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Triglycerides and high-density lipoprotein cholesterol are associated with insulinemia in adolescents

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Ramírez-López G, González-Villalpando C, Salmerón J, González-Ortiz M, Valles-Sánchez V.
Triglicéridos y colesterol de lipoproteína de alta densidad asociados con insulina en adolescentes.
Salud Publica Mex 2006;48:293-299.

Abstract
Objective: The aim of this study was to evaluate the association between lipids and insulin concentration in adolescents. Material and Methods: A cross-sectional study of 350 adolescents aged 14-19 years old from a public high school in Guadalajara, in the state of Jalisco, Mexico, was conducted. Fasting insulin concentration was determined using microparticle enzyme immunoassay; total cholesterol and triglycerides were detected by standard enzymatic procedures; and low- and high-density lipoproteins were found using standard precipitation methods. Statistical analysis included linear multivariate regression. Results: Serum triglycerides were associated positively with insulin fasting (β = 0.003, p = 0.0001) and high-density lipoprotein cholesterol was negatively associated with insulin fasting in male adolescents 18-19 years old (β = -0.03, p = 0.012). Conclusions: The relationships between triglycerides and insulin and between high-density lipoprotein cholesterol and insulin are already present in adolescence.

Key words: triglycerides, high-density lipoprotein cholesterol, lipids, insulin, obesity, adolescents, Mexico

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Palabras claves: triglicéridos; lipoproteínas de alta densidad; lípidos; insulina; obesidad; adolescentes, México

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Type 2 diabetes and cardiovascular disease are the leading causes of mortality in Mexico. Both appear to begin early in life. Considering the recent findings of high incidence of type 2 diabetes in the Mexican population, the problem is likely to reach more serious proportions. Moreover, it has been shown that type 2 diabetes incidence in adolescents has increased in recent years and a higher prevalence of metabolic syndrome has been shown among Mexican-American adolescents.

Hyperinsulinemia is the strongest predictor for type 2 diabetes and is associated with lipid-profile abnormalities. Obesity is related with hyperinsulinemia and altered lipid and lipoprotein concentrations in adults, especially in those with abdominal fat distribution. Insulin, lipid, and lipoprotein concentrations might be altered by environmental as well as genetic factors. In adults, triglycerides, low-density lipoprotein cholesterol (LDL), and very-low-density lipoprotein cholesterol (VLDL) are positively associated with insulin resistance, while high-density lipoprotein cholesterol (HDL) is negatively associated with insulin resistance.

Hyperinsulinemia, obesity, and lipid and lipoprotein metabolism abnormalities may be present during adolescence and may persist through adulthood, at which time they contribute to the establishment of metabolic syndrome and eventually influence the development of diabetes along with cardiovascular risks later in life. The higher concentrations of insulin, lipids, and lipoproteins observed during early adolescence as compared with late adolescence are explained mainly by pubertal growth spurt related insulin secretion increases. The association among insulin, lipids, and lipoproteins during this period of life is not completely understood. There is controversy concerning this matter, as some researchers have found that triglycerides are positively associated with insulin, whereas others have also found associations with LDL, HDL, and VLDL. Total cholesterol has not been associated with insulin. Furthermore, the association between insulin, abdominal fat, blood lipids, and lipoproteins in adolescents is not as clear as it is in adults.

The aim of this study was to determine the relationship among lipids, lipoprotein profile, and fasting insulin concentration, as well as the relationships between lipids, lipoproteins, insulin, and abdominal obesity in adolescents, as evaluated by waist circumference (WC) and waist-to-hip ratio (WHR).

Material and Methods

Subjects. The relationship among lipids, lipoprotein profile, insulin, and obesity in adolescents was investigated using a cross-sectional study. Recruitment and data collection were carried out from October 1998 to March 1999. Methods and procedures pertinent to this study have been reported previously. Briefly, 350 adolescents –113 boys and 237 girls– were randomly recruited from 10th to 12th-grade classes at a state-funded Mexican high school in the Jalisco state capital of Guadalajara. Within the sample, 45.4% of adolescents were classified as high socioeconomic status, 33.4% as middle, and 21.1% as low. Adolescents who worked comprised 27.0% of the sample. Both adolescents and parents gave written informed consent in accordance with the Institutional Review Board of the Instituto Mexicano del Seguro Social (Mexican Institute of Social Security) in Guadalajara.

Main outcome measurements. Fasting blood samples were obtained for serum lipid, lipoprotein, and insulin determinations after 12 h. Serum samples were stored frozen at -25°C until analyzed. Serum insulin was determined based on microparticle enzyme immunoassay using anti-insulin (mouse-monoclonal)-coated microplates. Regarding lipids and lipoproteins, total serum cholesterol and triglycerides were determined by standard enzymatic procedures, while LDL and HDL were determined using standard precipitation methods with polyvinyl sulphate and phosphotungstic acid, respectively. A BM analyzer (Hitachi 705, Indianapolis, IN, USA) was used for all assays. VLDL was estimated according to the following equation: VLDL = total cholesterol –(HDL + LDL). Intra- and interassay variation coefficients were 4.0 and 6.2% for insulin and <2.7 and <3.7% for all lipids, respectively.

A systematic physical examination was performed on all study participants, and body weight, height, and waist and hip circumference measurements were assessed according to standardized protocols. Overweight was defined as body mass index (BMI, kg/m²) for age ≥85th percentile. Unfavorable abdominal fat distribution was defined as a WHR ≥0.85 for females and ≥0.94 for males.

In addition, a validated 7-day physical-activity recall questionnaire was administered by a trained dietitian. Activities were classified according to metabolic equivalents (METS) (ratio of working metabolic rate/resting metabolic rate). Energy expenditure (EE) was estimated as follows: kcal/day = \sum [weight...
Association of lipids and insulin concentration in adolescents

Statistical analysis. Descriptive analysis was performed to estimate the study population’s clinical and anthropometric characteristics; results are expressed as mean ± standard deviation (X ± SD) or as percentages. Differences between means were obtained with the Student t test for continuous variables and proportions were compared using a χ² test. Partial correlation coefficients were computed to determine any correlation among serum lipids, lipoproteins, and insulin, adjusted for age and sex. Adjusted blood lipids and lipoprotein means were obtained across anthropometric variables (BMI, WC, and WHR). Confounders included age, sex, BMI, WC, EE, caloric intake, and smoking status. Linear trend was tested with multivariate analysis. Adjusted means of lipid and lipoprotein concentrations according to insulin quartiles were also obtained and tested for linear trend after performing multivariate analysis. Due to the skewed distribution of insulin, this was log-transformed for analysis. The association among fasting lipid, lipoprotein, and insulin concentration was assessed using multiple linear regression analysis. A model was built for each lipid and lipoprotein, with insulin as the dependent variable. The inflation factor was analyzed in order to evaluate possible multicollinearity among studied variables. Data were analyzed with Stata version 7.0 software (Stata Corp., TX, USA). Differences were regarded as statistically significant if corresponding p values were ≤0.05.

Results

The study population consisted of 350 adolescents, 68% female, with a mean age of 16 ± 1.19 years (range, 14-19 years old). Nineteen percent of all adolescents were overweight, 3% had unfavorable abdominal fat distribution, 22% were current smokers, and 8.3% had a family history of type 2 diabetes. Mean fasting serum insulin concentration was 54.8 ± 29.4 pmol/l; triglycerides, 100.3 ± 35.4 mg/dl; total cholesterol (CHOL), 157.2 ± 27.0 mg/dl; LDL, 95.2 ± 26.3 mg/dl; VLDL, 18.5 ± 7.3 mg/dl; and HDL, 43.5 ± 8.9 mg/dl. Lipid and lipoprotein profile distribution by sex and socioeconomic status in this population has been reported elsewhere.32

Under partial correlation analysis adjusting for age and sex, fasting insulin concentration correlated positively with lipids and lipoproteins, except VLDL, and correlated negatively with HDL. BMI and WC correlated positively with insulin, lipids, and lipoproteins, and negatively with HDL. BMI showed strongest correlations for nearly all parameters, WHR also correlated positively with all these parameters except total cholesterol and LDL, and WC showed stronger correlations with these parameters in comparison with WHR (Table I).

Linear trend results of lipids and lipoproteins across anthropometric parameters demonstrated that total cholesterol, triglycerides, and LDL increased from the lowest to the highest BMI quartile (147.7-168.5 mg/dl, p= 0.02, 91.2-118.4 mg/dl, p= 0.008, and 85.2-
105.6 mg/dl, \( p = 0.02 \), respectivamente). Triglicéridos aumentaron de la más baja a la más alta cuartil (97.6-114.5 mg/dl, \( p = 0.046 \)), mientras que HDL disminuyó de la más baja a la más alta WHR cuartil (47.1-39.9 mg/dl, \( p <0.001 \)).

Tabla II muestra valores medianos de concentraciones de lípidos y lipoproteínas según cuartiles de insulina después de ajustar por factores conocidos. Después de realizar análisis de regresión multivariante así como un test tendencia para cada lípido y lipoproteína, solo triglicéridos se encontraron aumentando a lo largo de los cuartiles de insulina (93.1 mg/dl-110.4 mg/dl, \( p = 0.043 \)).

Total colesterol, triglicéridos, LDL, VLDL, y HDL, y razón total CHOL/HDL fueron asociados con insulina después de ajustar por edad y sexo. Sin embargo, la relación entre insulina y total colesterol, LDL, VLDL, y HDL no fue estadísticamente significativa cuando se incluyó BMI en el modelo. Además, cuando se incluyó triglicéridos y razón CHOL/LDL se mantuvieron independientemente asociados con la concentración de insulina. Finalmente, cuando EE se incluyó en el modelo solo los triglicéridos se asociaron con la concentración de insulina (Tabla III).

Cuando no se encontró significancia en el modelo ajustado por edad, sexo, BMI, WC, y EE, análisis adicionales múltiples lineales fueron realizados por grupo de edad (14-15, 16-17, y 18-19 años) y sexo (hombre y mujer). Estos análisis demostraron una relación significativa entre insulina y HDL en adolescentes varones 18-19 años de edad con BMI (\( \beta = -0.03, p = 0.012 \)), WC (\( \beta = -0.03, p = 0.009 \)), y EE (\( \beta = -0.03, p = 0.02 \)) fueron incluidos. La inflación de la varianza factor fue 3.8 y no se detectaron problemas para la multicolinealidad. Estas asociaciones no fueron estadísticamente significativas en menores adolescentes.

Cuadro IV muestra la relación entre triglicéridos y insulina, ajustada por factores socioeconómicos y factores ambientales. Triglicéridos se asociaron con concentración de insulina (\( \beta = 0.003, p = 0.07 \)).

## Tabla II

<table>
<thead>
<tr>
<th>Triglicéridos (mg/dl)</th>
<th>p valor</th>
<th>Total colesterol (mg/dl)</th>
<th>p valor</th>
<th>LDL (mg/dl)</th>
<th>p valor</th>
<th>VLDL (mg/dl)</th>
<th>p valor</th>
<th>HDL (mg/dl)</th>
<th>p valor</th>
<th>CHOL/HDL ratio</th>
<th>p valor</th>
<th>LDL/HDL ratio</th>
<th>p valor</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.1</td>
<td>0.043</td>
<td>156.0</td>
<td>0.381</td>
<td>94.8</td>
<td>0.521</td>
<td>17.7</td>
<td>0.453</td>
<td>43.7</td>
<td>0.511</td>
<td>3.7</td>
<td>0.249</td>
<td>2.3</td>
<td>0.340</td>
</tr>
<tr>
<td>(28.5)</td>
<td>(43.8)</td>
<td>(56.4)</td>
<td>(84.6)</td>
<td>(47.3)</td>
<td>(44.6)</td>
<td>(46.2)</td>
<td>(43.2)</td>
<td>(44.3)</td>
<td>(42.3)</td>
<td>(3.7)</td>
<td>(3.9)</td>
<td>(2.2)</td>
<td>(2.4)</td>
</tr>
</tbody>
</table>

* Ajustado por edad (años), índice de masa corporal (kg/m²), circunferencia de la cintura (cm), energía ingerida (kcal/día), saturado (g/día), monoinsaturado (g/día), poliinsaturado (g/día), consumo de cigarrillos (nunca, 1-100 y >100 cigarrillos al año), género (hembra/macho), y antecedente familiar de diabetes tipo 2 (si o no). Concentraciones medias de insulina según cuartiles están descritas en paréntesis.

† Valores de triglicéridos están expresados en mg/dl.

<table>
<thead>
<tr>
<th>Cuartiles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulina (pmol/l)</td>
<td>(28.5)</td>
<td>(43.8)</td>
<td>(56.4)</td>
<td>(84.6)</td>
<td></td>
</tr>
</tbody>
</table>

† Valores de triglicéridos están expresados en mg/dl.

## Tabla III

<table>
<thead>
<tr>
<th>Modelo†</th>
<th>Edad</th>
<th>Edad, sexo</th>
<th>Edad, BMI</th>
<th>Edad, sexo, WC</th>
<th>Edad, sexo, BMI, WC</th>
<th>Edad, sexo, BMI, EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglicéridos (mg/dl)</td>
<td>0.006a</td>
<td>0.006a</td>
<td>0.003a</td>
<td>0.003a</td>
<td>0.003a</td>
<td></td>
</tr>
<tr>
<td>Total colesterol (mg/dl)</td>
<td>0.004a</td>
<td>0.004a</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>0.004a</td>
<td>0.004a</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>0.010a</td>
<td>0.010a</td>
<td>0.004</td>
<td>0.004</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>-0.012a</td>
<td>-0.013a</td>
<td>-0.004</td>
<td>-0.001</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>CHOL/HDL</td>
<td>0.191a</td>
<td>0.191a</td>
<td>0.068a</td>
<td>0.064a</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>0.185a</td>
<td>0.185a</td>
<td>0.063a</td>
<td>0.060</td>
<td>0.044</td>
<td></td>
</tr>
</tbody>
</table>

a Resultado (b coeficientes) para análisis de regresión multivariante lineal ajustados para factores listados
† BMI: índice de masa corporal
‡ WC: circunferencia de la cintura
§ EE: energía ingerida
& <0.01
≠ <0.05

## Tabla IV

<table>
<thead>
<tr>
<th>Cuartiles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglicéridos (mg/dl)</td>
<td>(28.5)</td>
<td>(43.8)</td>
<td>(56.4)</td>
<td>(84.6)</td>
</tr>
<tr>
<td>Total colesterol (mg/dl)</td>
<td>156.0</td>
<td>153.3</td>
<td>159.0</td>
<td>160.9</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>94.8</td>
<td>91.9</td>
<td>95.3</td>
<td>98.5</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>17.7</td>
<td>18.0</td>
<td>18.7</td>
<td>19.7</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.7</td>
<td>43.7</td>
<td>44.6</td>
<td>42.3</td>
</tr>
<tr>
<td>CHOL/HDL ratio</td>
<td>3.7</td>
<td>3.6</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* Ajustado por edad (años), índice de masa corporal (kg/m²), circunferencia de la cintura (cm), energía ingerida (kcal/día), saturado (g/día), monoinsaturado (g/día), poliinsaturado (g/día), consumo de cigarrillos (nunca, 1-100 y >100 cigarrillos al año), género (hembra/macho), y antecedente familiar de diabetes tipo 2 (si o no). Concentraciones medias de insulina según cuartiles están descritas en paréntesis.

† Valores de triglicéridos están expresados en mg/dl.
The variance inflation factor was 4.2 and no problems were detected for multicollinearity.

**Discussion**

The findings of this study suggest that insulin resistance syndrome factors are already present in adolescence and, as demonstrated in adult studies, triglyceridermia, HDL, and obesity are related with insulinemia independently of other relevant factors. The results show that hyperinsulinemia correlates negatively with HDL and positively with total cholesterol, triglycerides, LDL, and the CHOL/HDL ratio, after age and sex adjustments. A further adjustment including BMI, WC, EE and smoking status was carried out. With the exception of triglycerides and HDL in 18-19-year-old male adolescents, associations among insulin, lipids, and lipoproteins disappeared. These results are similar to those reported by Bonora et al., except that those authors found no association with HDL. Other studies have found that insulin resistance is also related with LDL and VLDL, but these associations may have been confounded because BMI, WC, and EE were not controlled. Moreover, adolescents in those studies were younger than adolescent participants in the study presented here, which also may have contributed to the differences. Although only triglycerides and HDL in males aged 18-19 years were significantly associated with insulin in this study, it is important to point out the tendency toward higher fasting insulin with ad-
does in adults, in whom it was shown to be an important risk factor for insulin and lipid concentrations.

The relationship between serum insulin concentration and lipid and lipoprotein profile is better understood in adults than in adolescents. Perhaps there is a critical time-frame that could enable identification of an evolving dysfunctional metabolism. Improved understanding of several factors, including the genetics and physiology of puberty, would explain associations between lipids and insulin in adolescents. Due to the cross-sectional design of this study, no causal relationship between triglycerides and insulin or between HDL and insulin can be established. However, the data in this study support the hypothesis that high triglyceride concentration, low HDL concentration, obesity, and abdominal fat may be independently associated with hyperinsulinemia. Future cohort studies and interventions in adolescents would be useful to establish causality between triglycerides and insulin, and HDL and insulin. Meanwhile, the results of this study suggest that it is important to initiate primary prevention programs to reduce, in adolescence, these risk factors for chronic diseases, such as type 2 diabetes mellitus.

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