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Original article

Low serum uric acid concentration augments insulin effects on the prevalence of metabolic syndrome

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ABSTRACT

Aim: Insulin and uric acid were shown affect the prevalence of Metabolic Syndrome (MetS), but no studies examine their interaction. Therefore, we conducted this study to determine their biological interaction in subjects from central Mexico.
Methods: 433 subjects were enrolled for a cross-sectional study. MetS was defined according to the Harmonizing Definition. Hyperuricemia was defined as ≥7.0 mg/dL in males and ≥5.8 mg/dL in females. Hyperinsulinemia was defined as ≥11.0 μU/mL. Pearson correlation coefficient (r) was calculated to determine the association between uric acid or insulin and MetS. Logistic regression was used to determine the risk (odds ratio) of developing MetS. Biological interactions were determined by the PROCESS Macro and Anderson's method.
Results: Insulin and uric acid levels were elevated in MetS positive group ($p < .05$) and correlated with the number of MetS components ($r = 0.276$ and $r = 0.166$, $p < .001$, respectively). The interaction between uric acid and insulin was associated with the number of MetS components (PROCESS Model 1, interaction coefficient = −0.009, 95%CI: −0.017 to −0.001, $p = .036$). Johnson-Neyman analysis suggests the interaction is lost when uric acid concentration increased >7.0 mg/dL. When the cohort was separated by hyperinsulinemia and hyperuricemia, there was a significant risk of developing MetS for subjects with hyperuricemia (odds ratio = 2.3; 95%CI: 1.1–4.8, $p < .05$), hyperinsulinemia (odds ratio = 3.1; 95%CI: 1.9–4.9, $p < .05$), or both (odds ratio = 7.4; 95%CI: 3.2–17.2, $p < .05$); however, there was no multiplicative or additive interaction.
Conclusion: Here, we show that uric acid and insulin augments the prevalence of MetS; however, no biological interaction was determined for hyperuricemia and hyperinsulinemia.

1. Introduction

Metabolic syndrome (MetS) is a group of pathologies (central obesity, hypertension, hypertriglyceridemia, dyslipidemia, and hyperglycemia) that augments the risk of developing cardiovascular disease and Type 2 Diabetes (T2D) [1]. MetS' prevalence has increased dramatically over the past few decades, possibly due to a combination of an inactive lifestyle [2], higher energy diets [3], and increase use of artificial sweeteners that promote insulin resistance [4,5]. Depending on the age, gender, and ethnicity, the prevalence of MetS can range anywhere between 10 and 84% [1]. In Mexico, the prevalence of MetS is between 28 and 45% [6–8]. The mechanism that leads to the development of MetS remains elusive, probably due to the fact that MetS can develop through multiple, independent mechanisms. There is a large amount of strong evidence implicating the involvement of insulin resistance [1]. However, identification of risk factors and their interactions for MetS is essential for implementing interventions to mitigate MetS development and its associated comorbidities.

As a compensatory mechanism to elevated serum glucose levels, caused by diminished uptake by the muscle, liver, and adipose tissue, the pancreas releases insulin. If insulin prolongs in the bloodstream, this leads to a decreased insulin sensitivity and

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eventual onset of insulin resistance. Since insulin resistance and thus insulin are considered to be a precursor of MetS [9], this would suggest insulin could predict the development of MetS. Many studies have shown that elevated serum insulin concentrations, hyperinsulinemia, are associated with MetS and its components [10]. Most of these studies adjust the odds ratio by age, sex, and BMI, but fail to examine the interaction of other pathologies have on the development of MetS.

Uric acid is the end product of purine degradation and is linked with insulin resistance and T2D [11,12]. Therefore, it was speculated that uric acid could predict or influence the development of MetS or its components. Indeed, serum uric acid has been shown to associate with components of MetS [13]; moreover, cohort studies have shown that uric acid is an independent risk factor for MetS [14,15]. Interestingly, normal levels of uric acid were also associated with MetS [16]. For this reason, some consider hyperuricemia to be a component of MetS [17,18]. However, there remains a question as to the combined effect serum insulin and uric acid levels have on the development of MetS. Since both hyperinsulinemia and hyperuricemia are associated with the development of MetS, we undertook this study to determine the biological interaction of these two pathologies have on MetS prevalence in central Mexicans.

2. Materials and methods

2.1. Subjects and settings

Subjects were recruited, via random sampling, from the Mexican Social Security Institute (IMSS) Clinic 2, located in the City of Puebla, Mexico, from March 2012 to February 2014, for a cross-sectional study. The subjects were recruited from annual appointments and were excluded if they were admitted from the Emergency Room or receiving treatment from the clinic. Subjects were asymptomatic of any chronic disease (cancer, POCS, Thyroid disorders, etc.), other than T2D and hypertension. Subjects were also removed if they were anorexic ($<18.5\ kg/m^2$), were younger than 18 or greater than 70 years old, or the subjects failed to complete any part of the study. The protocol was approved by the Scientific Research Committee of IMSS. All participants provided written, informed consent to participate in the study, conducted in accordance with the Declaration of Helsinki.

2.2. Clinical characterization and biochemical assays

Subjects were clinically evaluated according to a standardized protocol, including personal and family medical history. With the subjects in fasting conditions, wearing light clothing and without shoes, their height (m) and weight (kg) were measured using the body composition analyzer (TBF-215, Tanita, Tokyo, Japan). BMI was calculated as weight/height^2 (kg/m^2) [19]. Waist circumference was measured at the midpoint between the highest point of the iliac crest and the lowest point of the costal margin at the mid-axillary line using a non-stretching anthropometric measuring tape. Blood pressure measurements (systolic and diastolic blood pressure) were taken on the left arm of the seated subject with a mercury-column sphygmomanometer with an appropriately sized cuff.

Whole blood samples were collected from the antecubital vein following a 10–12 h overnight fast. The samples were kept at room temperature to allow clotting. The serum fraction was recovered and frozen at −20 °C until use. Samples were used for the following endpoints: fasting plasma glucose, insulin, glycated hemoglobin (HbA1c), high-density lipoprotein, low-density lipoprotein, triglycerides, and uric acid. An additional blood sample was obtained 2 h after oral glucose administration (75 g) to determine oral glucose tolerance. Fasting plasma glucose and oral glucose tolerance were determined, in duplicate, using the enzymatic method/spectrophotometric glucose oxidation (Beckman Instruments, Brea, CA). Insulin levels were determined by automated immunoassay (Access, Beckman). The HbA1c levels were determined by the turbidimetric inhibition immunoassay. To determine high-density lipoprotein, low-density lipoprotein, triglycerides, and uric acid, serum samples were sent to the Central Laboratory of the Multidisciplinary Research Group. Insulin sensitivity was assessed by the quantitative insulin sensitivity check index (QUICKI) formula: 1/[log (fasting insulin in μU/mL) + log (fasting glucose in mg/dL)]. Insulin resistance was assessed by the homeostatic model assessment (HOMA1-IR) formula: (Glucose in mg/dL × Insulin in μU/ml)/405 [20].

2.3. Allocation of subjects into groups and subgroups

The Harmonizing definition was used to classify subjects as normal [MetS(−)] or having metabolic syndrome [MetS(+)]. The Harmonizing Definition [21] requires three of the following five criteria: 1) waist circumference: ≥90 cm for men or ≥80 cm for women; 2) triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides; 3) high-density lipoproteins <40 mg/dL for men or <50 mg/dL for women or treatment to augment high-density lipoproteins levels; 4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or an antihypertensive drug treatment; or 5) fasting plasma glucose ≥100 mg/dL or taking glucose lowering medicine. Hyperinsulinemia was defined as insulin levels ≥11 μU/mL [19]. Hyperuricemia was defined as uric acid levels ≥7.0 mg/dL for males and ≥5.8 mg/dL for females [22]. Using the American Diabetes Association recommendations [23], subjects were classified as either normal glucose tolerance (NGT; fasting plasma glucose: <100 mg/dL; oral glucose tolerance: <140 mg/dL; HbA1c: <5.6%), prediabetics (PT2D; fasting plasma glucose: 100–125 mg/dL; oral glucose tolerance: 140–199 mg/dL; HbA1c: 5.6–6.4%) and T2D (fasting plasma glucose: ≥126 mg/dL; oral glucose tolerance: ≥200 mg/dL; HbA1c: ≥6.5%). Subjects were evaluated for low insulin sensitivity (QUICKI score < 0.357) [24] and insulin resistance (HOMA1-IR score ≥ 2.5) [25].

2.4. Statistical analysis

The sample size was calculated *a prior* using G*power to determine the presence of an interaction between serum insulin and uric acid and the number of MetS component [26]. The following assumptions were used: 1) Model: Linear multiple regression: Fixed model, R^2 deviation from zero, 2) $\alpha = 0.05$ and power $(1\text{-}\beta) = 0.95$, 3) Cohen's $f^2 = 0.05$ (weak effect) based on previous published correlations for insulin or uric acid with MetS, and 4) number of predictors = 3 (insulin, uric acid, and the interaction). This gave a suggested sample size of 348.

Statistical analyses were performed using Statistical Package for the Social Sciences program, version 19 (SPSS, Chicago, IL) or Medcalc Statistical Software, version 13.3.3 (Medcalc, Ostend, Belgium). The normality of the data was assessed by the Shapiro-Wilk test. Differences between categorical data were assessed with the Chi-Square test. Homogeneity in parametric data was determined with the Levene's test. Differences between groups were determined with Student's T-test, or with Welch's test or ANOVA with a *post hoc* Dunnet't T3 or the Bonferroni test, according to their homogeneity. For non-parametric data, differences between groups were determined with either the Whitney-Mann *U* test or the Kruskal-Wallis Test with a *post hoc* Dunn's test. Linear contrast was used to determine a trend for parametric data and Jonckheere-Terpstra Test was used for non-parametric data. The Pearson correlation coefficient (r) was used to determine the

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