

The objective of our study was to measure the association between alterations in serum values of AST and ALT with the presence of IR, which was calculated using the HOMA-IR. After adjusting for confounding variables, we found an association between ALT and IR but not between AST and IR.

Table 2
Characteristics of the study population according to elevated serum transaminase levels.

Variable	Elevated AST (n = 36)	Normal AST (n = 225)	p-value	Elevated ALT (n = 68)	Normal ALT (n = 193)	p-value
Age (years)	41 (33–47)	39 (31–45)	0.41	40 (30.5–45.5)	38 (31–45)	0.79
Sex*			0.30			<0.01
Male	11 (17.74)	51 (82.26)		24 (38.71)	38 (61.29)	
Female	25 (12.56)	174 (87.44)		44 (22.11)	155 (77.89)	
BMI (kg/m ²)	31.8 (27.15–34.75)	27.9 (25.3–31.6)	<0.01	31.8 (27.95–34.85)	27.3 (25.1–30.7)	<0.01
Fasting glucose (mg/dL)	93 (86.5–100)	89 (82–95)	0.02	94 (87–100)	88 (82–95)	<0.01
2 h GTT (mg/dL)	112.5 (92–121.5)	93 (79–108)	<0.01	106.5 (92.5–126)	90 (78–106)	<0.01
Fasting insulin (mU/ml)	25.14 (15.35–34.17)	11.73 (8.17–17.52)	<0.01	24.20 (14.85–33.78)	11.03 (7.64–15.76)	<0.01
Glycosylated hemoglobin (%) **	5.55 (0.40)	5.41 (0.30)	0.02	5.54 (0.35)	5.39 (0.30)	<0.01
HOMA-IR Index	5.55 (3.31–8.13)	2.60 (1.76–4.08)	<0.01	5.31 (3.31–8.22)	2.40 (1.56–3.33)	<0.01
TSH (mIU/L)	2.18 (1.44–2.88)	2.28 (1.69–3.11)	0.34	2.12 (1.66–2.88)	2.35 (1.69–3.12)	0.23
FT3 (nmol/L)	3.41 (3.19–3.73)	3.12 (2.9–3.5)	<0.01	3.37 (3.11–3.73)	3.1 (2.89–3.45)	<0.01
FT4 (mcg/dL)	1.16 (1.07–1.26)	1.2 (1.11–1.35)	0.03	1.16 (1.09–1.3)	1.21 (1.12–1.32)	0.09

*Absolute frequency (Percentage); **Mean (Standard deviation); BMI: Body mass index; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Fig. 1. Scatterplot for the correlation between the logarithmic AST values and the logarithmic HOMA-IR values.

Fig. 2. Scatterplot for the correlation between the logarithmic ALT values and the logarithmic HOMA-IR values.

There is literature available that supports the relationship between the elevation in serum transaminases and different diseases such as diabetes mellitus and the metabolic syndrome [13–15]. However, we didn't find studies in Latin America that reported elevated serum transaminases levels with IR in euthyroid population and without diabetes. In a prospective study conducted with Pima Indians, it was found that patients with elevated ALT values

Table 4

Generalized linear model of the Poisson family to assess association between the serum elevation transaminases and insulin resistance.

Variables	Crude PR (IC 95%)	p-value	Adjusted PR (IC 95%)	p-value
Elevated AST	2.44 (1.81–3.30)	<0.01	1.23 (0.93–1.63)	0.15
Elevated ALT	3.18 (2.33–4.34)	<0.01	1.90 (1.31–2.77)	<0.01
Age (years)	0.99 (0.97–1.00)	0.10	0.99 (0.97–0.99)	0.03
Male sex	1.55 (1.10–2.18)	0.01	1.03 (0.75–1.41)	0.86
BMI (kg/m ²)	1.11 (1.08–1.14)	<0.01	1.09 (1.07–1.12)	<0.01
FT3 (nmol/L)	2.34 (1.60–3.44)	<0.01	1.33 (0.90–1.96)	0.15

BMI: Body mass index; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase. PR: Prevalence ratio.

presented an increased risk of IR and ALT elevation could be used as a predictor for the development of type 2 Diabetes Mellitus [16]. These findings are similar with the results of our study, in which we found that an abnormal elevation of ALT in blood is associated with a higher prevalence of IR.

There are several mechanisms that explain the reason why transaminases are elevated in patients with IR. It is known that elevated serum transaminases levels are associated with obesity and physical inactivity [19]. Patients with those characteristics present an accumulation of lipids in the hepatocytes and other in tissues. It is known that ALT is the best indicator of accumulation of fat in the liver [20]. The elevation of ALT can be interpreted as a marker of subclinical systemic inflammation. There is correlation between ALT and proinflammatory molecules such as cytokines, C-reactive protein and tumor necrosis factor- α [21]. These molecules intervene directly in the pathogenesis of IR, by altering their signaling pathways [22]. The increase in ALT in serum also reflects some degree of damage or inflammation in the liver. This injury would be occurring in patients who do not developed any metabolic disease yet. There is evidence that non-alcoholic fatty liver disease, a condition in which ALT levels are elevated, may precede the diagnosis of type 2 Diabetes Mellitus [23].

We believe that the finding of our study could be beneficial in the clinical practice. The serum measure of ALT could be used as part of the diagnostic tests performed in order to identify patients at risk of presenting alterations in carbohydrate metabolism, being the IR one of the first changes that occur in this set of disorders. However, more prospective studies are still needed in Latin American populations to clarify the association between transaminases and IR, and even as a bio-marker of the development of diabetes or metabolic syndrome.

Table 3

Characteristics of the study population according insulin resistance.

Variable	IR (n = 89)	No IR (n = 172)	p-value
Age (years)	39 (28–45)	39 (32–45.5)	0.20
Sex*			0.02
Male	29 (46.77)	33 (53.23)	
Female	60 (30.15)	139 (69.85)	
BMI (kg/m ²)	31.9 (29–36)	26.95 (24.5–30.2)	<0.01
Fasting glucose (mg/dL)	94 (88–99)	87 (81–94)	<0.01
2 h GTT (mg/dL)	106 (95–121)	87.5 (76.5–102.5)	<0.01
Fasting insulin (mcU/ml)	25.42 (20.02–32.14)	9.95 (7.12–12.14)	<0.01
Glycosylated hemoglobin (%) **	5.53 (0.33)	5.38 (0.30)	<0.01
HOMA-IR Index	5.65 (4.55–7.80)	2.20 (1.48–2.80)	<0.01
TSH (mIU/L)	2.05 (1.53–2.98)	2.44 (1.75–3.12)	0.08
FT3 (nmol/L)	3.39 (3.06–3.71)	3.09 (2.88–3.42)	<0.01
FT4 (mcg/dL)	1.17 (1.06–1.27)	1.21 (1.13–1.35)	0.01
Elevated AST (%)	25 (69.44%)	11 (30.56%)	<0.01
Elevated ALT (%)	47 (69.12%)	21 (30.88%)	<0.01

*Absolute frequency (Percentage); **Mean (Standard deviation); BMI: Body mass index; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Our study presents certain limitations. A limitation of the current study is the use of the mathematical model HOMA-IR to determine IR instead of the “Hyperinsulinemic-euglycemic Clamp Method”, which is the gold standard for the diagnosis of this disorder [24]. Another limitation is the design used in the study, since no causality relationship can be proven with a cross-sectional design. Our study was carried out in a specific patient population within a high socioeconomic stratum in a single private clinic center. Because we included a homogeneous population in our study, the results of our study may not be fully extrapolated in different settings. Finally, it is known that previous liver diseases can alter the body's normal response to insulin. We believe that if the necessary equipment had been available, it would have been opportune to exclude possible patients with previous liver disorders (e.g. Ultrasound). However, we believe that due to their condition of euthyroid and non-diabetic patients it is unlikely that there were previous liver damage in the participants.

In conclusion, an association between elevated serum values of ALT and IR was found. These results may be useful in clinical practice. The assessment of ALT levels could be used in the clinical practice, as part of the evaluations performed to identify patients with risk of presenting or developing IR, type 2 Diabetes Mellitus or metabolic syndrome.

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