Prevalence of hyperinsulinism, type 2 diabetes mellitus and metabolic syndrome among Saudi overweight and obese pediatric patients

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Aim. Obesity and overweight among children and adolescents is increasing at an alarming rate, which lead to the increase in the incidence of their related co-morbidities. Our objectives are to establish the following: 1) the prevalence of hyperinsulinism among overweight and obese pediatric patients. 2) The prevalence of type 2 diabetes mellitus (T2DM) among those with hyperinsulinism. 3) The prevalence of metabolic syndrome (MS) and its components among T2DM pediatric patients.
Methods. A retrospective cross-sectional study conducted on overweight and obese pediatric patients attending the pediatrics diabetes clinic at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia, from 2006 to 2010. Serum insulin level was measured for 387 patients (ages from 2 to 18 years). Those with hyperinsulinism underwent further investigations to assess the prevalence of T2DM and the prevalence of MS among T2DM patients.
Results. The overall prevalence of hyperinsulinism and T2DM were 44.7%, and 9.04%, respectively. Among children and adolescents with T2DM, 62.86% had a body mass index BMI≥85th percentile, 37.14% had a BMI ≥ 95th percentile, 14.29% had MS, 34.29% were hypertensive and 28.57% had dyslipidemia.
Conclusion. Obesity and its co-morbidities were prevalent among Saudi pediatric patients. We recommend preventing excessive weight gain through the promotion of a

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healthy lifestyle, family educational seminars and the reinforcement of indoor exercises.

Obesity is a condition that triggers the development of many diseases. Recently, all over the world pediatricians are reporting an alarming increase in obesity among children and adolescents.[1, 2] Such dilemma renders the child prone to insulin resistance, dyslipidemia, type 2 diabetes mellitus (T2DM) and ultimately metabolic syndrome (MS).[3] Pediatric diabetologists have recognized an emerging epidemic of T2DM among youth over the past 20 years, this phenomenon parallels increased prevalence of obesity in children and adolescents.[4] Furthermore, the incidence of pediatric T2DM increased 10-fold from 1982 to 1994.[5] The prevalence of hypertension is on the rise among overweight Children.[6] The definition of MS among children and adolescents varies greatly from that in adults, although several studies have utilized the adult criteria and modified them in various ways to be more applicable on the pediatric population.

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Such adult variables were modified for pediatrics by utilizing the age specific and gender specific percentiles and the Body Mass Index (BMI), blood pressure and lipid percentiles, all in light of establishing a feasible definition of MS among rapidly growing children and adolescents.[7-10] Our objectives are to establish the following: 1) the prevalence of hyperinsulinism among overweight and obese pediatric patients; 2) the prevalence of T2DM among those with hyperinsulinism; 3) the prevalence of (MS) and its components among T2DM pediatric patients.

Materials and methods

Study design and site

This is a retrospective cross-sectional study conducted on Saudi overweight and obese children and adolescents attending the pediatrics diabetes clinic at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia, from year 2006 to 2010. Serum insulin levels were reviewed for all cases. Further investigations were reviewed for those with hyperinsulinism mainly to assess the prevalence of T2DM among them. An extensive chart review was conducted to determine the Tanner staging, age of diagnosis with T2DM, family history of T2DM, blood pressure, waist circumference, weight and height for the calculation of the BMI. Furthermore, a review of their serum lipid profile, uric acid and C-peptide was conducted. In T2DM female adolescents, we assessed the prevalence of polycystic ovarian syndrome (PCOS) by using the revised Rotterdam criteria and LH/FSH ratio (described below). This study was approved by the biomedical ethics department at King Abdul-Aziz University, Faculty of Medicine.

Study subjects

The study population was 387 patients aged from 2 to 18 years. Mean, standard deviation (SD) and median for age were 13.46±3.22 and 14 years, respectively. Of the study population, 37% were males, 63%

were females, 40% were prepubertal and 60% were pubertal, Tanner staging system was used for the latter classification.

The inclusion criteria were: patient's age between 2 and 18 years old, BMI≥85th centile on age and gender specific center for disease control (CDC) BMI chart. The exclusion criteria were: presence of endocrine diseases causing the child overweight and obesity and pediatric patients on steroids.

MS

MS in childhood was defined by de Ferranti *et al.*, as the presence of three of the following; fasting serum glucose ≥6.1 mmol/L, waist circumference >75th percentile, triglycerides ≥1.1 mmol/L, high density lipoprotein HDL-C <1.3 mmol/L and systolic and/or diastolic blood pressure >90th percentile plotted on pediatric charts.[11]

T2DM and hyperinsulinism

The diagnosis of T2DM was established via fasting serum glucose ≥7 mmol/L. Random or two-hour postprandial serum glucose ≥11.1 mmol/L with classic symptoms of hyperglycemia and HbA1c ≥6.5% (4.6-5.7%). Hyperinsulinism was established by elevated serum levels of insulin >17 mIU/L (3-17 mIU/L) and C-peptide >1.47 nmol/L (0.37-1.47 nmol/L). Serum uric acid >428 umol/L was considered elevated (155-428 umol/L). Acanthosis nigricans AN was diagnosed clinically.

BMI

Overweight and obesity for children and adolescents were defined respectively as ≥85th and 95th percentile of BMI, respectively, plotted on the CDC BMI charts. Obesity was further divided into stage 1 and stage 2. Stage 1 obesity was defined as BMI between 95th and 99th percentiles. Stage 2 obesity was defined as BMI>99th percentile. Age and gender specific BMI z-scores were used as a continuous dependant variable for children and adolescents within our cohort. The BMI z-score was cal-

culated using the world health organization WHO age and gender specific BMI charts. A BMI z-score between 1 and 2 was considered as overweight, a BMI z-score >2 was considered as obese. Weight and height measurements at King Abdul-Aziz University Hospital are taken according to the CDC guidelines and are measured in kilograms and centimeters, respectively.[12] Weight and waist circumference measurements were taken with cloth. Waist circumference was measured in centimeters.

Hypertension

Hypertension in children and adolescents was defined as systolic blood pressure SBP and/or diastolic blood pressure DBP≥95th percentile, plotted on the CDC age-gender specific blood pressure charts and measured on ≥3 separate occasions.

Dyslipidemia

Dyslipidemia was defined as the presence of any of the following: cholesterol >5.2 mmol/L, triglycerides TGL>2.3 mmol/L, and low density lipoprotein (LDL) >3.57 mmol/L. High density lipoprotein (HDL)<0.9 mmol/L, was considered low. Reference ranges are reported in Table I.

PCOS

The diagnosis of PCOS was established via using the Rotterdam consensus on diag-

nostic criteria for PCOS.[13] The revised 2003 criteria were: 1) oligo- and/or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; 3) polycystic ovaries, by pelvic ultrasound, specifically looking for the presence of 12 or more follicles in each ovary measuring 2±9 mm in diameter, and/or increased ovarian volume (>10 mL). The presence of two out of three criteria confirmed the diagnosis of PCOS. The LH to FSH ratio was also calculated, a ratio greater than 1:1 was considered elevated. Normal ranges for LH, FSH and dehydroepiandrosterone sulfate DHEA used in this study were (0.8-6.1 mIU/L), (1.6-11 IU/L) and (between 5th and 95th percentile for age and gender), respectively. Additionally, we defined the onset of normal puberty as the development of thelarche by the age of 8 years or older in girls and testicular enlargement of >4 mL in volume, measured by Prader's orchidometer, by the age of 9 years or older in boys.

Laboratory methodology

At King Abdul-Aziz University Hospital serum glucose, HbA1c, HDL, cholesterol, triglycrides, LDL and uric acid are measured via the SEIMENS Dimension clinical chemistry system. GLU Flex reagent cartridge is used for measuring serum glucose and HbA1c via the hexokinase method. AHDL Flex reagent cartridge is used for measuring serum HDL. The method is a two reagent format based on accelerating the reaction

TABLE I.—*Descriptive characteristics of variables surveyed in the presented study and the corresponding reference ranges.*

	Mean	Standard Deviation	Median	Reference ranges
Age, years	13.46	±3.22	14	-
Weight for age percentile	75.9	±32.8	95	12
Height for age percentile	45.2	±31	50	12
BMI z-score	1.9	±0.86	2.05	-
Abdominal Circumference, cm	100.1	±19.47	100	-
Random glucose, mmol/L	9	±1.67	8.3	(5 to 7.2)
Uric acid, umol/L	311	±76.22	301	(155-428)
Total cholesterol, mmol/L	4.66	±1.43	4.65	(0-5.2)
Triglycerides, mmol/L	2.163	±2.41	1.18	(0.3-2.3)
HDL, mmol/L	1.11	±0.33	0.975	(0.9-1.55)
LDL, mmol/L	2.84	±1.04	3.205	(0-3.57)

of cholesterol oxidase with non-HDL unesterified cholesterol and dissolving HDL selectively via a specific agent. CHOL Flex reagent cartridge is used to measure cholesterol. The method is hydrolysis of cholesterol esters into free cholesterol, which is then oxidized. The absorbance is used to measure total cholesterol using a polychromatic endpoint technique. TGL Flex reagent cartridge is used to measure serum triglycerides. The method is the incubation of the sample with lipoprotein lipase and then catalysis with glycerol kinase. The change in absorbance is used to measure triglycerides using the bichromatic endpoint technique. LDLC Flex reagent cartridge is used to measure serum LDL. The method used is a cholesterol assay that directly measures LDLC levels in the serum. It's a two reagent format, used to solubilize non-LDL particles and then solubilize the remaining LDL particles which are oxidized producing a color that is measured using a bichromatic endpoint technique. URCA Flex reagent cartridge is used to measure serum uric acid. The method used is conversion of uric acid by uricase to allantoin, the change in absorbance is measured using a bichromatic endpoint technique.

Serum DHEA, LH and FSH are measured via the cobas clinical chemistry system trademark of Roche diagnostics. The method is an immunoassay for the in vitro quantitative determination of DHEA, LH and FSH in the serum. The method is done via 2 incubation assays of the sample using the competition principle for DHEA and the sandwich principle for LH and FSH. The first assay is done to form an immunocomplex and the second to bind the complex forming a solid phase. Unbound substances are removed. Then the reaction mixture is aspirated magnetically onto an electrode, a photomultiplier is used to measure a voltage induced emission. Results are determined via a calibration curve.

Statistical analysis:

The data was gathered on a datasheet from the university hospital database and patients clinical charts. All laboratory information was taken from the university hospital centralized laboratory phoenix database system. Tables were exported to the SPSS (version 16) and Epi info (version 3.5.1) software, where the data was analyzed and the formation of tables commenced. Descriptive characteristics were calculated from the data collected. Characters such as mean, median and SD for variables collected in this study were calculated. Analysis of quantitative data was done via the two-sample t-test. The level of significance was expressed as P-value; $P>0.05$=non- significant (NS), $P<0.05$=significant (S), and $P<0.001$=highly significant (HS).

Results

Hyperinsulinism

Of the study population 173 patients (44.7%) had hyperinsulinemia, 35 of which (20.23%) had T2DM. Overall mean, SD and median for serum insulin were 40.12±20.45 and 32.2 mIU/L. Mean and SD for serum insulin were 30.04±12.7 mIU/L in prepubertal children and 46.15±22.1 mIU/L in pubertal children and adolescents, P=0.0136 (S). Mean and SD of serum insulin were 42.32±20.6 mIU/L in T2DM obese patients and 32.42±27.67 mIU/L in non-diabetic obese children and adolescents, P=0.024 (S). AN was present in 28.75% of T2DM pediatric patients.

MS among children and adolescents with T2DM

The overall prevalence of (MS) among T2DM pediatric patients was 14.29%. Only 1 of those with (MS) was prepubertal. The prevalence of each of the diagnostic components were 31.43% had elevated fasting serum glucose, 23% had a waist circumference > 95th percentile, 28.57% had high triglyceride levels, 22.86% had low levels of HDL and 14% had high blood pressure (11 % for SBP and 3% for DBP). Of (T2DM)

pediatric patients, 2.86% had hyperuricemia.

T2DM among children and adolescents

The overall prevalence of T2DM was 9.04%. Mean, SD and median for the age of diagnosis with (T2DM) were 13.1±2.02 and 13.5 years, only 20% were > 13 years of age at the time of diagnosis. Of those with (T2DM), 28.57% were pre-pubertal. Of (T2DM) pediatric patients, 77.14% had an HbA1c<10%. Mean, SD and median for HbA1c were 8.52±1.53 and 7.7%. 40% of (T2DM) pediatric patients complained of diabetic symptoms, 5.71% presented with diabetic ketoacidosis (DKA) and 37.14% had a positive family history of (T2DM).

BMI of children and adolescents with (T2DM):

Among T2DM pediatric patients, 62.86% had a BMI ≥ the 85th percentile and 37.14% had a BMI≥95th percentile. Mean, SD and median for the BMI z-score were 2.54±0.4 and 2.46% for obese children and adolescents and 1.42±1.4 and 1.1% for overweight children and adolescents, P=0.002 (S). In our cohort, obesity was higher in females than males, 71.43% of obese children were females and 28.57% were males. The majority of obese children had stage 2 obesity 85.71%, while only 21.43% had stage 1 obesity. The prevalence of stage 2 obesity was higher among obese females than males (80% in females and 75% in males).

Hypertension among children and adolescents with T2DM

In our cohort, 34.29% of T2DM pediatric patients had a SBP and/or DBP≥95th percentile, thus were considered hypertensive. Elevated SBP was present in 83.3% and 16.67% had elevated DBP. Mean, SD and median were 124±18.73, 120.5 mmHg for systolic blood pressure and 71.667±10.56, 73.5 mm/Hg for diastolic blood pressure among T2DM children and adolescents, only 8.83% of hypertensive children and adolescents were on hypertensive medication.

Dyslipidemia among children and adolescents with T2DM:

In our cohort, the overall prevalence of dyslipidemia was 28.57%. Of T2DM pediatric patients, 25.71% had elevated triglycerides, 2.86% had elevated LDL, 8.5% had low levels of HDL and 20% had elevated serum total cholesterol.

PCOS among pubertal overweight and obese females with T2DM

Of the female population in our cohort, 60.87% were pubertal and had already started their menses, 42.86% of menstruating girls complained of irregular cycles and 34.78% had AN. The prevalence of PCOS in our cohort was 21.74%. All pubertal females with PCOS had a BMI>85th percentile, 40% had a BMI>95th percentile, all complained of menstrual irregularities, 60% had MS and 80% had AN, all had serum DHEAS>95th age-gender specific percentile and all showed multiple ovarian cysts by pelvic ultrasound. Mean, SD and median for the LHFSH ratio among pubertal females with PCOS were 1.735±0.162 and 1.74, respectively. All pubertal females with PCOS had an LH/FSH ratio of >1:1.

Discussion

Children and adolescents develop secondary hyperinsulinism as a result of obesity. The stress of obesity and the increased demand for insulin at the time of adolescence explain the largely pre-pubertal and pubertal onset of T2DM in children and adolescents.[14] In our cohort, the prevalence of secondary hyperinsulinism (44.7%) was lower than what was reported by a study conducted in San Diego, California (51.9%)[15] and higher than another study in London (40%).[16] The prevalence of T2DM in our population (9.04%) was within the American Diabetes Association (ADA) issued con-

sensus statement regarding the prevalence of T2DM in children and adolescents. The ADA stated that T2DM now accounts for as many as 8 to 46% of new cases of pediatric diabetes.[17] Several studies attempted to establish the prevalence of T2DM among children and adolescents, A study in Thailand had a higher prevalence than what we reported (17.9%),[18] two other studies in Germany reported a lower prevalence (1.5%) and (5.9%).[19, 20]

Dyslipidemia in children and adolescents has become a frequent clinical condition, especially due to the increase in overweight and obesity prevalence in this age range.[21] Dyslipidemia was prevalent among T2DM children and adolescents within our cohort (28.57%), however it was less than what other studies have reported, range of dyslipidemia (30% to 55%).[16, 22-24] The global increase in the prevalence of obesity among children and adolescents is also favoring an increase in blood pressure and therefore, the prevalence of arterial hypertension.[25] We reported the prevalence of hypertension within our cohort as 34.29%, two other studies in London and Turkey reported a lower prevalence (32% and 22%, respectively).[16, 24] MS was originally described by Reaven in 1988 as "syndrome X" or "insulin resistance syndrome".[26] The prevalence of MS in studies using the WHO criteria was: 4.5% to 38.7%. The overall prevalence of (MS) in our cohort was within the prevalence range used by the WHO.[27] Furthermore, the overall prevalence of MS within our cohort (14.29%) was higher than a study in the USA reported (10%),[11] and less than what studies in Turkey, Spain and Bolivia have reported (27.2%, 18.6% and 36%, respectively).[24, 28, 29] We also reported that the prevalence of MS was higher among females with T2DM than males, other studies reported a higher prevalence among males,[28] and some reported no difference in the prevalence with respect to gender.[24, 29] Furthermore, the prevalence of MS was greater among pubertal children and adolescents then pre-pubertal children in our cohort. As for the prevalence of the diagnostic components for MS, there were

great variation between the present study and other publications.[28, 29] For instance, we reported low HDL in 22.8% of MS cases while, some reported a higher percentage of low HDL as a diagnostic component of MS [28] and others reported lower readings.[29]

In the present study, all enrolled patients had a BMI>85th percentile. The prevalence of obesity within our cohort was slightly higher than what was reported by a recently published Saudi Arabian study that attempted to establish a baseline for the national prevalence rates for overweight, obesity and severe obesity in Saudi children and adolescents.[30] Another study conducted in the eastern province of Saudi Arabia reported that the prevalence of obesity was higher in male than female students (19.3% *versus* 11.8%).[31] We reported a much higher prevalence of obesity than the latter study (37.14%). Both local studies however reported a higher prevalence of obesity among males,[30, 31] as we reported a higher prevalence among females. Overweight and obesity are major contributing factor in the development of PCOS.[32] Hyperinsulinemia promotes ovarian and adrenal androgen output, suppress hepatic production of sex hormone binding globulin and raises free circulating testosterone. Together, hyperandrogenism and hyperinsulinemia impair ovarian follicle development. Long term exposure to high levels of LH promotes ovarian androgen output. LH excess seems to be a result of an increased frequency of gonadotrophin releasing hormone pulses from the hypothalamus. The abnormal hormonal milieu also probably contributes to incomplete follicular development which results in polycystic ovarian morphology. The prevalence of PCOS in our population (21.74%) was higher than what was reported by a study conducted by the University of Alabama (6.6%).[33] MS had a significantly higher prevalence among females with PCOS in our cohort (60%) than what a study in York, England reported, range of MS and PCOS prevalence overlap was 1.6% to 46.4%.[34] Children with AN showed significantly more glucose intolerance and T2DM compared with those

children without AN. In fact, some studies proposed that AN can be used as a reliable clinical index in the detection of hyperinsulinemia and glucose intolerance.[35, 36] Compared to other studies conducted in China and New Mexico, where the prevalence of AN was 25% and 17%, respectively,[35, 37] the prevalence of AN within our cohort (28.75%) was rather high.

Conclusions

In conclusion, the prevalence of obesity was rather high in our population, as was the prevalence of some of its related co-morbidities, mainly T2DM and hypertension. We believe that an endemic of unhealthy indulgences is sweeping across children and adolescents within our populace and is responsible for the increasing blight that is MS and its components, which is mainly due to behavioral and environmental factors. Although, we had a lower prevalence of dyslipidemia when compared to others, we would like to see it decrease even further in order to prevent its related consequences. Hence our recommendations, which are indeed common knowledge, nonetheless poorly practiced. We would like to tackle a number of issues we believe might give pediatricians worldwide a fighting chance against the menace that is obesity. Firstly, we address the dietary habits of children and adolescents within our population. Addiction to fast food, which has a high content of sodium, simple carbohydrates, saturated fats and calories, is ever so prevalent. We believe this is due to several reasons; lack of family education seminars and the abundance of fast food establishments accessible to our youth are the most salient of reasons. As many studies have proven, parents have an integral role in the management of childhood obesity.[38] Thus we recommend the promotion of family education seminars in Saudi Arabia, mainly to increase the awareness of obesity and its co-morbidities and the reinforcement of a healthier diet, primarily one with high fiber, low sodium, simple carbohydrates and saturated fats content.

Furthermore, the availability of specialized pediatric dietitians, whom can give more appealing advice to children, will ultimately improve the overall adherence of the child to a healthier life style. Saudi Arabia has a desert landscape with a harsh climate, such conditions discourage children and adolescents from outdoor activities, mainly exercises and sports. The availability of media based distractions is another major contributor to the sedentary life style children and adolescents abide by in our population. In order to overcome such issues, we recommend the promotion of indoor exercises for at least 30 minutes per day and to limit television usage hours to a maximum of two hours per day.

Riassunto

Prevalenza di iperinsulinismo, diabete mellito di tipo 2 e sindrome metabolica tra pazienti pediatrici obesi in Arabia Saudita

Obiettivo. L'obesità e il sovrappeso stanno crescendo a un ritmo allarmante tra bambini e adolescenti, comportando un aumento nell'incidenza delle loro comorbilità associate. Obiettivo del presente studio è stato quello di determinare: 1) la prevalenza dell'iperinsulinismo tra pazienti pediatrici sovrappeso e obesi; 2) la prevalenza del diabete mellito di tipo 2 (DMT2) in pazienti pediatrici iperinsulinemici; 3) la prevalenza della sindrome metabolica (SM) e delle sue componenti in pazienti pediatrici con DMT2.

Metodi. Abbiamo condotto uno studio trasversale retrospettivo su pazienti pediatrici obesi e sovrappeso presso il centro pediatrico di cura del diabete dell'ospedale universitario di King Abdul-Aziz, Jeddah, Arabia Saudita, tra il 2006 e il 2010. Il livello sierico di insulina è stato misurato in 387 pazienti (di età compresa tra i 2 e i 18 anni). I pazienti con iperinsulinismo sono stati sottoposti a ulteriori esami per valutare la prevalenza del DMT2 e la prevalenza della SM in pazienti con DMT2.

Risultati. La prevalenza complessiva dell'iperinsulinismo e del DMT2 è stata rispettivamente del 44,7% e del 9,04%. Tra i bambini e gli adolescenti con DMT2, il 62,86% aveva un indice di massa corporea (IMC) ≥85° percentile, il 37,14% aveva un IMC≥95° percentile, il 14,29 % aveva SM, il 34,29% era iperteso e il 28,57% soffriva di dislipidemia.

Conclusioni. L'obesità e le sue comorbilità erano prevalenti tra i pazienti pediatrici in Arabia Saudita. Raccomandiamo di prevenire un eccessivo aumento di peso mediante la promozione di uno stile di vita

sano, seminari sull'educazione familiare e il rafforzamento degli esercizi indoor.

Parole chiave: Iperinsulinemia - Sindrome metabolica X - Obesità - Indice di massa corporea - Diabete mellito di tipo 2.

References

1. Kiess W, Galler A, Reich A, Müller G, Kapellen T, Deutscher J et al. Clinical aspects of obesity in childhood and adolescence. Obes Rev 2001;2:29-36.
2. Berenson GS. Obesity-a critical issue in preventive cardiology: the Bogalusa Heart Study. Prev Cardiol 2005;8:234-41.
3. Verhulst SL, Schrauwen N, Haentjens D, Rooman RP, Van Gaal L, De Backer WA et al. Sleep-disordered breathing and the metabolic syndrome in overweight and obese children and adolescents. J Pediatr 2007;150:608-12.
4. Glaser NS. Non-insulin-dependent diabetes mellitus in childhood and adolescence. Pediatr Clin North Am 1997;44:307-37.
5. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128:608-15.
6. Reich A, Müller G, Gelbrich G, Deutscher K, Gödicke R, Kiess W. Obesity and blood pressure results from the examination of 2365 schoolchildren in Germany. Int J Obes Relat Metab Disord 2003;27:1459-64.
7. Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. J Clin Endocrinol Metab 2004;89:108-13.
8. Goodman E, Daniels SR, Morrison JA, Huang B, Dolan LM. Contrasting prevalence of and demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. J Pediatr 2004;145:445-51.
9. Molnar D. The prevalence of the metabolic syndrome and type 2 diabetes mellitus in children and adolescents. Int J Obes Relat Metab Disord 2004; 28:S70-S74.
10. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350:2362-74.
11. 11 de Ferranti SD, Gauvreau K, Ludwig DS, Newfeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the third national health and nutrition examination survey. Circulation 2004; 110: 2494-7.
12. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R et al. CDC growth charts: United States. Adv Data 2000;314:1-27.
13. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 onsensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
14. Rosenbloom AL. Age-related plasma insulin response to glucose ingestion in children and adolescents. IRCS Metab Nutr: Pediatr 1974;2:1210.
15. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. JAMA 2003;289:1813-9.

16. Viner RM, Segal TY, Lichtarowicz-Krynska E, Hindmarsh P. Prevalence of the insulin resistance syndrome in obesity. Arch Dis Child 2005;90:10-4.
17. American Diabetes Association. Type 2 diabetes in children and adolescents. Pediatrics 2000;105:671-80.
18. Likitmaskul S, Kiattisathavee P, Chaichanwatanakul K, Punnakanta L, Angsusingha K, Tuchinda C. Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity. J Pediatr Endocrinol Metab 2003;16:71-7.
19. Wabitsch M, Hauner H, Hertrampf M, Muche R, Hay B, Mayer H et al. Type II diabetes mellitus and impaired glucose regulation in Caucasian children and adolescents with obesity living in Germany. Int J Obes Relat Metab Disord 2004;28:307-13.
20. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Grüters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity a problem that is no longer restricted to minority groups. Eur J Endocrinol 2004;151:199-206.
21. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
22. Newfield RS, Dewan AK, Jain S. Dyslipidemia in children with type 2 diabetes vs. obesity. Pediatr Diabetes 2008;9:115-21.
23. Sellers EA, Yung G, Dean HJ. Dyslipidemia and other cardiovascular risk factors in a Canadian First Nation pediatric population with type 2 diabetes mellitus. Pediatr Diabetes 2007;8:384-90.
24. Atabek ME, Pirgon O, Kurtoglu S. Prevalence of metabolic syndrome in obese Turkish children and adolescents. Diabetes Res Clin Pract 2006;72:315-21.
25. MacMahon SW, Blacket RB, Macdonald GJ, Hall W. Obesity, alcohol consumption and blood pressure in Australian men and women. The National Heart Foundation of Australia Risk Factor Prevalence Study. J Hypertens 1984;2:85-91.
26. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
27. Moraes AC, Fulaz CS, Netto-Oliveira ER, Reichert FF. Prevalence of metabolic syndrome in adolescents: a systematic review. Cad Saude Publica 2009;25:1195-202.
28. Caceres M, Teran CG, Rodriguez S, Medina M. Prevalence of insulin resistance and its association with metabolic syndrome criteria among Bolivian children and adolescents with obesity. BMC Pediatr 2008;8:31.
29. Tapia Ceballos L, López Siguero JP, Jurado Ortiz A. Prevalence of metabolic syndrome and its components in obese children and adolescents. An Pediatr (Barc) 2007;67:352-61.
30. El Mouzan MI, Foster PJ, Al Herbish AS, Al Salloum AA, Al Omer AA, Qurachi MM et al. Prevalence of overweight and obesity in Saudi children and adolescents. Ann Saudi Med 2010;30:203-8.
31. Al-Almaie SM. Prevalence of obesity and overweight among Saudi adolescents in Eastern Saudi Arabia. Saudi Med J 2005;26:607-11.
32. Diamanti-Kandarakis E. Role of obesity and adiposity in polycystic ovary syndrome. Int J Obes (Lond) 2007;31;S31-2.
33. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745-9.
34. Kandaraki E, Christakou C, Diamanti-Kandarakis

E. Metabolic syndrome and polycystic ovary syndrome... and vice versa. Arq Bras Endocrinol Metabol 2009;53:227-37.
35. Fu JF, Liang L, Dong GP, Jiang YJ, Zou CC. Obese children with benign acanthosis nigricans and insulin resistance: analysis of 19 cases. Zhonghua Er Ke Za Zhi 2004;42:917-9.
36. Yamazaki H, Ito S, Yoshida H. Acanthosis nigricans is a reliable cutaneous marker of insulin resistance in obese Japanese children. Pediatr Int 2003;45:701-5.
37. Kong AS, Williams RL, Smith M, Sussman AL, Skipper

B, Hsi AC *et al*. Acanthosis nigricans and diabetes risk factors: prevalence in young persons seen in southwestern US primary care practices. Ann Fam Med 2007;5:202-8.
38. Neyzi O, Furman A, Bundak R, Gunoz H, Darendeliler F, Bas F. Growth references for Turkish children aged 6 to 18 years. Acta Paediatr 2006;95:1635-41.