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RISK FACTORS FOR PREDIABETES IN OVERWEIGHT AND OBESE PRE-TEENS AND ADOLESCENTS

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Abstract

We looked for easy-to-use and predictable tools for identifying early risk of prediabetes (PD) and preventing the natural course to diabetes in overweight and obese pre-teens and adolescents. In 89 children (9-18 years) family history, body mass index (BMI), waist circumference (WC), acanthosis nigricans, blood pressure (BP), lipids, HbA1c, fasting glucose and oral glucose tolerance test were determined. We found 69 (77.5%) obese (BMI≥95th percentile) and 20 (22.5%) overweight children (BMI 85th-95th percentiles); thirty-six (41.4%) had PD; two had type 2 diabetes mellitus; two had metabolic syndrome. PD was associated with obesity (RR 5.1), HbA1c>5.5% (RR 2.5), acanthosis nigricans (RR=1.9), male gender (RR = 1.9), total cholesterol ≥170 mg/dL (RR=1.8), high BP (RR=1.7), urban area (RR = 1.6). BMI, WC, HbA1c and acanthosis nigricans are the major predictors for PD in this population. All blood values are both easy to measure and to accept by children, using finger prick method.

key words: *children, BMI, waist circumference, prediabetes, metabolic syndrome, risk factors.*

Introduction

Obesity and associated insulin resistance are considered the main risk factors for developing Type 2 diabetes mellitus (T2DM), regardless of genetic predisposition [1,2]. The current worldwide increase in obesity, already from childhood is associated with an increase of T2DM and prediabetes (PD), defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [3,4]. Using fasting glucose levels as the main screening tool appears to be insufficient in detecting children at risk [5]. When compared to First Nation children and adolescents in Canada and Native Americans, African Americans and Latin-

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Americans in the USA, while IFG and T2DM are still relatively rare in European children and adolescents, IGT occurred in 10% up to 30% of obese Caucasian children and adolescents [1,2]. Early identification of obese children and adolescents with IGT is beneficial because: IGT in childhood predicts T2DM later in life [6]; in adults, approximately 30% of patients with IGT, naturally will convert to T2DM within 5 years [7,8]; both children and adults with IGT have an increased risk of developing cardiovascular diseases (CVD) or cardiovascular risk factors prior to progressing to diabetes [9,10]. In addition, developing tools to predict which children are at greater risk could provide early diagnostic and therapeutic insights [6]. This could help provide therapeutic approaches that could slow down or even reverse the current trends of the obesity and T2DM pandemic in children and adolescents [6]. Additionally, a group of disorders that include obesity, insulin resistance, dyslipidemia, arterial hypertension and other metabolic anomalies (the metabolic syndrome - MS), is defined as associated with cardiovascular disease (CVD) [11,12] and it is possible that this syndrome is already affecting children even before they start school [13]. Furthermore, screening for the MS in overweight children and adolescents (as opposed to screening for individual diseases related to the syndrome) may help simplify screening strategies and raise awareness for the risk of both T2DM and CVD among overweight children both at the physician level and in the individual member or family level. Thus, it may simplify the need for multiple recommendations and guidelines for the identification and treatment in overweight children for separate disease processes (*e.g.* obesity, hypertension, T2DM), which in reality overlap due to a shared pathophysiology [14]. Regarding lipid levels, it is important to establish the natural course of the lipid profile in obese children, especially during puberty, because they are at increased risk for CVD and dyslipidemia. Questions remain unanswered as to whether obese children enjoy the same spontaneous improvement in lipid profile during puberty as do normal weight children or whether obesity overrides puberty and, therefore, exposes them to increased risk [15]. The oral glucose tolerance test (OGTT) is necessary for the diagnosis of IGT but is time-consuming and not easy to use on every obese pre-teen and adolescent. Therefore, some reliable and easy to use tools for identifying the risk of PD (IGT, FGT or both) in this population would be very helpful. Child compliance for measurement of weight, height, waist circumference (WC), blood pressure (BP), screening for acanthosis nigricans and asking the parents about family history (FH) is very good. Also, using the finger prick method, we could determine from a single drop, more markers: glucose, HbA1c and lipids: total cholesterol (TC), LDL-c, HDL-c, triglycerides and TC/HDL ratio). But, contrary to this collaborative attitude, when it comes to OGTT, many of children have a low compliance. The aim of our study was to identify if these markers, easy-to-use and accepted by the children, and witch of them, are predictable for identifying the risk for PD (IGT or/and FGT).

Material and Methods

We examined a sample of 89 overweight children aged 9 to 18 years, who asked for

nutrition counseling in our outpatient center, specialized in pediatric nutrition, diabetes and metabolic disease. Over 90% originated from Bihor County, the rest coming from the neighboring counties of Arad, Satu Mare and Cluj. None of the children suffered from known or diagnosed endocrine or syndromal disorders, or were on any medication. All the children were screened for the degree of overweight, using body mass index (BMI); abdominal obesity, using (WC); cardiovascular risk, using blood pressure (BP) values and lipids: total cholesterol (TC), HDL-c, LDL-c, triglycerides, TC/HDL-c ratio; and disturbed glucose metabolism, using fasting glucose, OGTT and HbA1c. We also looked for metabolic and cardiovascular family history (FH) and acanthosis nigricans. Two children were diagnosed with T2DM and were excluded from the study.

Height was measured to the nearest centimeter, using a rigid wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg in the morning, in underwear, using a calibrated balance scale. Acanthosis nigricans was examined at fingers, elbows, neck, armpits, and groin. We considered it positive if present in any anatomic zone. Obesity was defined by BMI (calculated as the weight in kilograms divided by the height in meters squared) above the 95th percentile and overweight by a BMI between 85th and 95th percentile, using Centers for Disease Control and Prevention guidelines and charts [16]. Abdominal obesity was defined by WC above 90th percentile for age and gender [17] and was measured using a tape measure at the umbilical level, just above the iliac crest, at the end of normal expiration [17]. Pubertal stage was determined according to Marshall and Tanner [18]. For pre-teens both girls and boys, Tanner II breast development or Tanner II genital staging were considered the earliest stages of puberty until Tanner V development at maturity. The lowest age of pre-teens was 9 years and the highest was 15 years. We considered adolescence between 16 and 18 years, after puberty developmental. Systolic and diastolic BP was measured at the right arm, twice, after a 10 min rest, in the supine position by using a calibrated sphygmo-manometer and averaged [19]. BP was measured twice: first when weight and height were measured, and the second time when all data were listed and the children return for nutritional counseling. We diagnosed hypertension when systolic or diastolic BP was above 90th blood pressure levels for gender by age and height percentile [20]. We considered only the second scheduled physical examination for each patient, using US Guidelines for Hypertension in Children and Adolescents by Age and Height Percentile [20]. Blood sampling was performed in the fasting status, according to European Reference Laboratory, methods and equipment.

Children were instructed to fast for 12 hours before tests, and compliance was determined by interview on the morning of the examination. They were on their regular diet for a minimum 4 weeks before lipid testing and none of them had recent severe illness in the previous month. Lipids (TC, LDL-c, HDL-c, triglycerides and TC/HDL) and HbA1c were measured from capillary blood, using CardioChek Analyzer (manufactured by Polymer Technology Systems, Inc. USA) and NycoCard Reader II (manufactured by Axis-Shield PoC AS). Intra- and interassay

variations for the concentrations (CV) of these variables were less than 5%. We diagnosed dyslipidemia (according to the current NCEP Expert Panel on Blood Cholesterol levels in Children and Adolescents [21]) in any of these circumstances: TC level equal or above 170 mg/dl, triglycerides value equal or above 125 mg/dL, (>95th percentile for triglycerides in boys and girls during childhood and adolescence); HDL-c level equal or less than 45 mg/dL and LDL-c concentration above 100 mg/dL; we considered at risk TC/HDL-c ratio above 4. An OGTT, according to World Health Organization (WHO) guidelines, was performed on all children [22]. IFG was defined as fasting serum glucose ≥ 100 to 125 mg/dL; IGT was defined by 2 h serum glucose between ≥ 140 to 199 mg/dL, diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, or 2 hour post-load glucose ≥ 200 mg/dL, according to the global guidelines of WHO, International Diabetes Federation and International Society of Pediatric and Adolescent Diabetes [23]. Linearity of the method for HbA1c determination with NycoCard Reader II is 3-18%, and normal values are in the range 4.5 to 6.3%.

Statistical analyses were carried out with EPIINFO, version 6.0. Significance was tested by student t-test and χ^2 method, as appropriate. We calculated the relative risk (RR) for PD related to different factors. Since the numbers of combinations of the risk factors are too many, we calculated only the quantitative, not qualitative combinations. A P value < 0.05 was considered significant. Data are presented as mean and standard deviation or percentages.

Results

The characteristics of the 87 analyzed overweight and obese children are listed in Table 1.

Table 1. Study characteristic of 87 overweight and obese pre-teens and adolescents (data as mean ± SD or percentage).

Age (years)	13.8±5.2
Gender	53.9% girls
Pre-teens	67.7%
Weight (kg)	77.3±20.6
Height (m)	161.3±12.3
BMI (kg/m²)	29.1±6.0
Waist circumference (cm)	101.6±15.3
Systolic BP(mmHg)	125.4±14.3
Diastolic BP(mmHg)	77.5±10.6
Triglyceride(mg/dL)	117.7±25.8
Total cholesterol (TC) (mg/dL)	158.9±21.3
HDL-c(mg/dL)	41.9±10.7
LDL-c(mg/dL)	93.1±14.8
TC/HDL(mg/dL)	4.08±1.33
Fasting glucose (mg/dL)	90.2±10.4
2 hours glucose (OGTT) (mg/dL)	127.6±17.7
HbA1c (%)	5.5±2.3

Prevalence of PD was 41.4% in whole study population. PD was significant more frequent in obese (50.7%) than overweight (10.0%) children ($p<0.01$) and 1.3 times greater in the pre-teen (44.8%) than in adolescent (34.5%) group ($p=0.03$). IFG

prevalence was 9.2%, and was seen only in the obese subpopulation (11.9%). The prevalence of IFG was significantly higher in pre-teens than in adolescents (12.1% versus 3.5%, p<0.01). The prevalence of IGT was 17.2%, significantly higher in obese than in overweight children (19.4% versus 10.0%, p=0.02), and in pre-teens than in adolescents (20.7% versus 10.3%, p=0,01). Combined IFG and IGT was seen in 14.9% of subjects, more frequently in adolescents than in pre-teens (20.7% versus 12.1%, p<0.01), but only in the obese subpopulation (19.4%). (Table 2)

The prevalence of the risk markers for **IFG, IGT and IFG with IGT** are presented in Table 3.

Table 2. Prediabetes (IFG, IGT, IFG+IGT) in overweight and obese pre-teens and adolescents (data as number and percentage).

Parameters	IFG alone		IGT alone		IFG+IGT		PD	
	Nr.	%	Nr.	%	Nr.	%	Nr.	%
Pre-teens (total 58; 67.4%)	7	12.1	12	20.7	7	12.1	26	44.8
Overweight	0	0.0	1	9.1	0	0.0	1	9.1
Obese	7	14.9	11	23.4	7	14.9	25	53.2
Adolescents (total 29; 32.6%)	1	3.5	3	10.3	6	20.7	10	34.5
Overweight	0	0.0	1	11.1	0	0.0	1	11.1
Obese	1	5.0	2	10.0	6	30.0	9	45.0
Total	8	9.2	15	17.2	13	14.9	36	41.4
Overweight	0	0.0	2	10.0	0	0.0	2	10.0
Obese	8	11.9	13	19.4	13	19.4	34	50.7

Table 3. Prevalence of risk markers for IFG, IGT & IFG+IGT (data as number and percentage).

ITEMS	IFG 25.8%		IGT 31.5%		IFG+IGT 14.6%	
	No.	%	No.	%	No.	%
Weight						
Overweight	0	0.0	2	10.0	0	0.0
Obese	8	11.9	13	19.4	13	19.4
Gender						
Girls	1	2.1	7	14.6	6	12.5
Boys	7	18.0	8	20.5	7	18.0
Area						
Urban	7	14.3	13	26.5	11	22.5
Rural	1	5.6	2	11.1	2	11.1
Family history	2	6.1	5	15.2	6	18.2
WC>90th percentile	8	11.4	14	20.0	11	15.7
Acanthosis nigricans	5	8.9	12	21.4	11	19.6
Blood pressure >90th percentile	6	11.5	10	19.2	10	19.2
Lipids						
TC ≥170 mg/dl	4	12.1	7	21.2	8	24.2
LDLc>110mg/dl	3	9.1	6	18.2	7	21.2
HDLc<45mg/dl	2	4.1	11	22.5	5	10.2
Triglycerides≥125mg/dl	3	9.1	9	27.3	4	12.1
TC/HDL >4	3	4.9	14	23.0	8	13.1
HbA1c >5.5%	6	13.3	11	22.2	10	24.4

We found that any combination of 3 factors increases the risk of PD 1.7 times (RR=1.7). (Table 4)

Table 4. The predictive risk factors for PD (data as relative risk) for the whole study group.

Total
Obesity (RR=5.0) Abdominal obesity (RR=2.6) HbA1c>5,5% (RR=2.4) Acanthosis nigricans (RR=1.9) Male gender (RR=1.9) Total cholesterol ≥170 mg/dL (RR=1.8) High BP (RR=1.7) Urban area (RR=1.6) LDL-c>100 mg/dL (RR=1.3) HDL-c≤ 45 mg/dL (RR=1.1)

Table 5. The predictive risk factors for PD in Pre-teens and Adolescents (data as relative risk).

Pre-teens (9-15 years)	Adolescents (16-18 years)
Obesity (RR=5.8) Abdominal obesity (RR=4.0) Acanthosis nigricans (RR=3.7) HbA1c>5,5% (RR=2.5) Total Cholesterol ≥170 mg/dL (RR=1.9) HDL-c≤45mg/dL (RR=1.7) High BP (RR=1.5) Triglyceride ≥ 125 mg/dL (RR=1.5) LDL-c >100 mg/dL (RR=1.2)	Obesity (RR=6.3) HbA1c>5,5% (RR=4.9) High BP (RR=2.1) Family history (RR=2.1) Abdominal obesity (RR=1.8) Total cholesterol ≥170 mg/dL (RR=1.6) LDL-c >100 mg/dL (RR= 1.6) TC/HDL>3,3 (RR=1.4) Acanthosis nigricans (RR=1.3) HDL-c ≤45mg/dL (RR=1.1)

The **risk factors** for PD in the **pre-teen subpopulation** were: obesity (RR=5.8), abdominal obesity (RR=4.0), acanthosis nigricans (RR=3.7), HbA1c>5.5% (RR=2.5), TC ≥170 mg/dL (RR=1.9), HDL-c≤45mg/dL (RR=17), high BP (RR=1.5), triglycerides ≥ 125 mg/dL (RR=1.5), and LDL-c>100 mg/dL (RR=1.2). (Table 5)

The risk factors for PD in the **adolescent subpopulation** were: obesity (RR=6.3), HbA1c>5,5% (RR=4.9), hypertension (RR=2.1), FH (RR=2.1), abdominal obesity (RR=1.8), TC ≥170 mg/dL (RR=1.6), LDL-c >100 mg/dL (RR= 1.6), TC/HDL≥3,3 (RR=1.4), acanthosis nigricans (RR=1.3) and HDL-c ≤45mg/dL (RR=1.1). (Table 5)

It should be noted that many of the assocations presented in Tables 4 and 5 are not independent.

Discussions

Our study indicated that 41.4% of overweight and obese children in a population from the western part of Romania have PD during puberty and adolescence. IGT had a high prevalence in children with dyslipidemia, from urban area and when acanthosis nigricans was present (Table 3). IFG was identified particularly in the male subpopulation, from urban area, when cardiovascular risk factors were present and in the obese subpopulation (Table 3). PD (IFG alone, IGT alone and IFG with IGT) had a high prevalence when dyslipidemia was present, in urban area, when acanthosis nigricans was present and in the obese subpopulation. Increased HbA1c had the highest prevalence only in the obese subpopulation having IFG with IGT (Table 3).

Our findings are similar with those of another study that reported a higher prevalence of IGT in males [24], but in contrast with a more recent study [25] that showed no gender difference. Possible explanations for the higher prevalence of PD in boys might include: the higher number of boys during puberty than in the adolescence group in comparison with girls; the higher number of boys from urban area in comparison with girls and the more positive FH in boys than in girls.

The most frequent disturbance of PD was IGT (31.5%), indicating the importance of OGTT in diagnosing of PD in this subpopulation, wich would remained unknown if only fasting glucose would be determined.

Onset of puberty is associated with an increase in insulin resistance [15,26], suggesting that this change could be the cause for the high prevalence of PD in our study. Accordingly, we found as predictive markers, both abdominal obesity (RR=4.0) and acanthosis nigricans (RR=3.7), both markers of insulin resistance in pre-teens subpopulation. However, further operating factors may be involved. Thus concentrations of sex hormones and adipocytokines change dramatically during pubertal development. Adiponectin, for example, decreases with the onset of puberty and is negatively correlated to insulin resistance and many cardiovascular risk factors [27].

Furthermore, this study suggests that factors of the MS such as abdominal obesity, low HDL-c, high value of triglycerides and elevated BP are associated with PD. Thus, TC, HDL-c, BP and triglycerides are predictable risk factors for PD in pre-teens while BP, TC, LDL-c are predictable risk markers for PD in adolescents (Table 4). These findings are in agreement with studies reporting a clustering of these cardiovascular risk factors among children with IGT [10,28] suggesting a link between these cardiovascular risk factors and PD (particularly IGT). In our population, MS was seen in 2 children according to IDF [29], but in 4 children when we apply De Ferranti definition [30].

This study indicated a direct relationship between obesity and prediabetes both in adolescents (RR=6.3) and in pre-teens (RR=5.8). Other similar studies demonstrated that extreme obesity in particular is a strong risk factor for IGT, and weight loss is associated with an improvement in IGT [3].

High prevalence of waist circumference $\geq 90^{th}$ percentile in PD (IFG, IGT and IFG+IGT) supports the role of abdominal obesity in the deterioration of glucose metabolism (Table 3).

Changes of HbA1c could predict PD, especially in obese adolescents (Table 5), but OGTT cannot be replaced by other measurements, such as HbA1c. In obese adolescents with components of the MS, especially in those with a positive FH, OGTT may be also helpful to detect T2DM. It was reported that children and adolescents with T2DM in Europe were predominately pubertal and suffered from hypertension and dyslipidemia [2,4]. In our study, 2 obese adolescents have been diagnosed with T2DM after OGTT, both having IFG. This is a reason more to recommend OGTT even in PD diagnosed only like IFG.

In SUMMARY, more than 40% of overweight and obese children during puberty and adolescence had PD in our non-random sample of overweight and obese children referred for nutritional advice in Western Romania. Most of them had IGT, suggesting the necessity of screening with OGTT in such at-risk populations. Risk factors for developing PD in this study were puberty, weight and BMI percentiles, deterioration of parameters of the MS when followed sequentially (increase of waist circumference, blood pressure, and lipids levels), HbA1c>5,5%, acanthosis nigricans, male gender and urban residence. Using the IDF definition, half of the children defined as MS

with the DeFerranti definitions are missed. Using finger prick method for HbA1c and lipids, we can decrease the burden of diagnosis and increase early identification of cardiometabolic risk factors in overweight and obese children. Screening for IGT is important for identifying PD in overweight patients who don't develop IFG, or in diagnosing T2DM.in obese children with IFG ...

REFERENCES

1. **Reinehr T, Andler W, Kapellen T et al.** Clinical characteristics of type 2 diabetes mellitus in overweight European Caucasian adolescents. *Exp Clin Endocrinol Diabetes* 113: 167–170, 2005.

2. **Reinehr T.** Clinical presentation of type 2 diabetes mellitus in children and adolescents. *Int J Obes (Lond)* 29: S105-S110, 2005.

3. **Reinehr T, Kleber M, Toschke AM.** Lifestyle intervention in obese children is associated with a decrease of the metabolic syndrome prevalence. *Atherosclerosis* 207: 174-180, 2009.

4. **Reinehr T, Schober E, Roth CL et al.** Type 2 diabetes in children and adolescents in a 2-year follow-up: insufficient adherence to diabetes centers. *Horm Res* 69: 107-113, 2008.

5. **Wiegand S, Maikowski U, Blankenstein O et al.** 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 151: 199-206, 2004.

6. **Morrison JA, Glueck CJ, Horn PS et al.** Pre-teen insulin resistance predicts weight gain, impaired fasting glucose, and type 2 diabetes at age 18-19 y: a 10-y prospective study of black and white girls. *Am J Clin Nutr* 88: 778-788, 2008.

7. **Rasmussen SS, Glümer C, Sandbaek A et al.** Progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screening programme in general practice: the ADDITION Study, Denmark. *Diabetologia* 50: 293-297, 2007.

8. **Rasmussen SS, Glümer C, Sandbaek A et al.** Determinants of progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screened population: 3 year follow-up in the ADDITION study, Denmark. *Diabetologia* 51: 249-257, 2008.

9. **Reinehr T, Kiess W, de Sousa G et al.** Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. *Metabolism* 55: 113-118, 2006.

10. **Reinehr T, Wunsch R, de Sousa G et al.** Relationship between metabolic syndrome definitions for children and adolescents and intima-media thickness. *Atherosclerosis* 199: 193-200, 2008.

11. **Chen W, Berenson GS.** Metabolic syndrome: definition and prevalence in children. *J Pediatr (Rio J)* 83: 1-2, 2007.

12. **Ferreira AP, Oliveira CE, Franca NM.** Metabolic syndrome and risk factors for cardiovascular disease in obese children: the relationship with insulin resistance (HOMA-IR). J *Pediatr (Rio J*) 83: 21-26, 2007.

13. **Harrell JS, Jessup A, Greene N.** Changing our future: obesity and the metabolic syndrome in children and adolescents. *J Cardiovasc Nurs* 21: 322–330, 2006.

14. **Cruz ML, Goran MI.** The metabolic syndrome in children and adolescents. *Current Diabetes Reports* 4: 53–62, 2004.

15. **Pinhas-Hamiel O, Lerner-Geva L, Copperman NM, Jacobson MS.** Lipid and insulin levels in obese children: changes with age and puberty. *Obesity (Silver Spring)* 15: 2825–2831, 2007.

16. **O'Neill JL, McCarthy SN, Burke SJ et al.** Prevalence of overweight and obesity in Irish school children, using four different definitions. *Eur J Clin Nutr* 61: 743–751, 2007.

17. **Fernández JR, Redden DT, Pietrobelli A, Allison DB.** Waist circumference percentiles in

nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr* 145: 439-444, 2004.

18. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45: 13-23, 1970.

19. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114: 555-576, 2004.

20. Brookes L. New US guidelines for hypertension in children and adolescents. *Medscape* **http**://www.nhlbi.nih.gov/**guidelines**/**hypertension**/child_tbl.htm, 2004.

21. Rohrs HJ, Schatz D, Winter WE, Davis V. Pediatric lipid disorders in clinical practice workup. *Medscape* http://emedicine.medscape.com/article/1825087-clinical, 2010.

22. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. www.who.int/**diabetes**/currentpublications/en, 1999.

23. IDF. Global IDF/ISPAD guideline for diabetes in childhood and adolescence. http://www.ispad.org/NewsDetail.html?ItemID=20, 2011.

24. Nguyen QM, Srinivasan SR, Xu J-H, Chen W, Berenson GS. Changes in risk variables of metabolic syndrome since childhood in pre-diabetic and type 2 diabetic subjects: the Bogalusa Heart Study. *Diabetes Care* 31: 2044-2049, 2008.

25. Kleber M, de Sousa G, Papcke S, Reinehr T. Risk factors for impaired glucose tolerance in obese children and adolescents *World J Diabetes* 1: 129-134, 2010.

26. Reinehr T, **Toschke AM.** Onset of puberty and cardiovascular risk factors in untreated obese children and adolescents: a 1-year follow-up study. *Arch Pediatr Adolesc Med* 163: 709-715, 2009**.**

27. Korner A, Kratzsch J, Gausche R, Schaab M, Erbs S, Kiess W. New predictors of the metabolic syndrome in children-role of adipocytokines. *Pediatr Res* 61: 640-645, 2007.

28. The DECODA Study Group. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care 26: 1770-1780, 2003.

29. Zimmet P, Alberti KG, Kaufman F et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatric Diabetes* 8: 299–306, 2007.

30. De Ferranti SD, Osganian SK. Epidemiology of paediatric metabolic syndrome and type 2 diabetes mellitus. *Diab Vasc Dis Res* 4: 285-296, 2007.