

SERUM IL-17, OBESITY, AND METABOLIC RISK IN MEXICAN YOUNG ADULTS.

IL-17 SERICO, OBESIDAD Y RIESGO METABOLICO EN ADULTOS JOVENES MEXICANOS.

Aradillas-García Celia^{1,2}, Monreal-Escalante Elizabeth¹, Vargas-Morales Juan Manuel¹, Alegría-Torres Jorge³, Rosales-Mendoza Sergio^{1,2}, Terán-García Margarita^{1,4}, Portales-Pérez Diana P.^{1,2}

1 Autonomous University of San Luis Potosí, México. 2 UP AMIGOS Research Project. 3 Univeristy of Guanajuato, México. 4 University of Illinois at Urbana-Champaign. EUA.

ABSTRACT

Introduction: Obesity and several inflammatory pathways contribute to the development of metabolic diseases. Some pro-inflammatory cytokines and other signal proteins produced in fat and liver appear to propagate inflammation systemically. IL-17 is a pro-inflammatory cytokine secreted by activated T-cells. Upon binding to its receptor, IL-17 activates a cascade of signals that include MAPK, NF-kB and other pro-inflammatory cytokines. **Objective:** Determine if the IL-17 levels are associated with obesity and its metabolic comorbidities in young adults. **Method:** Cross-sectional study in the UP AMIGOS 2009 cohort. Anthropometric measurement and blood samples were collected. Fasting glucose, insulin, and serum lipid profile was measured by conventional methods. Serum IL-17 was determined by ELISA assay in 102 individuals with obesity and overweight also in 306 lean students (aged 18 to 26 years old). **Results:** Higher levels of IL-17 were found in the group with obesity (34.99 pg/mL) when compared to lean subjects (26.57 pg/mL). In addition, a positive correlation between serum IL-17 and body mass index and waist circumference in the group with obesity were detected. **Conclusions:** Increased IL-17 levels in young individuals with obesity and overweight are associated with risk factors for developing chronic metabolic diseases.

Key words: IL-17, Metabolic risk, Obesity.

RESUMEN

Introducción: La obesidad y vías inflamatorias contribuyen al desarrollo de enfermedades metabólicas. La masa grasa e hígado producen citoquinas proinflamatorias que pudieran promover la inflamación sistémica. La IL-17 es una citoquina proinflamatoria secretada por células T activadas. Cuando la IL-17 se une al receptor, se activa una casada de señales incluidas MAPK, NFkB y otras citoquinas proinflamatorias. **Objetivo:** Determinar si los niveles IL-17 están asociados con la obesidad y sus comorbilidades en adultos jóvenes. **Método:** Un estudio transversal del estudio de cohorte UP AMIGOS 2009. Se tomaron medidas antropométricas y muestras de sangre. Se midió glucosa en ayuno, insulina y perfil lipídico. La IL-17 en suero se determinó por la prueba ELISA en 102 individuos con obesidad o sobrepeso y en 306 con normopeso de 18 a 26 años de edad. **Resultados:** Se encontraron mayores cifras de IL-17 en el grupo con obesidad (34.99 pg/mL) que en el de normopeso (26.57 pg/mL). Se observó una relación positiva entre IL-17 y el índice de masa corporal y circunferencia de cintura en el grupo con obesidad. **Conclusiones:** Niveles elevados de IL-17 en adultos jóvenes con sobrepeso u obesidad se asocian con factores de riesgo para el desarrollo de enfermedades crónicas.

Palabras Clave: IL-17, Riesgo metabólico, Obesidad.

Correspondencia: Diana P. Portales-Pérez dportale@uaslp.mx

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Introduction

Obesity is a major public health problem because its prevalence is increasing rapidly in the world. It is considered a chronic disease, defined as an excessive body weight due to the dysfunctional accumulation of energy reserves as fat depots, that is caused predominantly by an imbalance between energy intake and energy expenditure, however, the quality of the diet and macronutrients distribution are important as well as genetic factors, and physical activity (Gregor & Hotamisligil, 2011; San-Cristobal, Navas-Carretero, Martínez-González, Ordovas & Martínez, 2020). The overweight and obesity present in childhood and young adults are risk factors for developing hypertension, dislipidemy, glucose tolerance, vascular diseases, metabolic syndrome, and chronic metabolic diseases in later life (Calabro & Yeh, 2007; Donath & Shoelson, 2011). In adults, obesity is associated with increases in systemic inflammatory markers, as evidenced by studies documenting the association of body mass index (BMI) and visceral obesity with circulating levels of cytokines and acute-phase reactants (Esposito, Giugliano, Scuderi & Giugliano, 2006; Ferrante, 2007). In children, the presence of obesity also appears to be associated with increased levels of cytokines as well as other inflammatory mediators and a higher BMI during childhood is associated with an increased risk of cardiovascular disease in adulthood (Baker, Olsen, & Sørensen, 2008; Kim et al., 2010; Santos, Pegoraro, Sandrini & Macuco, 2008). In fact, immune response alterations because of a low-grade inflammation are presented with a consequent increase in circulating levels of proinflammatory cytokines such as IL-6, IL-1 β and TNF- α (Alexandraki et al., 2006; Balistreri, Caruso, & Candore, 2010; Hotamisligil, 2006; Skrha, 2010; Wellen & Hotamisligil, 2005).

Pini & Fantuzzi (2010) described the involvement of IL-17A during acute inflammation in two different animal models of obesity. The authors demonstrated that neutrophils from both obese mice models produced high amounts of this proinflammatory cytokine in a model of acute inflammation (Galgani & Matarese, 2010; Pini & Fantuzzi, 2010). The data are also in agreement with reports where a higher IL-17A production in obese women than a control group has been observed (Sumarac-Dumanovic et al., 2009). Th17 is a Th cells population characterized by their productions of the cytokine IL-17, and in 2005

that factors determining their generation have been identified. The role of Th17 cells in mediating autoimmune pathology is also now becoming recognized, interestingly in events that were previously thought to be Th1-mediated (Chen- & O'Shea, 2008; Fouser et al, 2008; McGeachy, Cua & Gaffen, 2019)

The IL-17 is a proinflammatory cytokine and is one of the six family members which includes five additional molecules (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F). IL-17 is produced in high amounts by activated memory CD4⁺ and CD8⁺ T cells in humans and mice. The role of IL-17A, produced by T lymphocytes is able to induce secretion of chemokines such as CXCL8, CXCL6, CXCL1, growth factors (G-CSF, GM-CSF, IL-6) and adhesion molecules (ICAM-1), leading to an augmented accumulation of neutrophils in inflammatory sites (Korn, Bettelli, Oukka, & Kuchroo, 2007, 2009). However, the IL-17 levels in apparently healthy young individuals have not been studied. Therefore, the aim of this study was to evaluate the association of IL-17 with risk factors for developing chronic metabolic diseases in young adults.

Methods

Study population

The cases group consisted of 102 students fulfilling the World Health Organization (WHO) diagnostic criteria for obesity and overweight, whereas in the control group 306 lean students were included according to the WHO criteria (WHO, 2000). Participants were selected from the UP AMIGOS cross-sectional Study (University of San Luis Potosí and Illinois: A Multidisciplinary Investigation on Genetics, Obesity and Social Environment). A cross-sectional study of young adults aged 18 to 26 years old who were applicant for new enrollment in a Public University in the State of San Luis Potosí, México. According to The National Survey of Health and Nutrition (ENSANUT) in 2018 7 of 10 adults presented overweight or obesity and (ENSANUT, 2018). Inclusion criteria were as follows: students ranging in age from 18 to 26 years, and letter of consent signed by the student. For the cases group apparently healthy, without medical treatment, venous blood glucose above 100 mg/dL, plasma insulin above 15 mU/ml (Donner et al., 1985), and Insulin Resistance Index (IRI) greater than 2.7

(Matthews et al., 1985; Ten & Maclaren, 2004), while control group presented the aforementioned parameters as normal. Exclusion Criteria: Diagnosed with illness, under medication which alters the biochemical values, and in case of female, state of gestation or lactation. Elimination criteria: not completing the evaluation. This study was approved by the ethics committee of health agency of San Luis Potosí (Approval number SLP/012-2010), and informed consent from all participants was obtained.

Determination of anthropometric parameters and sampling

Anthropometric parameters such as weight, height and waist circumference (WC) were measured, and body mass index (BMI) was calculated by dividing weight (Kg) by the squared value of height in meters. The reference interval of BMI was defined as 18 – 24.9 Kg/m² (control group). Over-weight and obesity were considered with a BMI of more than 25 Kg/m² (cases group). The WC was measured with a flexible measuring tape, taking as a reference the midway line between the costal inferior border and the iliac crest. Samples of venous blood were collected in the morning, after overnight fast, using vacutainer tubes, which were cooled to 4°C and centrifuged 15 min to obtain serum and subsequently stored at -70°C.

Biochemical analysis

Glucose and lipid profile. Serum samples were used to measure the concentrations of total cholesterol, HDL-c, triglycerides, and fasting plasma glucose (FPG). Measurements were performed with a Hitachi 912 autoanalyzer equipment (Roche Diagnostic, Switzerland) with appropriate standards.

Insulin measurements. Insulin was determined by radioimmunoassay kit (immulite 1000). The lower limit of detection for insulin was 0.6 IUml-1, whereas the intra-assay coefficients of variation were ≤5%.

Interleukin-17 measurement. IL-17A was measured using ELISA kit (Bio Legend, San Diego, CA, US). Lower limit of detection was 1.95 pg ml-1, whereas the intra-assay precision was 6.0%.

Calculation of insulin resistance. Insulin resistance was determined on the basis of the homeostasis model assessment (HOMA) index, calculated from

the fasting glucose and insulin concentrations: $HOMA = \text{fasting insulin (IUml-1)} \times \text{fasting glucose (mmol-1)} / 22.5$.

Statistical analysis

Case and control groups were compared using the Mann-Whitney U test or t-test according to the distribution of the data. Spearman correlation was employed to assess the correlation between different parameters. Differences were considered significant at $p < 0.05$. All statistical analyzes were conducted using the statistical package SPSS (version 19.0).

Results

Blood concentrations of biochemical parameters

The main clinical parameters assessed in the study are presented in Table 1. According to our results, all variables were statistically different between cases and control group; in comparison with control group, case group showed increased values for body mass index, waist circumference, systolic and diastolic pressure, triglycerides, total cholesterol, fasting glucose, insulin and HOMA index. Only HDL-cholesterol presented low serum levels in cases group. The age was not different between the groups, but the sex distribution was different ($\chi^2 = 14.7$; $P < 0.001$). The male sex had body mass index, waist circumference, blood pressure, triglycerides, total cholesterol and glucose with higher values than the female sex; however, HDL-cholesterol and IL-17 were higher in girls than in boys ($P < 0.05$).

Table 1. Mean values of the parameters evaluated in the study population.

Variables	All n = 408	Controls n = 306	Cases* n = 102	P-value
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	
Boys n (%)	187 (45.8)	123	64	
Girls n (%)	221 (54.2)	183	38	<0.001 ^a
Age (years)	18.3 (18.2-18.5)	18.2 (18-18.3)	18.8 (18.4-19.2)	0.04 ^d
BMI (kg/m ²) ^e	22.97 (22.55-23.39)	21.3 (21.02-21.58)	28.45 (27.7-29.2)	<0.001 ^b
Waist circumference (cm) ^f	77.85 (76.65-79.06)	73.02 (72.21-73.82)	93.7 (91.76-95.63)	<0.001 ^b
SBP (mmHg) ^g	112.54 (111.43-113.65)	109.54 (108.69-110.39)	122.37 (119.36-125.38)	<0.001 ^b
DBP (mmHg) ^g	73.56 (72.67-74.45)	71.51 (70.71-72.32)	80.25 (78.03-82.46)	<0.001 ^b
Triglycerides (mg/dl) ^h	111.79 (105-118.58)	87.4 (84.37-90.44)	191.66 (172.88-210.44)	<0.001 ^b
Total cholesterol (mg/dl) ^h	173 (168.39-177.61)	168.51 (163.6-173.42)	187.72 (176.73-198.71)	0.012 ^d
HDL-cholesterol (mg/dl) ^h	51.69 (50.353-07)	55.22 (53.82-56.61)	40.13 (37.67-42.58)	0.012 ^d
Glucose (mg/dl) ^h	90.12 (89.17-91.07)	88.05 (87.24-88.85)	96.91 (94.26-99.56)	<0.001 ^b
Insulin (IU/ml1)	7.45 (6.75-8.16)	5.72 (5.31-6.13)	13.13 (10.8-15.47)	<0.001 ^b
HOMA-IR	1.72 (1.52-1.92)	1.25 (1.16-1.34)	3.26 (2.57-3.95)	<0.001 ^b
IL-17 (pg/ml) ⁱ	28.54 (26.43-30.65)	26.57 (24.8-28.34)	34.99 (28.16-41.82)	0.002 ^d

*With metabolic Syndrome according to the population-specific and harmonized criteria. ^aChi square test, ^bT-test, ^cLogarithmically transformed data (T-test), ^dMann-Whitney U-test. ^eStatistically significant differences between sexes, only IL-17 and HDL were higher in girls than boys ($P < 0.05$). CI, confidence intervals; BMI: body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure

Correlation between IL-17 and anthropometric parameters

A correlation analysis to assess the possible associations between IL-17 and anthropometric parameters was carried out, finding a positive

association between serum IL-17 and BMI and WC (Table 2). The correlations were statistically significant only in case group and the association was stronger by adjusting for sex and age ($r = 0.413$, $P < 0.001$; $r = 0.337$, $P = 0.003$, respectively).

Correlation between IL-17 and traits of metabolic syndrome

Systolic and diastolic pressure, triglycerides, total cholesterol, and insulin had a positive association when these variables were analyzed with respect to serum IL-17 in all participants ($P < 0.05$), adjusting for sex and age (Table 2). However, this trend only remained with the variable diastolic pressure when the case group was analyzed separately ($r = 0.277$, $P = 0.014$) (Table 2).

Table 2. Correlation analysis between serum IL-17 and the other variables considered traits of metabolic syndrome

Variable	serum IL-17 (pg/ml)					
	All participants (n=408)		Control group (n=306)		Cases (n=102)	
	Non-adjusted	Adjusted ^a	Non-adjusted	Adjusted ^a	Non-adjusted	Adjusted ^a
BMI (kg/m ²)	$r = 0.067^{**}$	$r = 0.278^{***}$	$r = 0.028$	$r = 0.062$	$r = 0.297^{**}$	$r = 0.413^{***}$
Waist circumference (cm)	$r = 0.104^{*}$	$r = 0.243^{***}$	$r = -0.02$	$r = -0.022$	$r = 0.197^{*}$	$r = 0.337^{**}$
SBP (mmHg)	$r = 0.067$	$r = 0.142^{**}$	$r = 0.027$	$r = 0.054$	$r = -0.019$	$r = 0.148$
DBP (mmHg)	$r = 0.101^{*}$	$r = 0.181^{***}$	$r = 0.033$	$r = 0.044^{*}$	$r = 0.095$	$r = 0.277^{*}$
Triglycerides (mg/dl)	$r = 0.140^{**}$	$r = 0.189^{***}$	$r = 0.051$	$r = 0.071$	$r = 0.177$	$r = 0.085$
Total cholesterol (mg/dl)	$r = 0.067$	$r = 0.107^{*}$	$r = 0.047$	$r = 0.102$	$r = 0.061$	$r = 0.067$
HDL-cholesterol (mg/dl)	$r = -0.089$	$r = -0.074$	$r = -0.008$	$r = -0.013$	$r = -0.101$	$r = 0.149$
Glucose (mg/dl)	$r = 0.061$	$r = 0.063$	$r = 0.036$	$r = -0.040$	$r = -0.047$	$r = -0.019$
Insulin (IU/ml)	$r = 0.1^{*}$	$r = 0.118^{*}$	$r = -0.005$	$r = -0.066$	$r = 0.214^{*}$	$r = 0.093$
HOMA-IR	$r = 0.101^{*}$	$r = 0.104$	$r = -0.005$	$r = -0.065$	$r = 0.18$	$r = 0.058$

Spearman correlation coefficient * $P < .05$, ** $P < .01$, *** $P < .001$

^aadjusted for sex and age

Discussion

Obesity is considered a risk factor for the development of chronic metabolic diseases, due to an increase of proinflammatory cytokines produced in primary stages of this condition (Dandona, Aljada, & Bandyopadhyay 2004). Several studies have shown that a higher BMI during childhood could be associated with an increased risk of coronary heart disease in adulthood (Baker et al., 2008). In addition to obesity, high glucose levels as well as hypertension in childhood have been strongly associated with increased rates of premature death from endogenous causes (Franks et al., 2010).

Several studies have shown that the immune response and acute inflammation are influenced by obesity and overweight through IL-17; therefore, this cytokine may represent a key to the inflammation observed during obesity (Qu et al., 2016) and promote atherosclerosis (Tarantino et al., 2014). Human Th17 cells have a different role in the immune system, participating in the resistance against extracellular bacteria and the pathogenesis of

several inflammatory autoimmune conditions (Wilson et al., 2007). Th17 cells induce the release of IL-17, IL-17F and IL-22, which in turn induce the synthesis of proinflammatory cytokines and chemokines by resident cells (Ouyang, Kolls, & Zheng, 2008). Th17 cells may be an important element in the inflammatory process observed in diabetes. Therefore, in this work we decided to explore the levels of IL-17 in serum of young Mexican people and its relationship with anthropometric parameters and traits of metabolic syndrome.

Our results demonstrated that blood concentration of proinflammatory cytokine IL-17 was increased as the weight increased, finding a considerable positive correlation between IL-17 and anthropometric parameters such as BMI and WC in case group. This is in agreement with another report where increased serum IL-17 levels have been correlated with anthropometric parameters (Ribeiro et al., 2017). Although, others authors reports no correlation between IL-17 levels with BMI or WC (Sumarac-Dumanovic et al., 2009). This could be due to the BMI is not the most accurate indicator of body fatness. Even though in clinical practice the BMI offers many benefits evidence indicates that this indicator could fail at identifying obesity subgroups such as metabolically unhealthy but normal weight individuals, and visceral obesity (Swainson, Batterham, Tsakirides, Rutherford & Hind, 2017).

In addition, our data also showed that IL-17 displayed a positive correlation with systolic and diastolic blood pressure, triglycerides, total cholesterol, and insulin when all participants were analyzed. However, only diastolic pressure was positively correlated with serum IL-17 in case group; therefore, these findings do not support the pathogenic role of IL-17 cytokine in the metabolic syndrome, although it could be explained for obesity. It is possible that IL-17 could promote low-grade inflammation in obese patients, as it is capable of inducing other proinflammatory mediators such as TNF α , IL-6 and nitric oxide in different cell types (Galgani & Matarese 2010; Qu et al., 2016). Although, it has been reported the IL-17 role in glucose homeostasis and adipogenesis (Shin, Shin, & Noh 2009; Zúñiga et al., 2011).

Our data also indicated that the increase in IL-17 in obese individuals is independent of the insulin resistance, hyperinsulinemia and hypercholesterolemia, since no association was found in the case group; this suggests that insulin resistance occurs by an independent mechanism (Korn et al., 2007).

While IL-17 is introduced as additional markers of the inflammatory syndrome that accompanies obesity, our results reveal that IL-17 is an indicator associated with risk factors such as overweight and obesity during the youth stage, before eventually developing chronic metabolic diseases such as type 2 diabetes mellitus. However, more studies of IL-17 at an early age to determine risk factors of chronic metabolic diseases are needed to understand the innate and adaptive sources of IL-17 and its role in the pathogenesis of metabolic diseases and obesity.

Conclusions

The levels of serum IL-17 were positively associated with body mass index, waist circumference and diastolic blood pressure in young adults in comparison with a control group. Therefore, IL-17 could have a role in promoting low-grade inflammation in individuals with obesity, being able to induce other proinflammatory mediators.

Limitations One of the limitations of this research was that the diagnosis method of obesity was based on the BMI rather than on the fat body mass since the absence of this variable. Therefore, not all individuals with a BMI greater than 25 must have increase fat body mass.

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