Is fasting insulin associated with blood pressure in obese children?

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Summary.
Primary objective: We tested whether fasting insulin levels are associated with blood pressure in a large sample of obese children.
Subjects and methods: Three hundred and fifty obese children (F:M ratio = 1.03) of 10.1 ± 2.7 y of age (mean ± SD) were consecutively enrolled at an Outpatient Paediatric Clinic. Obesity was diagnosed on the basis of a relative weight for age > 120% and hypertension on the basis of a systolic (SBP) or diastolic (DBP) blood pressure > 95th percentile for age after adjustment for height (Ht).
Main outcome and results: Insulin was significantly higher in hypertensive (n = 202, 58%) than normotensive (n = 148, 42%) children (16 vs 14 μU mL⁻¹, geometric mean, p < 0.01, ANOVA) but the difference was not clinically relevant. Moreover, (log-transformed) insulin explained only 7 and 4% of SBP and DBP variance, respectively (p < 0.0001 for both) and this contribution disappeared after the confounding effects of age, weight or other anthropometric dimensions were taken into account (p = ns, ANCOVA).
Conclusions: This study does not support the hypothesis of a clinically relevant association between fasting insulin and blood pressure in obese children.

1. Introduction
In recent years, there has been considerable interest in the cardiovascular effects of insulin (Scherrer and Sartori 1997). This interest has been stimulated by epidemiological studies suggesting a link between insulin and cardiovascular disease (Lucas, Estigarribia, Darga, et al. 1985, Modan, Halkin, Almog et al. 1985, Després, Lamarche, Maurière et al. 1996) and by experimental studies showing that insulin has cardiovascular effects in addition to its effects on intermediary metabolism (Laakso, Edelman, Brechtel et al. 1990). Although hyperinsulinaemia often accompanies essential hypertension, especially when associated with obesity, it is still open to question whether there is a cause–effect relationship between hyperinsulinaemia and hypertension (Hall, Brands, Zappe et al. 1995).

Obese individuals are often both hyperinsulinaemic and hypertensive so that they appear as the ideal subjects in whom to study this relationship. Moreover, along with impaired glucose tolerance and dyslipidaemia, hyperinsulinaemia and hypertension are recognized as the main factors responsible for the so-called ‘metabolic syndrome’ associated with obesity (WHO 1998). However, the majority of studies on insulin and hypertension have been performed in obese adults and less information is available for obese children. Kanai, Matsuzawa, Tokunaga et al. (1990) studied the relationship between fasting insulin and blood pressure in 324 obese children (mean age: 9.5 y) and reported that insulin was able to explain 36% and 19% of systolic (SBP) and diastolic (DBP) blood pressure variance (p < 0.001 for both)
independently of age, body mass index (BMI) and waist:hip ratio (WHR). However, in a study conducted by Horswill and Zipf (1991) on 114 obese children (mean age: 7.3 y), the contribution of insulin to SBP ($R^2 = 0.19, p < 0.05, n = 50$) disappeared after the effects of age and body weight were taken into account and no association was found between DBP and insulin ($p = ns, n = 50$). Moreover, while some studies have suggested that insulin levels may be used as a marker for the development of hypertension in children (Moussa, Shaltout, Nkansa-Dwamena et al. 1998), other studies have shown that insulin does not enhance the rise in blood pressure occurring during growth (Taittonen, Uhari, Nuutinen et al. 1996). Also, the clustering of insulin, blood lipids and blood pressure has been studied more thoroughly in adults than children so that the existence of the metabolic syndrome is still debated in the latter (Raitakari, Porkka, Ronnemaa et al. 1995, Sinaiko, Gomez-Marin and Prineas 1997, Moussa et al. 1998).

The present study aimed therefore to ascertain whether fasting insulin is associated with blood pressure in obese children also taking into account the effects of anthropometric dimensions and blood lipids.

### 2. Subjects and methods

#### 2.1. Subjects

Three hundred and fifty children were consecutively enrolled in the study at an Outpatient Paediatric Clinic on the basis of a relative weight for age (RWt) > 120% according to the National Center for Health Statistics growth charts (Frisancho 1990). The children were unselected for blood pressure values but among hypertensive subjects only those with essential hypertension were considered for the study. Children were classified as pre-pubertal (stage 1), early pubertal (stages 2 and 3) and late pubertal (stages 4 and 5) according to Tanner (1978). The characteristics of the subjects are given in table 1. The study protocol had been approved by the local Ethical Committee and the parents of the children gave their informed consent.

#### 2.2. Anthropometry

Weight (Wt), Height (Ht), waist circumference (WC) and hip circumference (HC) were measured following the Anthropometric Standardization Reference Manual (Lohman, Roche and Martorell 1988). BMI was calculated as Wt (kg)/Ht$^2$ (m$^2$) (Garrow and Webster 1985) and WHR as WC (cm)/HC (cm) (Van Itallie 1992).

#### 2.3. Blood pressure

Blood pressure was measured following the American Heart Association guidelines (Perloff, Grim, Flack et al. 1993). The fifth Korotkoff sound was used to define DBP (National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents (NHBPEP) 1996). The values of SBP and DBP employed for analysis are the mean of three recordings made during the visit at the Clinic. Subjects were classified as hypertensive if their SBP or DBP was higher than the 95th percentile for age after adjustment for Ht (NHBPEP 1996).

#### 2.4. Laboratory measurements

Blood glucose, cholesterol (CH), tryglicerides (TG) and high-density lipoproteins (HDL) were measured using common laboratory methods. Insulin was measured by radioimmunoassay (Radim, Rome, Italy).
2.5. Statistical analysis

Statistical analysis was performed on a MacOS computer using the Statview 5.1 and SuperANOVA 1.1 software packages (SAS, Cary, NC, USA). Insulin values were log-transformed to better approach the normal distribution. All between-group comparisons were performed by ANOVA using Scheffé’s test for post hoc analysis. The ‘zero’ hypothesis that insulin had no effect on blood pressure was tested using a general linear model (GLM) in which SBP or DBP was entered as the dependent variable and insulin as the predictor. The same approach was used to establish the effect of age, Wt, Ht, BMI, WC, HC, WHR, TG, CH, HDL and glucose on blood pressure. The contribution of each covariate to blood pressure was determined on the basis of its associated (adjusted) $R^2$ value. Interaction factors between the covariate of interest (X) and sex (x sex) or pubertal status (X x pub) were entered into the GLM to control for their confounding effects (Horswill and Zipf 1991). The confounding effect of age was controlled for by regressing the covariate of interest against age and using the residuals of the regression as the predictor variable in the GLM. Statistical significance was set to a value of $p < 0.05$.

3. Results

The characteristics of the study subjects are given in table 1. A similar number of female ($n = 178$) and male ($n = 172$) children was (randomly) recruited into the study. Age did not differ between sexes ($p =$ ns). There was a similar percentage of early pubertal subjects among females and males (28% vs 27%) but a lower percentage of pre-pubertal (44% vs 65%) and a higher percentage of late pubertal subjects (28% vs 8%) among females. Wt, Ht and BMI did not differ between sexes ($p =$ ns for all) while RWt was significantly lower in females than males ($p < 0.05$).
HC was similar (p = ns) but WC and WHR were lower in female than male children (p < 0.001 and p < 0.0001, respectively). No differences were seen in plasma levels of TG, CH, HDL and glucose between sexes (p = ns for all) while insulin was significantly higher in females than males (p < 0.01). SBP was similar in the two sexes while DBP was significantly lower in females than males (p < 0.05). Two hundred and two children (104 female and 98 male; 58% of the study sample) were hypertensive. Insulin was significantly higher in hypertensive than normotensive children (16 vs 14 μU mL⁻¹, geometric mean, p < 0.01) but the between-group difference could not be considered clinically relevant. The variance of SBP and DBP explained by insulin and the other covariates is given in table 2.

Table 2. Variance of blood pressure explained by selected variables in the pooled sample of obese children (n = 350).

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adj R²</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>0.25</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Wt</td>
<td>0.32 (0.07)*</td>
<td>&lt; 0.0001 (&lt; 0.0001)*</td>
</tr>
<tr>
<td>Ht</td>
<td>0.27 (0.02)*</td>
<td>&lt; 0.0001 (&lt; 0.005)*</td>
</tr>
<tr>
<td>BMI</td>
<td>0.25 (0.07)*</td>
<td>&lt; 0.0001 (&lt; 0.0001)*</td>
</tr>
<tr>
<td>WC</td>
<td>0.23 (0.05)*</td>
<td>&lt; 0.0001 (&lt; 0.0001)*</td>
</tr>
<tr>
<td>HC</td>
<td>0.26 (0.05)*</td>
<td>&lt; 0.0001 (&lt; 0.0001)*</td>
</tr>
<tr>
<td>WHR</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>TG</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>CH</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>HDL</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Glucose</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Insulin†</td>
<td>0.07 (-)*</td>
<td>&lt; 0.0001 (ns)*</td>
</tr>
</tbody>
</table>

*Value after correction for age.
† Log-transformed.
Abbreviations: Wt, weight; Ht, height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist:hip ratio; TG, triglycerides; CH, cholesterol; HDL, high-density lipoproteins.

Age explained 25 and 20% of SBP and DBP variance, respectively (p < 0.0001 for both) and Wt was the best single predictor of SBP (adj R² = 0.32) and DBP (adj R² = 0.23; p < 0.0001 for both). However, after correction of blood pressure for age, Wt was able to explain only 7% (p < 0.0001) of SBP and 4% of DBP (p < 0.0005) variance. After correction for age, a similar loss in the explained variance of blood pressure was seen for all anthropometric dimensions (table 2). No associations were found between blood pressure, TG, CH, HDL or glucose (p = ns for all) and insulin explained only 7 and 4% of SBP and DBP variance, respectively (p < 0.0001; table 2 and figure 1). Moreover, after correction of SBP and DBP for age, Wt, BMI, WC or HC, insulin became uncorrelated with blood pressure (p = ns; data not shown).

The Wt × sex, BMI × sex, WC × sex and HC × sex interactions were significant for both SBP (p < 0.01 for all) and DBP (p < 0.005 for all) while the age × sex, Ht × sex and insulin × sex interactions were not significant (p = ns). After correction of the covariate for age, however, only the BMI × sex and HC × sex interactions remained significant for SBP (p < 0.05 and p < 0.01, respectively) and DBP (p < 0.01 and p < 0.005, respectively). Surprisingly, none of the X pub interactions was significant (with the obvious exception of age × pub, p < 0.0005) neither for SBP nor for DBP (p = ns). Owing to the different number of pre-pubertal and late pubertal subjects (randomly) enrolled in the study, this result should however be taken with caution.
The variance of insulin explained by age, anthropometric dimensions and blood parameters is given in table 3. Wt was the best single predictor of insulin but its contribution was substantially reduced after correction of insulin for age and the same was seen for all anthropometric dimensions. Insulin was not associated with glucose and only weakly associated with TG, CH and HDL. Moreover, the association with CH and HDL disappeared after correction for age. (It should be pointed out that the X sex interaction was not significant for any of the covariates.)
4. Discussion

Our study does not support the hypothesis of a clinically relevant association between fasting insulin and blood pressure in obese children (Kanai et al. 1990). Although we found significantly higher values of insulin in hypertensive than normotensive children (16 vs 14 μU mL⁻¹, geometric mean, \(n = 350, p < 0.01\)), this between-group difference cannot be considered clinically relevant. The high frequency of hypertension in our children (58%) deserves some comments. It is explained by the fact that at our clinic we see mainly morbidly obese children who are sent by general paediatricians after traditional therapies have failed or complications of overweight have ensued. This is reflected by the high mean RWt (160%) of the study sample (table 1). We cannot exclude, however, that the use of the NHBPEP standards may have led to some degree of misclassification of blood pressure in our children. These standards were developed in American children and it is not known whether they can be applied with confidence to Italian children. However, the use of these standards is encouraged wherever no local reference standards are available, such as in Italy (NHBPEP 1996).

At any rate, the loss of the already weak association between insulin and blood pressure (adj \(R^2 = 7\%\), \(p < 0.0001\)) after correction for age, weight or other anthropometric dimensions, argues against a clinically relevant role of fasting insulin as a determinant of blood pressure in obese children. Our results are therefore in agreement with those of Horsswill and Zipf (1991) who showed a lack of association between insulin and SBP after correction for age and Wt in obese children. We found also a very modest contribution of insulin to DBP (adj \(R^2 = 0.04, p < 0.0001\)) that also disappeared after correction for age, Wt or other anthropometric dimensions.

It appears from our study that age does influence not only the relationship between insulin and blood pressure but also the relationship between blood pressure and anthropometric dimensions. In fact, the contribution of Wt, Ht, BMI, WC and HC to SBP and DBP was substantially reduced—and no more clinically relevant—after correction for age. Interestingly, the BMI sex and HC sex interactions remained

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Table 3. Contribution of anthropometric and blood parameters to explain fasting insulin in the pooled sample of obese children (\(n = 350\)).

<table>
<thead>
<tr>
<th></th>
<th>adj (R^2)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.13</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Wt</td>
<td>0.15 (0.02)*</td>
<td>&lt; 0.0001 (&lt; 0.001)*</td>
</tr>
<tr>
<td>Ht</td>
<td>0.13 (—)*</td>
<td>&lt; 0.0001 (ns)*</td>
</tr>
<tr>
<td>BMI</td>
<td>0.09 (0.01)*</td>
<td>&lt; 0.0001 (&lt; 0.05)*</td>
</tr>
<tr>
<td>WC</td>
<td>0.13 (0.03)*</td>
<td>&lt; 0.0001 (&lt; 0.001)*</td>
</tr>
<tr>
<td>HC</td>
<td>0.13 (0.02)*</td>
<td>&lt; 0.0001 (&lt; 0.05)*</td>
</tr>
<tr>
<td>WHR</td>
<td>—</td>
<td>ns</td>
</tr>
<tr>
<td>TG</td>
<td>0.04 (0.03)*</td>
<td>&lt; 0.0005 (&lt; 0.005)*</td>
</tr>
<tr>
<td>CH</td>
<td>0.01 (-)*</td>
<td>&lt; 0.05 (ns)*</td>
</tr>
<tr>
<td>HDL</td>
<td>0.01 (-)*</td>
<td>&lt; 0.01 (ns)*</td>
</tr>
<tr>
<td>Glucose</td>
<td>—</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Value after correction for age.

Abbreviations: Wt, weight; Ht, height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist : hip ratio; TG, triglycerides; CH, cholesterol; HDL, high-density lipoproteins.
significant after correction for age, suggesting that body fatness and its distribution may have an independent effect on blood pressure.

As regards the other parameters of the metabolic syndrome, namely blood glucose and lipids, we found no association of blood pressure with glucose, TG, CH or HDL. While insulin levels were associated with anthropometric dimensions, this relationship was dependent mostly from age. Moreover, the association of insulin with blood lipids was very weak.

In summary, our study shows that in obese children: (1) there is a weak association between fasting insulin and blood pressure, which disappears after the confounding effects of age and body composition are taken into account, and (2) there is only a very weak association (clustering) of blood pressure, anthropometric characteristics and blood lipids. It should nevertheless be pointed out that, since transversal studies cannot by their nature test any cause–effect hypothesis, the controversy of the relationship between hyperinsulinaemia and hypertension can be solved only by longitudinal studies.

References


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**Zusammenfassung.**

**Prämisches Ziel:** An einer umfangreichen Stichprobe adipöser Kinder wurde untersucht, ob es eine Assoziation zwischen dem Insulin-Nüchternwert und dem Blutdruck gibt.

**Probanden und Methoden:** In die Studie wurden 350 adipöse Kinder (F:M Verhältnis = 1.03) im Alter von 10.1 ± 2.7 Jahren eingeschlossen, es handelte sich um fortlaufende Patienten einer ambulanten Pädiatrischen Klinik. Zur Definition von Adipositas wurde ein altersbezogenes relatives Gewicht von > 120% herangezogen. Als Kriterium für Bluthochdruck galt das Überschreiten der 95. Percentile des körperhöhenadjustierten altersspezifischen Normwertes für den systolischen (SBP) oder den diastolischen (DBP) Blutdruck.

**Ergebnisse:** Die Insulin-Konzentration war bei Kindern mit Bluthochdruck (n = 202, 58%) signifikant höher als bei Kindern mit normalem Blutdruck (n = 148, 42%; 16 vs 14 μU/mL, geometrisches Mittel, p < 0.01, ANOVA), der Unterschied war jedoch klinisch nicht relevant. Die logarithmisch transformierten Insulin-Konzentrationen kamen jedoch nur 7 bzw 4% der Varianz des SBP bzw. DBP. Dieser Anteil verschwand nach Berücksichtigung des Effekts von Confoundern, wie Alter, Gewicht und andere anthropometrische Dimensionen (p = ns, ANCOVA).

**Schlussfolgerung:** Die Hypothese einer klinisch relevanten Assoziation zwischen Insulin-Nüchternwerten und dem Blutdruck bei adipösen Kindern wird durch die vorliegende Studie nicht gestützt.

**Résumé.**

**Objectif:** on a examiné si les niveaux d’insuline en période de jeûne étaient associés à la pression artérielle, dans un grand échantillon d’enfants obèses.

**Méthodes et sujets:** trois cent cinquante enfants obèses (rapport F:M = 1,03) de 10,1 ± 2,7 ans (moyenne ± écart-type) ont été consécutivement enrôlés dans le service externe d’une clinique pédiatrique. L’obésité a été diagnostiquée sur la base d’un poids relatif par rapport à l’âge > 120% et l’hypertension sur la base d’une pression sanguine systolique (PSS) ou diastolique (PSD) > 95ème percentile pour l’âge, après ajustement pour la stature (St)

**Résultats:** l’insuline est significativement plus haute chez les enfants hypertensifs (n = 202, 58%) que normotensifs (n = 148, 42%) (moyenne géométrique 16 contre 14 μU/mL, p < 0,01 ANOVA), mais la différence n’est pas significative au niveau clinique. Qui plus est, le logarithme de l’insuline n’explique que 7% et 4% des variances respectives de la PSS et de la PSD (p < 0,0001) et cette contribution disparaît après que les effets de l’âge, du poids ou d’autre dimensions anthropométriques aient été pris en compte (p = ns, ANCOVA).

**Conclusions:** Cette étude n’est pas favorable à l’hypothèse d’une association clinique significative entre l’insuline de jeune et la pression artérielle chez les enfants obèses.