

Relationship between body mass index and insulin measured during oral glucose tolerance testing in severely obese children and adolescents

L. IUGHETTI[†], M. DE SIMONE[‡], S. BERNASCONI[§], B. PREDIERI[†],
N. BATTISTINI[¶] and G. BEDOGNI[¶]

[†]Paediatrics Clinic, University of Modena and Reggio Emilia, Modena, Italy

[‡]Paediatrics Chair, University of L'Aquila, L'Aquila, Italy

[§]Paediatrics Chair, University of Parma, Parma, Italy

[¶]Human Nutrition Chair, University of Modena and Reggio Emilia, Modena, Italy

Received 15 July 2003; revised 21 October 2003; accepted 30 October 2003

Summary. *Primary objective:* The study evaluated the accuracy of body mass index (BMI) in detecting hyperinsulinaemia during oral glucose tolerance testing (OGTT) in severely obese children.

Research design: A cross-sectional study was carried out.

Materials and methods: A total of 118 obese children and adolescents (49 females and 69 males) aged 6-19 years were consecutively studied at an outpatient paediatric clinic. Hyperinsulinaemia was defined as a value of log-transformed fasting insulin \geq 80th percentile and OGTT hyperinsulinaemia as a value of the log-transformed area under the curve (AUC) of insulin \geq 80th percentile. The study hypothesis was tested using a logistic regression model with hyperinsulinaemia as the outcome variable and the z -score of BMI corrected for age (z -BMI_{age}) as the predictor variable. Receiver-operator characteristic (ROC) curves were used to evaluate accuracy.

Results: The mean (SD) BMI for age of the children was 28.6 (4.0) kg m⁻², corresponding to 2.2 (0.5) standard deviation scores. The odds ratio (OR) of OGTT hyperinsulinaemia was 2.0 (95% CI 1.2-3.3; $p = 0.007$) for each unit increase of z -BMI_{age} and the corresponding ROC-AUC was 0.74 (95% CI 0.61-0.86; $p = 0.0001$). In comparison, the OR of fasting hyperinsulinaemia was 1.1 (95% CI 0.7-1.7; $p = 0.716$) for each unit increase of z -BMI_{age} and the corresponding ROC-AUC was 0.49 (95% CI 0.35-0.62; $p = 0.863$).

Conclusion: BMI is reasonably accurate in detecting OGTT hyperinsulinaemia in severely obese children.

1. Introduction

Body mass index (BMI) is a simple index of adiposity with a proven prognostic value in adults (Calle *et al.* 1999, Bedogni *et al.* 2001). The fact that childhood BMI tracks to adulthood (Guo and Chumlea 1999, Guo *et al.* 2000) suggests that it could be used as the main index of adiposity in children and adolescents (Bellizzi and Dietz 1999, Dietz and Bellizzi 1999, Cole *et al.* 2000). However, for BMI to gain a role of a prognostic index in childhood and adolescence, an association of it with disease has to be demonstrated (Must *et al.* 1992, Bellizzi and Dietz 1999, Freedman *et al.* 1999). In the last two decades, insulin has been increasingly shown to play a central role in the pathogenesis of the metabolic syndrome (WHO 1998). While BMI and insulin are generally correlated, we have recently found only a weak association between fasting insulin and BMI in a population of severely obese children and adolescents (Bedogni *et al.* 2002). In particular, the large inter-individual variability of this association hindered the utilization of BMI as a predictor of fasting insulin.

Measurement of insulin during oral glucose tolerance testing (OGTT) provides, however, a better means of evaluating insulin sensitivity (Matsuda and De Fronzo 1999) and BMI may be associated more strongly with OGTT insulin than with fasting insulin. In the present study, we evaluated the ability of BMI to detect hyperinsulinaemia during OGTT in a sample of severely obese children.

2. Materials and methods

2.1. Subjects

A total of 118 obese children were consecutively enrolled into the study at an outpatient paediatric clinic. Obesity was diagnosed on the basis of a BMI \geq 90th percentile for age using the growth charts of Cacciari *et al.* (2002). 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 study protocol was approved by the local Ethical Committee and the parents of the children gave their informed consent.

2.2. Anthropometry

Weight and height were measured following the *Anthropometric Standardization Reference Manual* (Lohman *et al.* 1988). BMI was calculated as weight (kg)/height (m)².

2.3. Laboratory measurements

Glucose and insulin were measured at 0, 30, 60, 90 and 120 min during an OGTT performed with 1.75 g glucose/kg weight (up to 75 g). Glucose was measured by common laboratory methods and insulin by radioimmunoassay (Radim, Roma, Italy). The insulin/glucose ratio (IGR) was calculated as insulin ($\mu\text{U mL}^{-1}$)/glucose (mg dL^{-1}). The areas under the curve (AUC) of insulin, glucose and IGR were calculated using the trapezoid rule.

2.4. Statistical analysis

Insulin, insulin-AUC, glucose-AUC, IGR and IGR-AUC were log-transformed to reach the normal distribution. None of these variables was associated with age ($p > 0.05$, correlation analysis). Between-sex comparisons were performed with unpaired *t*-tests. Interactions in contingency tables were analysed with Pearson's Chi-square. Age explained 25% of BMI variance ($p < 0.0001$), so BMI was corrected for age by linear regression. Residuals of the BMI-age regression (BMI_{age}) were then transformed in *z*-scores ($z\text{-BMI}_{\text{age}}$) to control for internal variability. In the absence of internationally accepted cut-points, fasting hyperinsulinaemia was arbitrarily defined as a value of log-transformed fasting insulin \geq internal 80th percentile ($3.2 \mu\text{U mL}^{-1}$). Likewise, OGTT hyperinsulinaemia was defined as a value of log-transformed insulin-AUC \geq 80th percentile ($9.1 \mu\text{U mL}^{-1}$). The study hypothesis was tested using a logistic regression model with hyperinsulinaemia as the outcome variable and $z\text{-BMI}_{\text{age}}$ as the predictor variable. A sample size of 120 subjects ensured a power of 88%, at an alpha level of 0.05, to detect a change in the probability of ($Y = 1$) from a value of 0.22 at the mean of X to a value of 0.36 when X is increased to one standard deviation (SD) above the mean, corresponding to an odds ratio (OR) of 2.0. Stratified logistic regression was used to control for the possibly confounding effect of sex and pubertal status. Receiver-operator characteristic (ROC) curves, obtained by plotting sensitivity versus (1 - specificity), were used to evaluate accuracy (Zhou *et al.* 2002). Statistical significance was set to a value of

$p < 0.05$ for all tests. Statistical analysis was performed using SPSS 11 (SPSS, Chicago, IL, USA) and LogXact 4 (Cytel, Cambridge, MA, USA).

3. Results

A total of 118 children and adolescents (49 females and 69 males) aged 6–19 years were consecutively studied (table 1).

There was a significant between-sex difference in pubertal status ($p < 0.0001$), explained mainly by a greater number of late-pubertal males than females (67 vs 31%). The mean (SD) BMI for age of the children was $28.6 (4.0) \text{ kg m}^{-2}$, corresponding to 2.2 (0.5) standard deviation scores (Cacciari *et al.* 2002). This equals severe obesity, with a high risk of metabolic complications (Iughetti *et al.* 2000). The values of anthropometric and laboratory measurements were similar in males and females ($p > 0.05$).

The OR of OGTT hyperinsulinaemia was 2.0 (95% confidence intervals (95% CI) 1.2–3.3; $p = 0.007$) for each unit increase of $z\text{-BMI}_{\text{age}}$ and the corresponding ROC-AUC was 0.74 (95% CI 0.61–0.86; $p = 0.0001$) (Figure 1). After stratification for sex, there was no change in the estimate (OR = 2.0; 95% CI 1.2–3.3; $p = 0.007$). Likewise, only a trivial change of significance was noted after stratification for pubertal status (OR = 2.0; 95% CI 1.2–3.3; $p = 0.009$). Thus, neither sex nor pubertal status influenced the BMI–OGTT hyperinsulinaemia relationship. In comparison, the OR of fasting hyperinsulinaemia was 1.1 (95% CI 0.7–1.7; $p = 0.716$) for each unit increase of $z\text{-BMI}_{\text{age}}$ and the corresponding ROC-AUC was 0.49 (95% CI 0.35–0.62; $p = 0.863$) (Figure 1).

4. Discussion

For BMI to be considered a prognostic indicator in children and adolescents such as in adults (Calle *et al.* 1999, Bedogni *et al.* 2001), associations of it with clinically relevant variables have to be demonstrated. Among these variables, insulin is considered of central importance because of its role in the pathogenesis of the

Table 1. Measurements of the children. Data are means and standard deviations unless specified otherwise. Abbreviations: BMI = body mass index; $z\text{-BMI}$ = z -score of BMI; SDS = standard deviations score; AUC = area under the curve; IGR = insulin/glucose ratio.

	All	Females	Males
<i>n</i>	118	49	69
Pubertal status (pre-pubertal/early pubertal/late pubertal; %)	33/15/52	41/28/31	28/5/67*
Age (years)	11 ± 2	11 ± 3	11 ± 2
Weight (kg)	63.8 ± 17.1	63.5 ± 17.9	64.1 ± 16.6
Height (m)	1.48 ± 0.12	1.47 ± 0.11	1.48 ± 0.13
BMI (kg m^{-2})	28.6 ± 4.0	28.7 ± 4.9	28.6 ± 3.3
$z\text{-BMI}$ (SDS)	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.4
Insulin ($\mu\text{U mL}^{-1}$)†‡	14	14	14
Insulin-AUC†	5889	6442	5525
Glucose (mg dL^{-1})§	74 ± 9	74 ± 10	75 ± 9
Glucose-AUC†§	10 947	10 825	11 036
IGR†	0.2	0.2	0.2
IGR-AUC†	57	62	53

* $p < 0.0001$; Pearson's Chi-square.

† Geometric mean.

‡ To convert to SI units (pmol L^{-1}), multiply by 7.175.

§ To convert to SI units (mmol L^{-1}), multiply by 0.05551.

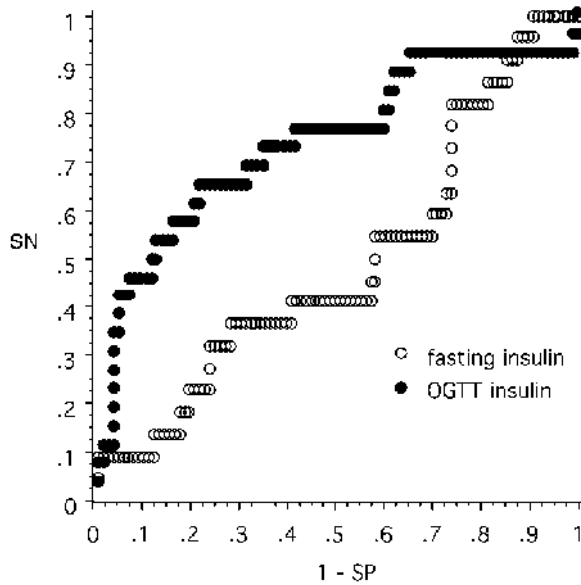


Figure 1. Accuracy of BMI in detecting fasting and OGTT hyperinsulinaemia. Abbreviations: SN = sensitivity; SP = specificity.

metabolic syndrome (Bellizzi and Dietz 1999, Dietz and Bellizzi 1999). A large inter-individual variability in the BMI–insulin relationship hinders the utilization of BMI as a predictor of fasting insulin in severely obese children (Bedogni *et al.* 2002). However, this may not apply to OGTT insulin, which is a better indicator of insulin sensitivity.

In this study, the OR of OGTT hyperinsulinaemia associated with an increase of one unit of z -BMI_{age} was 2.0, but no association was found between fasting hyperinsulinaemia and z -BMI_{age}. This may be of pathophysiological significance because OGTT hyperinsulinaemia is a better index of insulin sensitivity than fasting hyperinsulinaemia (Matsuda and De Fronzo 1999). However, the 95% CI of the OR are wide enough (1.2–3.3) to make this relationship less useful at the individual level. Likewise, while a ROC-AUC of 0.74 denotes acceptable accuracy, its 95% CI ranged from 0.61 to 0.86, again suggesting some caution when making inferences at the individual level.

The limitations of this study should be kept in mind. Even if it was powerful enough to test the hypothesis of interest, it was performed on a selected sample of severely obese children and adolescents and its conclusions may not apply to children with less severe obesity. However, as we have discussed elsewhere (Iughetti *et al.* 2000, Bedogni *et al.* 2002), these children are the ideal subjects where the relationship between insulin and disease can be studied. Another limitation of this study is the lack of a control group of normal-weight children, explained by the invasive nature of OGTT and its ethical implications. Even if our aim was to test whether BMI can be employed to predict hyperinsulinaemia in *obese* children, a control group of non-obese children is clearly needed to test whether a BMI–OGTT insulin relationship exists also in physiological conditions. Moreover, we defined hyperinsulinaemia as a value of insulin \geq 80th internal percentile. Even if this is a common practice in epidemiology, there is no reason why other cut-points should not be chosen. Ideally,

cut-points should be based on clinical outcomes, but few data are available for children at present so a purely epidemiological approach seems unavoidable. The BMI–OGTT insulin relationship was unaffected by sex and pubertal status, confirming our previous findings with fasting insulin (Bedogni *et al.* 2002). It should, however, be considered that there was a significant between-sex difference in pubertal status.

In conclusion, BMI is reasonably accurate in detecting OGTT hyperinsulinaemia in severely obese children. Because BMI is just a rough indicator of body composition, it is important that future studies analyse the relative contribution of fat and fat-free tissues to the BMI–OGTT insulin relationship.

References

- BEDOJNI, G., PIETROBELLI, A., HEYMSFIELD, S., BORCHI, A., MANZIERI, A. M., MORINI, P., BATTISTINI, N., and SALVIOLI, G., 2001, Is body mass index a measure of adiposity in elderly women? *Obesity Research*, **9**, 17–20.
- BEDOJNI, G., IUGHETTI, L., FERRARI, M., MALAVOLTI, M., DE SIMONE, M., FIORI, G., BATTISTINI, N., and BERNASCONI, S., 2002, Association of waist circumference and body mass index with fasting blood insulin in severely obese children: a cross-sectional study. *Diabetes, Nutrition and Metabolism*, **15**, 160–164.
- BELLIZZI, M. C., and DIETZ, W. H., 1999, Workshop on childhood obesity: summary of the discussion. *American Journal of Clinical Nutrition*, **70**, 173S–175S.
- CACCIARI, E., MILANI, S., BALSAMO, A., DAMMACCO, F., DE LUCA, F., CHIARELLI, F., PASQUINO, A. M., and VANELLI, M., 2002, Italian cross-sectional growth charts for height, weight and BMI (6–20 y). *European Journal of Clinical Nutrition*, **56**, 171–180.
- CALLE, E. E., THUN, M. J., PETRELLI, J. M., RODRIGUEZ, C., and HEATH, C. W., 1999, Body mass index and mortality in a prospective cohort of US adults. *New England Journal of Medicine*, **341**, 1097–1105.
- COLE, T. J., BELLIZZI, M. C., FLEGAL, K. M., and DIETZ, W. H., 2000, Establishing a standard definition for child overweight and obesity worldwide: international survey. *British Medical Journal*, **320**, 1240–1243.
- DIETZ, W. H., and BELLIZZI, M. C., 1999, Introduction: the use of body mass index to assess obesity in children. *American Journal of Clinical Nutrition*, **70**, 123S–125S.
- FREEDMAN, D. S., DIETZ, W. H., SRINIVASAN, S. R., and BERENSON, G. S., 1999, The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*, **103**, 1175–1182.
- GUO, S. S., and CHUMLEA, W. C., 1999, Tracking of body mass index in children in relation to overweight in adulthood. *American Journal of Clinical Nutrition*, **70**, 145S–148S.
- GUO, S. S., HUANG, C., MAYNARD, L. M., DEMERATH, E., TOWNE, B., CHUMLEA, W. C., and SIERVOGEL, R. M., 2000, Body mass index during childhood, adolescence and young adulthood in relation to adult overweight and adiposity: the Fels Longitudinal Study. *International Journal of Obesity and Related Metabolic Disorders*, **24**, 1628–1635.
- IUGHETTI, L., BEDOJNI, G., FERRARI, M., PAGLIATO, E., MANZIERI, A. M., DE SIMONE, S., BATTISTINI, N., and BERNASCONI, S., 2000, Is fasting insulin associated with blood pressure in obese children? *Annals of Human Biology*, **5**, 499–506.
- LOHMAN, T. G., ROCHE, A. F., and MARTORELL, R., eds, 1988, *Anthropometric Standardization Reference Manual* (Champaign, IL: Human Kinetics Books).
- MATSUDA, M., and DE FRONZO, R., 1999, Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic clamp. *Diabetes Care*, **22**, 1462–1470.
- MUST, A., JACQUES, P. F., DALLAL, G. E., BAJEMA, C. J., and DIETZ, W. H., 1992, Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *New England Journal of Medicine*, **327**, 1350–1355.
- WHO, 1998, *Obesity: Preventing and Managing the Global Epidemic* (Geneva: WHO).
- TANNER, J. M., 1978, *Foetus into Man. Physical Growth from Conception to Maturity* (Cambridge: Harvard University Press).
- ZHOU, X., OBUCHOWSKI, N. A., and MCCLISH, D. K., 2002, *Statistical Methods in Diagnostic Medicine* (New York: John Wiley & Sons).

Address for correspondence: Giorgio Bedogni, Human Nutrition Chair, Department of Hygiene, Microbiology and Biostatistics, Faculty of Medicine and Surgery, University of Modena and Reggio Emilia, Via Campi 287, 41100 Modena, Italy. email: giorgiobedogni@libero.it

Zusammenfassung. *Studienziel:* Die Studie bewertete die Genauigkeit des Körpermasse-Index (BMI, body mass index) für die Erfassung von Hyperinsulinämie während eines oralen Glukose-Toleranztests (OGTT) bei erheblich adipösen Kindern.

Studiendesign: Es wurde eine Querschnittsuntersuchung durchgeführt.

Material und Methoden: Insgesamt 118 adipöse Kinder und Jugendliche (49 Mädchen und 69 Knaben) im Alter von 6–19 Jahren wurden fortlaufend an einer pädiatrischen Ambulanz untersucht. Hyperinsulinämie wurde definiert als ein log-transformierter Nüchterninsulin-Wert ≥ 80 . Perzentile. Eine OGTT-Hyperinsulinämie wurde definiert als Insulinwerte ≥ 80 . Perzentile für die log-transformierte Fläche unter der Kurve (AUC, area under the curve). Die Studienhypothese wurde mittels eines logistischen Regressionsmodells getestet mit Hyperinsulinämie als abhängiger Variable und dem alterskorrigierten z-Wert für Körpermasse-Index ($z\text{-BMI}_{\text{age}}$) als unabhängiger Variable. Receiver-operator characteristic (ROC)-Kurven wurden genutzt, um die Genauigkeit zu bestimmen.

Ergebnisse: Der Mittelwert des BMI betrug 28,6 (Standardabweichung 4,0) kg m^{-2} , entsprechend einem z-Wert für BMI von 2,2 (Standardabweichung 0,5). Die odds ratio (OR) für OGTT-Hyperinsulinämie war 2,0 (95% Konfidenzintervall 1,2–3,3; $p=0,007$) für jeden Anstieg des $z\text{-BMI}_{\text{age}}$ um 1; und die entsprechende ROC-AUC war 0,74 (95% Konfidenzintervall 0,61–0,86; $p=0,0001$). Demgegenüber betrug die odds ratio für die Nüchtern-Hyperinsulinämie 1,1 (95% Konfidenzintervall 0,7–1,7; $p=0,716$) für jeden Anstieg des $z\text{-BMI}_{\text{age}}$ um 1; und die entsprechende ROC-AUC war 0,49 (95% Konfidenzintervall 0,35–0,62; $p=0,863$).

Zusammenfassung: Der BMI ist verhältnismäßig gut geeignet für die Erfassung von Hyperinsulinämie während eines oralen Glukose-Toleranztests (OGTT) bei erheblich adipösen Kindern.

Résumé. *Objectif premier:* Cette étude évalue la précision de l'indice de masse corporelle (IMC) pour la détection de l'insulinémie mesurée par la tolérance orale du glucose (MTOG) chez les enfants à forte obésité.

Type de recherche: étude transversale

Matériel et méthode : un ensemble de 118 enfants et adolescents obèses (49 filles et 69 garçons) âgés de 6 à 19 ans ont été étudiés comme clients externes d'une clinique pédiatrique. L'hyperinsulinémie a été définie comme une valeur logarithmique égale au 80^{ème} percentile de l'insuline de jeûne et l'hyperinsulinémie lors de la MTOG comme une valeur logarithmique de l'aire limitée supérieurement par la courbe (AUC) du 80^{ème} percentile d'insuline. L'hypothèse étudiée a été éprouvée au moyen d'un modèle de régression logistique dans lequel l'insulinémie est la variable expliquée et le z-score d'IMC pondéré pour l'âge ($z\text{-IMC}_{\text{age}}$) est la variable explicative. Des courbes de type receveur-opérateur (CRO) ont été utilisées afin d'évaluer la précision.

Résultats: La moyenne (ET) de l'IMC par rapport à l'âge des enfants est de 28,6 (4,0) kg m^{-2} , correspondant à 2,2 (0,5) scores d'écart-type. L'odds ratio (OR) de l'hyperinsulinémie MTOG est de 2,0 (intervalle de confiance à 95% 1,2–3,3 $p=0,007$) pour chaque accroissement d'unité du $z\text{-IMC}_{\text{age}}$ et la CRO-AUC correspondante est de 0,74 (IC à 95% 0,61–0,86; $p=0,0001$). En comparaison, l'OR de l'hyperinsulinémie de jeûne est de 1,1 (IC à 95% 0,7–1,7; $p=0,716$) pour chaque accroissement d'unité du $z\text{-IMC}_{\text{age}}$ et la CRO-AUC correspondante est de 0,49 (IC à 95% 0,35–0,62; $p=0,863$).

Conclusion: L'IMC est un moyen relativement précis de détecter l'hyperinsulinémie MTOG chez les enfants fortement obèses.

Resumen. *Objetivo principal:* El estudio evaluó la precisión del índice de masa corporal (IMC) para la detección de hiperinsulinemia durante la realización del test de tolerancia a la glucosa oral (TTGO) en niños con obesidad severa.

Diseño de la investigación: Se realizó un estudio transversal.

Material y métodos: Se estudiaron sucesivamente un total de 118 niños y adolescentes obesos (49 mujeres y 69 varones), de 6 a 19 años de edad, en una clínica pediátrica de consultas externas. La hiperinsulinemia se definió como el valor transformado en logaritmos de la insulina plasmática en ayunas, mayor o igual al percentil 80, y la hiperinsulinemia TTGO como el valor de la transformación logarítmica del área situada bajo la curva (AUC) de la insulina en ayunas, mayor o igual al percentil 80. La hipótesis del estudio fue testada utilizando un modelo de regresión logística en el que la hiperinsulinemia era la variable dependiente y la puntuación z del IMC corregido para la edad ($z\text{-IMC}_{\text{edad}}$) la variable predictora. Se utilizaron curvas ROC (curvas de características operativas del receptor) para evaluar la precisión.

Resultados: El valor medio (SD) del IMC corregido para la edad de los niños fue de 28,6 (4,0) kg m^{-2} , que corresponde a un valor 2,2 (0,5) de las puntuaciones estándar. La razón de productos cruzados (odds ratio, OR) de la hiperinsulinemia TTGO fue de 2,0 (95% IC 1,2–3,3; $p=0,007$) para cada incremento en una unidad de la $z\text{-IMC}_{\text{edad}}$ y el ROC-AUC correspondiente fue de 0,74 (95% IC 0,61–0,86; $p=0,0001$). En comparación, el OR de la hiperinsulinemia en ayunas fue de 1,1 (95% IC 0,7–1,7; $p=0,716$) para cada incremento en una unidad de la $z\text{-IMC}_{\text{edad}}$ y el ROC-AUC correspondiente fue de 0,49 (95% IC 0,35–0,62; $p=0,863$).

Conclusión: El IMC es razonablemente preciso para detectar hiperinsulinemia TTGO en niños con obesidad severa.