ORIGINAL ARTICLE

Glucose alteration and insulin resistance in asymptomatic obese children and adolescents ☆

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Abstract

Objective: Obesity is associated with the abnormal glucose metabolism preceding type 2 diabetes mellitus. Thus, further investigation on the prediction of this lethal outcome must be sought. The objective was the profile glycemic assessment of asymptomatic obese children and adolescents from Salvador, Brazil.

Method: A fasting venous blood sample was obtained from 90 consecutive obese individuals aged 8–18 years, of both sexes, for laboratory determinations of glycated hemoglobin, basal insulin, and the Homeostasis Model Assessment Insulin Resistance index. The clinical evaluation included weight, height, waist circumference, assessment of pubertal development, and acanthosis nigricans research. The body mass index/age indicator was used for the severity of overweight assessment.

Results: Glycemic alterations were evidenced clinically and biochemically, although these individuals had no complaints or symptoms related to blood sugar levels. Quantitative and qualitative variables were respectively expressed measures of central tendency/dispersion and simple/relative frequency, using the SPSS, version 20.0. A *p*-value <0.05 was considered significant.

Conclusion: Notably, this study found a high prevalence of glucose and insulin disorders in asymptomatic obese children and adolescents.

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PALAVRAS-CHAVE
Obesidade;
Diabetes mellitus;
Hiperglicemia;
Glicemia

Alteração de glicose e resistência à insulina em crianças e adolescentes obesos assintomáticos

Resumo

Objetivo: A obesidade está associada ao metabolismo da glicose anormal que antecede a diabetes mellitus tipo 2. Assim, uma investigação adicional sobre a predição desse resultado letal deve ser antecipada. O objetivo era a avaliação do perfil glicêmico de crianças e adolescentes obesos assintomáticos de Salvador, Brasil.

Método: Uma amostra de sangue venoso em jejum foi obtida de 90 indivíduos obesos consecutivos com idade entre 8-18 anos, de ambos os sexos, para determinações laboratoriais de hemoglobina glicosilada, insulina basal e Índice do Modelo de Avaliação da Homeostase de Resistência à Insulina (HOMA-IR). A avaliação clínica incluiu peso, estatura, circunferência da cintura, avaliação do desenvolvimento puberal e pesquisa sobre a acantose nigricans. Utilizamos o indicador de índice de massa corporal/idade referente à gravidade da avaliação de sobrepeso.

Resultados: Alterações glicêmicas foram comprovadas clínica e bioquimicamente, apesar de esses indivíduos não apresentarem queixas ou sintomas relacionados a níveis de açúcar no sangue. Variáveis quantitativas e qualitativas foram, respectivamente, medidas expressas de tendência central/dispersão e amostra/frequência relativa, utilizando o software Pacote Estatístico para as Ciências Sociais, versão 20.0. O valor de p < 0,05 foi considerado significativo.

Conclusão: Observamos, contudo, alta prevalência de distúrbios de glicose e insulina em crianças e adolescentes obesos assintomáticos.

Introduction

Obesity is a major change of nutritional metabolism, characterized by excessive fat deposition in the body, frequently observed in children and adolescents in worldwide. As a consequence, this population can develop adverse health effects favoring metabolic disorders such as dyslipidemia, hypertension, insulin resistance, glucose intolerance, and type 2 diabetes mellitus (T2DM).[1]

Although glycemic alterations in the obese are expected, T2DM is an infrequent comorbidity in children and adolescents.[2] This possibility is strongly associated with the occurrence of prior events, such as hyperinsulinemia and insulin resistance,[3] even considering how uncommon insulin resistance is in pre-pubertal children. Studies report the occurrence of peaks during pubertal period, becoming normal in adulthood.[4] In fact, in a study performed with Brazilian children and adolescents without excess weight, age variation of insulin levels and the HOMA-IR indicator was demonstrated.[5] Furthermore, these situations in obese pediatric patients require drug therapy before T2DM diagnosis has been established, in case of failure in lifestyle modification. This study used laboratory testing that is not part of the standard investigative routine in primary health care, in order to detect abnormalities that precede the diagnosis of T2DM in obesity. Thus, the purpose of this article is to present the evaluation of the glucose profile of asymptomatic obese children and adolescents.

Materials and methods

A cross-sectional study in 90 consecutive obese patients was conducted, aged 8–18 years, of both sexes, evaluated in a weekly pediatric nutrition outpatient screening at the Federal University of Bahia, Brazil, carried out from January to December 2015. All participants were only included if their Tanner criteria stage was normal for their age (Tanner stages I–IV).[6] The body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). The z-score of the indicator BMI/age (BMI/A) and gender was used to classify the anthropometric status of participants as obese (z-score >+2) or severely obese (z-score >+3).[7] The dermatosis acanthosis nigricans (indicative of insulin resistance) was assessed in the neck, armpits, interphalangeal space, and flexor surfaces of the limbs. When present, it was classified as mild, moderate, or severe.[8] Waist circumference was obtained with a soft and inelastic tape, at the midpoint between the last rib and the anterior iliac crest.[9] Those who were using drugs that could interfere with glucose metabolism were excluded, as well as patients with conditions that predispose them to being overweight (Cushing's syndrome, growth hormone deficiency, hypothyroidism, syndromic obesity, and abnormal puberty pattern). This study was approved by the Ethics Committee of the Federal University of Bahia, Brazil. Children's verbal assent was obtained and a written informed consent was obtained from their legal representatives.

Table 1 Main clinical and laboratory characteristics of 90 asymptomatic obese children and adolescents in Salvador, Brazil.

	Obese n = 27 (30.0%)	Severely obese n = 63 (70.0%)	p-value
Age (years)[a]	11.4 (2.3)	12.2 (2.9)	0.28
Sex			
Male	17 (64.6%)	31 (35.4%)	0.23
Female	10 (23.8%)	32 (76.2%)	
Waist circumference (cm)[a]	87.7 (9.1)	98.3 (13.8)	<0.001
BMI	28.25 (3.5)	33.57 (6.5)	<0.001
BMI (z-score)	2.52 (0.2)	3.60 (0.8)	<0.001
Acanthosis nigricans			
Mild	13 (35.1%)	24 (64.9%)	0.41
Moderate	12 (30.0%)	28 (70.0%)	
Severe	2 (15.4%)	11 (84.6%)	
Fasting plasma glucose (mg/dL)[a]	87.3(8.4)	91.1 (10.1)	0.15
Insulin (μUI/mL)[a]	12.0 (7.3)	14.1 (9.5)	0.51
HbA1C			
Normal values	18 (31.6%)	39 (68.4%)	0.25
High risk for DM	09 (33.3%)	18 (66.7%)	
Probably DM	–	06 (100.0%)	
HOMA-IR[a]	2.6 (1.6)	3.1 (2.1)	0.44

HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; BMI, body mass index.
  [a] Values expressed as mean (SD).

Laboratory analyses

A fasting venous blood sample was taken of all participants for laboratory determinations, in a single moment. Fasting plasma glucose was assessed by the hexokinase method (Wiener Lab.). Glucose levels between 100–125 mg/dL and $\geq$126 mg/dL were, respectively, classified as glucose intolerance and T2DM. The glycated hemoglobin (HbA$_1$C) levels were determined by the turbidimetry method HbA$_1$C (TUR-BITEST AA, Wiener lab®, SP, Brazil). Normal reference values were 4.8%-5.9%. HbA$_1$c values between 5.7% and 6.4% were considered as high risk for developing diabetes, and $\geq$6.5%, considered as probable diabetes mellitus (DM). American Diabetes Association[10] diagnosis criteria were used for both parameters. The insulin levels were evaluated by enzyme-linked immunosorbent assay (ELISA). Any values greater than 15.0 μUI/mL were considered abnormal.[11] The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index (fasting glucose [mg/dL] $\times$ fasting insulin [μIU/mL]/405) was used to identify insulin resistance.[12] The cut-offs adjusted by gender and age according to Almeida et al. were used,[5] summing the mean value to 2 standard deviations to determinate cutoffs.

Statistical analyses

Quantitative and qualitative data were respectively expressed by measures of central tendency, dispersion, and simple/relative frequency. The chi-squared test compared the frequency of individuals in each category. Continuous variables were tested for normality of distribution by the Kolmogorov–Smirnov test. The differences for these variables were analyzed using the Mann–Whitney U-test or Student's t-test, according to their distribution. Statistical Program for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. NY, USA) was utilized for statistical analyses. A p-value <0.05 was considered significant.

Results

Table 1 show the main clinical and laboratory characteristics of this population. The fasting blood glucose ranged from 70.7 to 128.0 mg/dL and was elevated in nine (10.0%) participants. One patient presented with glucose values above 126 mg/dL. Insulin levels ranged from 2.5 to 52.9 μUI/mL and were altered in 25 (27.8%) participants. As for HbA1c, the detected levels ranged from 4.2% to 6.8%, with 24 (26.6%) individuals presenting with abnormal values, six of them higher than 6.5%. The HOMA-IR index was abnormal in 47 (52.2%) participants. When comparing the group of severely obese and the obese group, a higher prevalence of insulin resistance was observed in the first group (65.4%; p < 0.003).

Discussion

These results report a high prevalence of glucose metabolism and insulin abnormalities in this population of obese and severe obese children and adolescents, similarly to the findings described by D'Adamo and Caprio.[13] It was also observed that almost 80% of the children and adolescents with severe obesity show altered glucose and insulin levels. In addition, this group also demonstrated the largest waist circumference measurements, regardless of age and sex. According to Martins and Marinho,[14] visceral obesity

is a leading cause of altered glucose/insulin homeostasis disorders. Thus, these findings reinforce the role of waist circumference as insulin resistance marker and an early predictor of T2DM.[15] In this study, no association was detected between severe or moderate dermatosis acanthosis nigricans, severe obesity, and increased waist circumference.

Fasting blood glucose above the reference value was detected in nine cases. Surprisingly, in the case of an obese individuals (z score = +2.77), it was 126 mg/dL and the HbA1c was in risk range for T2DM. The HbA1c values were higher than 6.5% in other six (9.5%) severely obese participants. These seven patients, therefore, show diabetes mellitus diagnostic parameters (prevalence of 7.8%). These tests were not repeated for confirmation.

The glycated hemoglobin reflects the degree of individual exposure to high glucose levels in the last 120 days. Although the proposed values of HbA1c in children and adolescents are not yet defined, values above 6.5% must be confirmed in another sample and waived in the event of symptoms or random blood glucose levels above 200 mg/dL. Values between 5.7% and 6.4% are indicative of high risk for developing diabetes, according to the American Diabetes Association consensus, 2016.[16]

Hyperinsulinemia was observed in almost 30% of children and adolescents studied. These values could have been even greater if lower cutoff points were used, such as the European parameter, estimated at $12.6 \mu IU/mL$. However, this finding was not followed by abnormal increase in fasting glucose. These data are compatible with the pathophysiological compensatory process of high blood glucose levels that leads to increased insulin production, secondary to resistance to insulin action in the target organs. This is detected by a significant increase in the HOMA-IR index, an indicator of such condition. However, after a certain period, this compensatory increase in insulin is lost, resulting in hyperglycemia, featuring glucose intolerance, and eventually, T2DM.[17] The current treatment with metformin for adolescents with documented insulin resistance, without the need of further laboratory diagnosis of DM, is recommended.[18–20] However, this recommendation is not a consensus in literature, being used in an experimental way in selected patients.[21]

There is no consensus on the cut-off point to define insulin resistance. Some authors[5,22,23] try to identify this cut-off by anthropometric measurements and metabolic indicators, among others, adjusted by age and sex. Cutoff values of approximately 3 are recommend to identify IR in children and adolescents.[24–28]

Similarly, the method used to determine insulin resistance is also controversial. In this study, HOMA-IR was used as a validated method for use in children and adolescents, easy to calculate when compared to quantitative insulin sensitivity check index (QUICKI) and for presenting values of measures that resemble those obtained with oral glucose tolerance test (OGTT) and hyperinsulinemic euglycemic clamp.[5] Although considered gold standard, these methods present limitations, such as the high cost and the difficulty of execution, making it unfeasible to use them routinely, being used only in clinical studies.[29]

Insulin resistance may become an important predictor of the development of diabetes mellitus (DM) in the future. Two obese individuals presented abnormal levels of glucose and HOMA-IR, with normal HbA1c and insulin levels. The other detected changes were more prevalent among severely obese individuals. These results demonstrate a high prevalence of abnormal blood glucose, basal insulin, HOMA-IR, and HbA1c in obese children and adolescents. Nearly 8% of patients met established criteria for diabetes mellitus. However, the most important finding relates to the high prevalence of changes that precede DM in asymptomatic individuals with severe obesity. An important limitation of this study refers to cross-sectional design. Thus, a cause-effect relationship cannot be established between obesity and the abnormal glucose metabolism, although a significant association was observed between severe obesity and insulin resistance.

These results provide compelling evidence about the need to expand the laboratory investigation of these patients, with the inclusion of insulin and glycated hemoglobin measurement and HOMA-IR determination, beyond the isolated blood glucose level. Finally, these findings reinforce the need to develop programs for the effective prevention and intervention in childhood obesity, considering that diabetes is a chronic and deadly disease that can be detected by proper glycemic/insulinemic profiling of asymptomatic obese individuals, as part of the investigative routine.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Codoner-Franch P, Valls-Belles V, Arilla-Codoner A, Alonso-Iglesias E. Oxidant mechanisms in childhood obesity: the link between inflammation and oxidative stress. Transl Res. 2011;158:369–84.
2. Zambon MP, Barro Filho AA, Mendes RT, Antônio MA. Características clínicas e laboratoriais de crianças e adolescentes obesos. Rev Paul Pediatr. 2007;25:27–32.
3. Kurtoglu S, Hatipoglu N, Mazicioglu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Pediatr Endocrinol. 2010;2:100–6.
4. Grant DB. Fasting serum insulin levels in childhood. Arch Dis Child. 1967;42:375–8.
5. Almeida CA, Pinho AP, Ricco RG, Pepato MT, Brunetti IL. Determination of glycemia and insulinemia and the homeostasis model assessment (HOMA) in schoolchildren and adolescents with normal body mass index. J Pediatr (Rio J). 2008;84:136–40.
6. Almeida C, Del Campo I, Ricco R, Crott G. Crescimento físico. Puericultura: princípios e práticas. São Paulo: Atheneu; 2001.
7. Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference of school-aged children and adolescents. Bull World Health Organ. 2007;85:660–7.
8. Higgins ST, Fremark M, Prose NS. Acanthosis nigricans: a practical approach to evaluation and management. Dermatol Online J. 2008;14:2.
9. World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a World Health Organization Consultation. Geneva: WHO; 2000. WHO Obesity Technical Report Serie n. 284.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37:S81–90.

11. Sociedade Brasileira de Pediatria (SBP). Departamento Científico de Nutrologia. Obesidade na infância e na adolescência – manual de orientação. 2nd ed. São Paulo: SBP; 2012.

12. Geloneze B, Tambascia MA. Avaliação laboratorial e diagnóstico da resistência insulínica. Arq Bras Endocrinol Metabol. 2006;50:208–15.

13. D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. Diabetes Care. 2011;34:S161–5.

14. Martins IS, Marinho SP. O potencial diagnóstico dos indicadores da obesidade centralizada. Rev Saude Publica. 2003;37:760–7.

15. Kobaissi HA, Weigensberg MJ, Ball GD, Cruz ML, Shaibi GQ, Goran MI, et al. Relation between acanthosis nigricans and insulin sensitivity in overweight Hispanic children at risk for type 2 diabetes. Diabetes Care. 2004;27:1412–6.

16. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2016;39:S1–106.

17. Guimarães IC, Guimarães A. Síndrome metabólica na infância e adolescência. Um fator maior de risco cardiovascular. Rev Baiana Saúde Pública. 2006;30:349–62.

18. Marques P, Limbert C, Oliveira L, Santos MI, Lopes L. Metformin effectiveness and safety in the management of overweight/obese nondiabetic children and adolescents: metabolic benefits of the continuous exposure to metformin at 12 and 24 months. Int J Adolesc Med Health. 2016;29(5), doi: 10.1515/ijamh-2015-0110.

19. Bouza C, López-Cuadrado T, Gutierrez-Torres LF, Amate J. Efficacy and safety of metformin for treatment of overweight and obesity in adolescents: an updated systematic review and meta-analysis. Obes Facts. 2012;5:753–65.

20. Park MH, Kinra S, Ward KJ, White B, Viner RM. Metformin for obesity in children and adolescents: a systematic review. Diabetes Care. 2009;32:1743–5.

21. Mead E, Atkinson G, Richter B, Metzendorf MI, Baur L, Finer N, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database Syst Rev. 2016;11:CD012436.

22. Schwimmer JB, Deutsch R, Rauch JB, Behling R, Newbury R, Lavine JE, et al. Obesity, insulin resistance and other clinic pathological correlates of pediatric nonalcoholic fatty liver disease. J Pediatr (Rio J). 2003;143:500–5.

23. Ascaso JF, Pardo S, Real JT. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care. 2003;26:3320–5.

24. Reinehr T, de Sousa G, Andler W. Longitudinal analyses among overweight, insulin resistance, and cardiovascular risk factors in children. Obes Res. 2005;13:1824–33.

25. Chandrasekhar T, Suchitra MM, Sachan A, Bitla AR, Srinivasa Rao PV. Indices of insulin resistance in paediatric obesity. J Clin Sci Res. 2014;3:7–13.

26. Madeira IR, Carvalho CN, Gazolla FM, de Matos HJ, Borges MA, Bordallo MA. Cut-off point for homeostatic model assessment for insulin resistance (HOMA-IR) index established from receiver operating characteristic (ROC) curve in the detection of metabolic syndrome in overweight pre-pubertal children. Arq Bras Endocrinol Metabol. 2008;52:1466–73.

27. Aradillas-García C, Rodríguez-Morán M, Garay-Sevilla ME, Malacara JM, Rascon-Pacheco RA, Guerrero-Romero F, et al. Distribution of the homeostasis model assessment of insulin resistance in Mexican children and adolescents. Eur J Endocrinol. 2012;166:301–6.

28. García Cuartero B, García Lacalle C, Jiménez Lobo C, González Vergaz A, Calvo Rey C, Alcázar Villar MJ, et al. The HOMA and QUICKI indexes, and insulin and C-peptide levels in healthy children. Cutoff points to identify metabolic syndrome in healthy children. An Pediatr (Barc). 2007;66:481–90.

29. American College of Endocrinology. Insulin resistance syndrome (position statement). Endocr Pract. 2003;9:9–21.