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1. Introduction

The hypertriglyceridemic-waist phenotype (Htg-WP), the combination of an increased waist circumference and hypertriglyceridemia, could be a useful and inexpensive screening tool to identify people who are at an increased risk of coronary artery disease and type 2 diabetes. (1-3). The concept of the Htg-WP was introduced by Lemieux and colleagues who suggested that this simple phenotype could be a useful marker for cardiovascular risk and a better predictor of cardiovascular disease. (4)

Imaging studies using techniques such as computed tomography or magnetic resonance imaging have shown that, among equally obese individuals, those with an excess of intra-abdominal or visceral adipose tissue have metabolic abnormalities and are at an increased risk for coronary artery disease and type 2 diabetes (5,6). The systematic measurement of waist circumference has been proposed as a crude anthropometric correlate of intra-abdominal adiposity (7). Because waist circumference cannot fully discriminate intra-abdominal from subcutaneous abdominal adiposity, it has been previously suggested that the presence of elevated triglyceride levels could be used as a marker of metabolic abnormalities in people with an increased waistline (4,8).

An association between parental metabolic syndrome and metabolic syndrome in their offspring has been observed among Korean adolescents (9). Family risk factors include their genetic history as well as their shared environment (9). Parents are in a key position to shape the environments of children, and there is an increasing interest in the contribution of parental behaviors to cardiovascular risk. Maternal feeding practices have received particular attention as a risk factor for childhood OB. A previous study of our group showed that mother’s waist circumference predicted their child’s metabolic syndrome (10); however, as maternal Htg-WP includes two metabolic disorders, it could increase risk of her child’s cardiovascular risk. As far as we know, there are no large studies in elementary school children showing the role that maternal Htg-WP plays in relation to the development of children’s Htg-WP. The objective of this study was to determine the association between mothers’ Htg-WP and the presence of Htg-WP in their offspring.

2. Methods

Data were collected cross-sectionally from 1009 children between the ages of 5 and 15 years in 6 elementary schools between April 2007 and March 2008. The schools were randomly
selected from 42 schools from the west side of Buenos Aires suburbs. Measurement of BMI, waist circumference, blood pressure, and serum glucose, lipids, and insulin were obtained in mothers and their offspring. Given the fact that the prevalence of OW/OB was approximately 33% among children in a similar population (11), the sample size was estimated to achieve that percentage with an error lower than 0.05. The sample size consistent with this error was 340 children. Five hundred and ninety-five children (296 boys) and their mothers were examined, which means that the sample error was less than 0.04. Exclusion criteria included: missing BMI and blood pressure information, missing lipid profile and glucose information, not being the biological offspring of their mothers, the informed consent not being signed, self-reported pregnancy at the time of the examination, not being in the fasting state for at least 10 hours, known diabetes or other chronic disease, and the use of medication that alters blood pressure or glucose or lipid metabolism. Only one child per family was included; because most families had more than one child, we randomized the sample to determine which child would be included. Originally 1009 children and their mothers were recruited from six elementary schools. All the offspring who attended on the day of the evaluation were examined (n=1009). To include only one child per mother, we assigned a random number to each child with uniform distribution. We chose the highest random number from the generated variable. This was the selection based on the random number assignment. As a result, 369 siblings were excluded from the study. Furthermore, one child taking a thyroid medication, eight who declined to participate, 16 missing BMI information, and 29 mothers with missing serum lipid and glucose measurements were also excluded. All subjects were examined by the same physician. The study was approved by the Human Rights Committee of Durand Hospital in Buenos Aires. Each parent gave written informed consent, and children gave assent after an explanation of the study and before its initiation.

Sociodemographic characteristics included age and level of parental education and the presence or absence of a refrigerator or a dirt floor. Questionnaires for socio-economic status have been described in detail elsewhere (11).

Measurements of height, weight, and waist circumference in mothers and in their offspring were determined as previously described (10). Because children BMI varies according to age and gender we standardized the values for age and sex by converting them to a z-score according to the Centers for Disease Control and Prevention (CDC) growth charts (12). The children were classified as normal weight (BMI<85 percentile) OW, (85<BMI<95percentile) or OB (BMI>95 percentile) per CDC norms (12). The physical examination also included determination of the stage of puberty according to the Tanner criteria (13). Three separate blood pressure measurements were recorded by a trained technician using a random-zero sphygmomanometer after the participant was seated at rest for five minutes. The averages of the three measurements of systolic and diastolic blood pressures were used (14). We used the National Heart, Lung and Blood Institute’s recommended cutoff point for hypertension (14).

Risk factors for cardiovascular disease were defined using the same cut off as Cook et al (15) used: central OB (waist circumference >90th percentile); fasting triglycerides >110 mg/dL; HDL-C <40 mg/dL; blood pressure>90th percentile for age, sex, and height; and fasting glucose >100 mg/dL.

Maternal Htg-WP was defined as a waist circumference of 85 cm or more and a triglyceride level of 132 mg/dL(1.5 mmol/L) or higher (16). The Htg-WP in children was defined using the same cut off for waist circumference and triglycerides as Cook et al used (15).

Homeostasis model assessment of insulin resistance (HOMA-IR) was performed. The equation for HOMA-IR was:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (mU/L)} \times \text{fasting glucose (mg/dL)}}{405}
\]
fasting insulin (in μU/L) × fasting glucose (in mmol/L)/22.5(17).

Baseline blood samples were obtained from subjects while they were fasting to measure glucose, insulin, and lipid levels. Plasma glucose was assayed by the glucose oxidase technique, and serum lipids were measured with a Modular P analyzer (Hitachi High Technologies Corp., Tokyo, Japan). Serum insulin levels were determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA), and insulin did not cross-react with proinsulin or C-peptide (percentage coefficient of variance, 5.2–6.8%).

3. Results

Characteristics of children

Physical and metabolic profiles are shown in table 1. Five hundred and ninety five children (296 males) aged 9.0 ± 1.9 years were examined. One hundred and five (17.6%) children

<table>
<thead>
<tr>
<th></th>
<th>Mothers (595)</th>
<th>Offspring(595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.8± 7.0</td>
<td>9.0 ± 1.9</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.3± 5.9</td>
<td>18.7 ± 3.5</td>
</tr>
<tr>
<td>z-BMI (per CDC)</td>
<td>89 ± 13</td>
<td>65± 11</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>111± 16</td>
<td>96± 13</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>79± 18</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>174± 37</td>
<td>152± 26</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>81(58-117)</td>
<td>51(67-90)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>52± 12</td>
<td>50± 12</td>
</tr>
<tr>
<td>Fasting insulin (µIU/mL)</td>
<td>5.7 (3.7-8.4)</td>
<td>4.9 (2.8-7.4)</td>
</tr>
<tr>
<td>HOMA -IR</td>
<td>1.0 (0.7-1.6)</td>
<td>0.9(0.5-1.4)</td>
</tr>
<tr>
<td>OW</td>
<td>182(30.6%)</td>
<td>110 (18.5%)</td>
</tr>
<tr>
<td>OB</td>
<td>158 (26.6%)</td>
<td>105 (17.6%)</td>
</tr>
<tr>
<td>Centrally OB</td>
<td>364 (61.2%)</td>
<td>91 (15.3%)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>57(9.8%)</td>
<td>38 (6.4%)</td>
</tr>
<tr>
<td>High fasting glucose</td>
<td>19(3.2%)</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>High triglyceride</td>
<td>103(17.3%)</td>
<td>75(12.6%)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>276 (46.4%)</td>
<td>129 (21.7%)</td>
</tr>
<tr>
<td>Htg-WP</td>
<td>93(15.6%)</td>
<td>32(5.4%)</td>
</tr>
</tbody>
</table>

Waist circumference (WC), blood pressure (BP), total Cholesterol (TC), triglyceride (TG) Data are mean ±SD or median (interquartile range) for continuous variables and percentage for categorical variables.

Significance: *p<0.05; **p<0.001. Children’s cardiovascular risk is defined by the following features:

- WC>90th percentile, fasting glucose level ≥100 mg/dL, BP >90th percentile, TG ≥110 mg/dL, and HDL-C ≤40 mg/dL.

Table 1. Clinical and Metabolic Characteristics of 595 family members.

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were obese, and 110 (18.5%) overweight. There was not a significant difference in the prevalence of overweight or obesity between genders. Sixty seven percent, 21.2%, 10.3%, and 1.2% were at Tanner stage 1, 2, 3, and 4 respectively. The prevalence of Htg-WP was 5.4% (n=32) in children.

Approximately 40% of the children had at least 1 risk factor for cardiovascular disease and 13% had 2 or more risk factors. The risk factors of low HDL (129/595; 21.7%), central obesity (95/595; 15.3%), and high triglycerides (75/595; 12.6%) were common while hypertension (39/595; 6.4%) and impaired fasting glucose (5/595; 0.8%) were infrequent. One child had diabetes and none had all 5 risk factors. There was no significant difference in the prevalence of individual risk factors and in the prevalence of Htg-WP between boys and girls. There was not a significant difference in the distribution of Tanner stages between the group with and that without Htg-WP. The mean z BMI was higher (p<0.001) in the Htg-WP group (z BMI=1.9 ± 0.3) than in the group without Htg-WP (z BMI=0.6 ± 0.9).

Characteristics of the Mothers

Physical and metabolic profiles are presented in table 1. The average maternal BMI was 27.3 which indicates that, as a group, they were overweight. Approximately 27% of the mothers were obese (BMI >30), and 30.6% overweight (25<BMI<30). The educational backgrounds of the mothers were as follows: 1.2% had no formal education, 30% had completed elementary school, 52% had completed high school and 17% had university and/or advanced degrees. Participants came from a low and a middle socio-economic class. Overweight and obesity were more common (p=0.003) in mothers with a lower level of education (divided into high school or less and more). Approximately 70% of mothers had at least 1 risk factor for cardiovascular disease, 34% had 2 or more risk factors. The risk factors of low HDL –C (276/595; 46.4%), central obesity (306/595;51.4%) and high triglycerides (103/595; 17.3%) were common while hypertension (47/595; 8%) and impaired fasting glucose (19/595; 3.2%) were less frequent. Four mothers had diabetes and none had all 5 risk factors. Htg-WP was present in 15.6% (93) overall, 2% (5) of the normal, 17.6% (32) of the overweight, and 35.4% (56) of the obese group (P < 0.01). There was not a significant difference in the educational backgrounds in the group with and without Htg-WP. The mean BMI (32.0 vs 26.4; p<0.01) and mean age (39.8 vs 35.0; p<0.01) were higher in the group with Htg-WP than without Htg-WP.

Children’s characteristics according to the presence of Htg-WP in their mothers

The prevalence of obesity was significantly higher in children with obese mothers than in the group of children whose mothers were not obese (27.2%vs 14.2%, p<0.001), respectively. The prevalence of obesity was significantly higher in children with mothers with Htg-WP than in the other group (29%vs 15.5%, p=0.002) , respectively. The prevalence of Htg-WP was significantly higher in children with mothers with Htg-WP than in the group of children with mothers without Htg-WP( 16.1%vs 3.4%, p<0.001) , respectively. Children of mothers with Htg-WP had values of z-BMI, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, insulin, and HOMA-IR which were higher (p<0.01) than those for the children of mothers without Htg-WP (Figure 1 and Table 2). Compared with children whose mothers did not have Htg-WP, the OR in children with maternal Htg-WP was [OR, 4.5 (95% CI 1.7-11.4)] for offspring’s Htg-WP adjusted for age, Tanner stage, gender, maternal HOMA-IR, offspring’s HOMA-IR, and offspring’s hypertension. When socioeconomic class was included in the model, results did not change. The stepwise regression analysis showed that the most strongly predictive
value of increased offspring’s hypertriglyceridemic waist was maternal increased hypertriglyceridemic waist. Therefore, compared with children whose mothers did not have Htg-WP, children of mothers with Htg-WP were four and a half times more likely to have Htg-WP.

Panel A

Panel B
Fig. 1. Boxplot: the boxes define the 25th and 75th percentiles, and enclose the median; the extensions define the range of values. Median values and interquartile range for children’s z-BMI, children’s WC and children’s TG are presented separately for children without and with mothers with Htg-WP in Panel A, panel B and panel C, respectively. Waist circumference (WC) and triglyceride (TG)

### 4. Discussion

In this cross-sectional analysis of school children and their mothers, our main finding was that Htg-WP in children was highly correlated with the maternal status of Htg-WP. We have previously demonstrated the association between maternal waist circumference and metabolic syndrome (a cluster of metabolic abnormalities that include glucose intolerance, central obesity, dyslipidemia, and hypertension) in their offspring (10). The maternal status of Htg-WP defined as an elevated waist circumference >85 cm in women) along with an elevated plasma triglyceride concentration (defined as a level ≥177 mg/dl) has been proposed and shown to be a stronger marker of cardiovascular risk and a better predictor of cardiovascular disease (4) than the waist circumference alone (18). As far as we know, there have not been large studies in elementary school children showing the association between maternal Htg-WP and their children’s Htg-WP. We found that compared to children whose mothers did not have high Htg-WP, children whose mothers had high Htg-WP were approximately four and a half times more likely to have high Htg-WP adjusted for confounding variables consistent with known familial associations of high Htg-WP and cardiovascular disease.

The prevalence and severity of obesity has been increasing in children and adolescents, as well as in adults (19,20). Excess body fat in children is associated with insulin resistance and predicts development of the metabolic syndrome in adulthood (21). This research showed a high prevalence of overweight and obesity in children (35%) and in their mothers (57%). The
## Table 2. Characteristics of offspring according to the presence of Htg-WP in their mothers

Increasing prevalence of obesity in children could be due to interactions between genetic and environmental factors (22). Recent changes in nutritional and physical activity patterns are considered to have produced changes in the fatness of children (22). Garn et al (23) suggest that childhood eating and exercise patterns are modeled after parental behaviors, and that parental behavior serves as the basis for developing and changing the health habits of children. A recent study showed that parental leanness confers significant protection against development of overweight in children, whereas parental obesity is associated with a prevalence of overweight in their children more than double that for children of lean parents (24). Excessive BMI gains of parents during childhood and adulthood were associated with a higher BMI and risk of obesity in the offspring (25). Substantial evidence now exists which demonstrates the importance of obesity in childhood in creating the metabolic conditions for cardiovascular disease and type 2 diabetes in young adulthood (26). Consistent with this study, we found that the prevalence of obesity was significantly higher in children whose mothers were obese than in the other group. An important epidemiologic aspect of cardiovascular risk in children is the tracking of these risk factors over time. Such tracking has been demonstrated in a number of studies, most notably the Muscatine Study and Bogalusa Heart Study (27, 28) which had demonstrated the presence of early lesions of coronary heart disease in the heart vessels of children and adolescents.

Despite the strong association of obesity, especially central obesity, to metabolic and cardiovascular disease, not all obese individuals carry the same metabolic and cardiovascular risk (18). Waist circumference is a simple and inexpensive marker of abdominal adiposity, but not all people with an increased waistline are at increased risk of coronary artery disease. The Htg-WP is a simple and inexpensive marker to help identify patients with intraabdominal obesity who have a deteriorated cardiometabolic risk profile.

<table>
<thead>
<tr>
<th></th>
<th>Mothers without Htg-WP</th>
<th>Mothers with Htg-WP</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>502(84.4)</td>
<td>93 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.9±1.9</td>
<td>9.4±1.8</td>
<td>0.237</td>
</tr>
<tr>
<td>Z-BMI</td>
<td>0.6±1.0</td>
<td>0.9±1.0</td>
<td>0.004*</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>18.5±3.4</td>
<td>19.9±3.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>64±10</td>
<td>70±12</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>57±10</td>
<td>61±8</td>
<td>0.001*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>95±13</td>
<td>100±13</td>
<td>0.001*</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>151±26</td>
<td>157±27</td>
<td>0.041*</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>50±12</td>
<td>47±11</td>
<td>0.073</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>65(50-85)</td>
<td>87(63-121)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>78±8</td>
<td>79±7</td>
<td>0.07</td>
</tr>
<tr>
<td>Insulin (uUI/ml)</td>
<td>4.8 (2.6-7.1)</td>
<td>5.4 (3.3-9.0)</td>
<td>0.03*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.9 (0.5-1.4)</td>
<td>1.0 (0.6-1.8)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Waist circumference (WC), blood pressure (BP), total Cholesterol (TC), triglyceride (TG) Data are means or median (interquartile range)+SD or percent. Group 1 (normal waist circumference and normal triglycerides; waist circumference<85 cm in women and triglycerides ≤132mg/dL, n =317); group 2 (high waist circumference and high triglycerides; waist circumference ≥85 cm in women and triglycerides ≤132mg/dL, n =278). Significance: *p<0.05.
and are thus at increased risk of coronary artery disease. An additional advantage is that the phenotype can be determined easily, without additional and expensive testing. Plasma triglyceride levels are available from any standard lipid profile obtained in clinical practice, and waist circumference can be measured at no cost. Therefore, elevated plasma triglyceride levels have been proposed as a marker of the metabolic alterations associated with excess intra-abdominal adiposity, such as ectopic fat deposition (liver, skeletal and epicardial fat) and insulin resistance (4). The association between mothers’ obesity and morbidity and their children’s obesity justifies looking for various markers of adiposity in all mothers. Parental obesity is a strong predictor of obesity in children (29,30). According to these studies, we showed that children of mothers with Htg-WP had significantly higher levels of z-BMI, waist circumference, blood pressure, insulin, and triglycerides than children whose mothers did not have Htg-WP. A previous study of our group showed that mother’s waist circumference predicted her child’s metabolic syndrome (11) consistent with known familial associations of OB and type 2 diabetes. However, maternal Htg-WP (the cluster) and its association with Htg-WP in their offspring have not been previously investigated. This study shows that children of mothers with Htg-WP had mean values of cardiovascular risk factors which were significantly higher than those for the children of mothers without Htg-WP. Furthermore, compared with children whose mothers did not have Htg-WP, children of mothers with Htg-WP were four and a half times more likely to have Htg-WP. As familial transmission is a risk factor for future cardiovascular disease, it is important to evaluate familial factors in order to identify strategies for the prevention and management of future diseases.

This study has several potential limitations. First, it is a cross-sectional study. Our data only show the association with present risk factor conditions but do not directly predict the future risk of cardiovascular events. Second, the fact that only mothers were included in the sample might decrease the power of the study. Third, we used criteria (Htg-WP) that has not been previously established for children. The final limitation was that as the sample was drawn from Buenos Aires neighborhoods of a middle and low socioeconomic level, it cannot be viewed as representative of Buenos Aires as a whole. However, it can be seen as representative of a large portion of Buenos Aires.

The strengths of our study include the large school age population-based sample, which was more likely to represent the general population, the high response rate of the children, the use of Tanner staging for measurement of puberty, the collection of fasting blood samples, and the use of multiple regression models, which allowed investigators to account for the complex interrelationships between these physiologic traits and potential confounders such as gender, pubertal development, children’s HOMA-IR and maternal BMI.

5. Conclusions

Markers for an increased risk of cardiovascular disease are already present in children consistent with known familial associations of cardiovascular risk. This study demonstrates the importance of maternal Htg-WP in predicting children’s Htg-WP even after adjustment for confounding variables. This criterion (Htg-WP) could be an easy and inexpensive tool to predict future cardiovascular disease. Health awareness efforts must include children whose mothers had Htg-WP and advocate lifestyle changes which may be easier to achieve in this group before they develop cardiovascular disease ant type 2 diabetes. Longitudinal studies should be conducted to confirm these findings.
6. References


Type 2 diabetes is estimated to affect 120 million people worldwide, and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to lessen the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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