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**Original Article**

# Predicting Metabolic Syndrome in Obese Children and Adolescents: Look, Measure and Ask

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**Key Words**
Children · Metabolic syndrome · Obesity · Impaired glucose tolerance · Impaired fasting glucose

**Abstract**
***Objective:*** To verify in obese children whether or not the presence of i) high waist-to-height ratio (WHtR), ii) family history for type 2 diabetes (T2D) and iii) acanthosis nigricans (AN), singularly or together, might predict the occurrence of metabolic syndrome or prediabetes. ***Methods.*** 1,080 Italian obese children (567 females) were enrolled. Blood pressure, fasting plasma glucose, insulin, and lipids were measured, and oral glucose tolerance test (OGTT) was performed. The WHtR was calculated, family history for T2D was assessed, and the presence of AN was noticed. The odds ratios for showing metabolic syndrome and/or prediabetes according to the presence of these features were calculated. ***Results:*** The prevalence of metabolic syndrome was 29.2%. AN (OR1.81; $p = 0.002$) and WHtR higher than 0.60 (OR 2.24; $p < 0.0001$) were the clinical signs linked to higher risk for showing metabolic syndrome, and the odds raised significantly when these elements occurred simultaneously (OR 3.34; $p < 0.0001$). T2D family history (OR 2.36; $p = 0.01$) and WHtR higher than 0.60 (OR 2.32; $p = 0.009$) were the two features associated with increased odds of showing prediabetes. ***Conclusions:*** Three simple actions, i.e., looking at the patient, asking about T2D family history, and measuring WHtR, may represent a powerful tool in the hands of pediatricians to identify obese children with high cardiovascular and metabolic risk.


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## Introduction

According to the latest estimates from the International Obesity Task Force about 200 million school-age children worldwide are overweight or obese [1]. The most frightening complications of obesity are represented by the early occurrence of metabolic syndrome and type 2 diabetes (T2D) [2]. The link between metabolic syndrome and T2D is represented by insulin resistance, which plays a key role in the development of both diseases [3].

Several studies have tried to identify clinical and biochemical markers able to predict the development of cardiovascular and metabolic complications in obese subjects with early onset obesity [4]. Longitudinal studies have clearly shown that the majority of subjects who were obese during their childhood will become obese adults and that obesity and cardiovascular risk factors track from childhood to adulthood [4]. Cornerstone studies from the Bogalusa Heart Study, providing information on long-term metabolic changes from childhood to early adulthood, clearly showed that adverse levels of risk variables of metabolic syndrome, when present in childhood, accelerate the occurrence of T2D and cardiovascular issues [5].

Given the proportion of the occurrence of metabolic complications in obesity and its consequent financial negative impact on the healthcare systems, it has become a priority to identify precociously children at elevated risk for cardiovascular and metabolic complications of obesity.

In the present study we sought to verify whether the use of clinical signs easily detectable during the daily clinical practice may be helpful in identifying obese children at high risk for metabolic complications. In particular, we aimed to assess whether or not i) the knowledge of the patients' family history for T2D, ii) the presence of the acanthosis nigricans (AN), and iii) the assessment of the waist-to-height ratio (WHtR) may lead the clinician to a rapid identification of obese children with metabolic syndrome or prediabetes.

## Material and Methods

*Study Population*

1,080 Caucasian obese children and adolescents, consecutively referred to the Department of Pediatrics of the Second University of Naples (Italy) from January 1998 to June 2008, have been enrolled in this study. All had a BMI exceeding the 95th percentile for age and sex, with an age ranging from 4 to 17 years.

Procedures followed were in accordance with the Helsinki Declaration of Principles 1975 as revised in 1983. The ethical committee of the Second University of Study of Naples approved the study. Written informed consent and assent were obtained from all parents before any procedures.

Patients underwent physical examination. Body weight was measured by a balance beam scale, the child being undressed, height was measured by a Harpenden stadiometer, and BMI was calculated by dividing the weight for the height square. Z-scores for BMI were calculated by using the LMS method [6]. Waist circumference was measured with a flexible tape measure after normal expiration, at the midpoint between the lowest rib and the iliac crest while the subjects were standing. The average value of 2 waist measurements was obtained and, as indirect measure of the amount of abdominal fat, the ratio between waist and height, both measured in centimeters, was calculated. Pubertal stage according to Tanner criteria was assessed. Measurements of systolic and diastolic blood pressure were taken three times at the left arm, while subjects were seated, and the mean of the last two measures was used for analysis. Each child was examined by a pediatric endocrinologist for the presence of acanthosis nigricans on the neck, elbow, groin, knee, and knuckles and assigned to one of two groups: those having AN and those without AN. All measurements were taken by the same operator.

*Metabolic Evaluation*

A blood sample was drawn from each patient at 8 a.m. after an overnight fast. Triglycerides and high-density lipoprotein (HDL) cholesterol were measured. All patients underwent a standard oral glucose tolerance test (OGTT) (1.75 g of glucose/kg body weight). Subjects were evaluated at 8 a.m. after an overnight

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fast; they consumed a diet containing at least 250 g of carbohydrates per day for 3 days before the study and refrained from vigorous physical activity. Glucose and insulin levels were measured during the OGTT at baseline and every 30 min for 120 min. Triglyceride levels were determined by an enzymatic colorimetric test with lipid clearing factor. Immunoreactive insulin was assayed by IMX (Abbott Diagnostics, Santa Clara, CA, USA). The mean intra- and inter-assay coefficients of variations were 4.7% and 7.2%, respectively. Analyses were performed in the same laboratory.

*Definitions*

Children and adolescents were defined as obese if the BMI exceeded the 95th percentile for age and sex according to Italian charts [7]. According to Tanner criteria, males with gonad stage 1 and girls with breast stage 1 were defined prepubertal, while boys with gonad stage ≥ 2 and girls with breast stage ≥ 2 were defined pubertal. Patients were considered to have a positive parental history of T2D when at least one of the two parents or one of the four grandparents was affected by T2D. The pigmentation and velvety thickening that occurs on the neck, axillae, and other skinfolds like groin, knee, and elbow was defined as acanthosis nigricans. Using Burke's quantitative scale for AN, a score from 0 to 4 was given for skinfold color [8]. Youths with a color score ≥ 1 were considered to have AN. Metabolic syndrome was defined using definition published previously by Ford et al. [9]. Metabolic syndrome was considered present when the child showed three or more of the following criteria: central adiposity (waist circumference ≥ 90th percentile for age and sex) [10], triglycerides ≥ 150 mg/dl (1.7 mmol/l), HDL cholesterol ≤ 40 mg/dl (1.03 mmol/l), systolic blood pressure or diastolic blood pressure ≥ 90th percentile for age, sex and height, fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed tT2D.

Hypertension was defined as systolic and/or diastolic blood pressure > 90th percentile for age, sex and height [11].

Subjects with dyslipidemia had triglycerides ≥ 110 mg/dl and/or HDL cholesterol ≤ 40 mg/dl. Impaired fasting glucose (IFG) was defined as serum basal glucose level ≥ 100 mg/dl and < 126 mg/dl. Impaired glucose tolerance (IGT) was defined as glucose level ≥ 140 mg/dl and < 200 mg/dl at 120 min. The isolated or simultaneous presence of IFG and of IGT was defined as prediabetes.

*Statistical Analysis*

To assess which value of WHtR had the best sensitivity/specificity ratio, we calculated a receiver operating characteristic (ROC) curve using age and gender as covariates [12]. The area under the curve (AUC) measures the degree of separation between an affected and a non-affected subject by a specific test. An AUC of 1 indicates perfect separation between affected and non-affected subjects, whereas an AUC of 0.5 indicates no discrimination between the test values. The optimal cut-off point was obtained using the Youden index (maximum (sensitivity + specificity – 1)) [13]. The predictive positive value (PPV) and the predictive negative value (PNV) were evaluated for T2D family history, AN, and high WHtR.

A logistic regression analysis was used to calculate the odds of presenting each of the components of the metabolic syndrome (hypertension, dyslipidemia, or prediabetes) and to assess the risk of detecting subjects with metabolic syndrome according the number of clinical features. Gender, age, z-score BMI, and pubertal stage were included as covariates. A chi square test was used to compare the distribution of discrete variables. The analysis of covariance (ANCOVA) was used to compare clinical features of patients according to the presence of metabolic syndrome. Age, gender z-score BMI, and pubertal stage were used as covariates. Data are presented as means and standard deviations (SD). The SAS Statistical Software Package version 8.2 (SAS institute, Clary, NC, USA) was used for all the statistical analyses. ROC curve analysis was made using Statistical Program for Social Sciences Version 13.0 (SPSS Inc, Chicago, IL, USA).

## Results

Clinical and metabolic features of the studied population are shown in table 1. 315 patients (29.2%) showed the features of metabolic syndrome. Clinical and metabolic characteristics of the study population according to the presence/absence of metabolic syndrome are shown in table 2. Of the single components of the metabolic syndrome, dyslipidemia was the most frequent, with a prevalence of 43.6%; the prevalence of hypertension was 24.1%

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**Table 1.** Physical and metabolic characteristics of the obese children involved in the study

| | N | % |
|---|---|---|
| Sex | | |
| Male | 513 | 47.5 |
| Female | 567 | 52.5 |
| Pubertal stage | | |
| Prepubertal | 598 | 55.4 |
| Pubertal | 482 | 44.6 |
| | **Mean** | **SD** |
| Age, years | 10.7 | 3 |
| Weight, kg | 65.8 | 21.6 |
| Height, cm | 145.4 | 15.2 |
| BMI, kg/m$^2$ | 30.3 | 5.2 |
| BMI-SDS | 2.8 | 0.8 |
| Waist circumference, cm | 88.6 | 12.7 |
| WHtR | 0.61 | 0.07 |
| Systolic blood pressure, mm Hg | 112.3 | 19 |
| Diastolic blood pressure, mm Hg | 64.8 | 12.9 |
| Triglycerides, mg/dl | 97.3 | 52.9 |
| HDL cholesterol, mg/dl | 47 | 19 |
| Fasting glucose, mg/dl | 80.5 | 9 |
| Fasting insulin, µUI/ml | 25.6 | 18.6 |

BMI-SDS = BMI standard deviation scores; WHtR = waist-to-height ratio; HDL cholesterol = high-density lipoprotein cholesterol.

and that of prediabetes 8.5%. Of the 92 patients showing prediabetes, 75 (6.9%) had IGT, 19 (1.8%) had IFG, and only 5 had both (0.5%); three subjects (0.3%) had T2D.

582 subjects (54%) had a family history of T2D. 605 subjects (56%) showed AN. In order to test the ability of the WHtR to detect metabolic syndrome and to calculate a cut-off, we run a ROC curve analysis. The area under the ROC curve for WHtR was 0.64 (95% CI 0.60–0.68; $p < 0.05$); the cut-off was 0.60, with a sensitivity of 61% and a specificity of 54% in detecting children with metabolic syndrome . In total, 606 subjects (56%) had a WHtR higher than 0.60.

The odds of showing the metabolic syndrome according to the three clinical characteristics considered are shown in table 3. The PPV and PNV have been calculated and were as follows: for family history of T2D, PPV and PNV was 0.31 (95% CI 0.27–0.35) and 0.73 (95% CI 0.69–0.77), respectively; for AN, PPV and PNV was 0.33 (95% CI 0.28–0.38) and 0.80 (95% CI 0.75–0.84), respectively; for WHtR, PPV and PNV was 0.37 (95% CI 0.33–0.41) and 0.79 (95% CI 0.75–0.83), respectively.

Children presenting with AN or high WHtR had a significantly higher risk of showing metabolic syndrome. Metabolic syndrome is more frequently detected in those subjects showing a co-occurrence of AN together with positive family history of T2D or high WHtR. The odds of showing metabolic syndrome was further increased by the presence of the three clinical features altogether. Both, positive family history of T2D and high WHtR were associated with increased risk of prediabetes.

The odds of showing dyslipidemia or hypertension according to the presence of one or more clinical signs are shown in table 4. The presence of AN or high WHtR was associated with increased risk of dyslipidemia, and the odds raised significantly when both features were present; only WHtR was tightly associated with increased risk of hypertension.

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**Table 2.** Clinical and metabolic characteristic of the obese children according to the presence of the metabolic syndrome[a]

| | Metabolic syndrome | | | | p |
|---|---|---|---|---|---|
| | present | | absent | | |
| | N | % | N | % | |
| Patients | 315 | 29.2 | 765 | 70.8 | |
| Sex | | | | | |
| Male | 157 | 49.8 | 356 | 46.5 | 0.6 |
| Female | 158 | 50.2 | 409 | 53.5 | 0.6 |
| Pubertal stage | | | | | |
| Prepubertal | 158 | 50.2 | 440 | 57.6 | 0.25 |
| Pubertal | 157 | 49.8 | 325 | 42.5 | 0.2 |
| | mean | SD | mean | SD | p |
| Age, years | 10.9 | 2.7 | 10.6 | 2.9 | 0.1 |
| Weight, kg | 72.9 | 22.9 | 63.4 | 20.3 | <0.0001 |
| Height, cm | 148.4 | 13.7 | 144.2 | 15.5 | <0.0001 |
| BMI, kg/m$^2$ | 32.3 | 5.7 | 29.7 | 4.8 | <0.0001 |
| BMI-SDS | 3 | 0.7 | 2.8 | 0.9 | <0.0001 |
| Waist circumference, cm | 93.4 | 13.4 | 86.8 | 11.7 | <0.0001 |
| WHtR | 0.63 | 0.07 | 0.6 | 0.06 | <0.0001 |
| SBP, mm Hg | 121.4 | 18.8 | 108.7 | 17.2 | <00001 |
| DBP, mm Hg | 69.8 | 13.6 | 62.8 | 11.4 | <0.0001 |
| Triglycerides, mg/dl | 145.2 | 65.3 | 77 | 29.1 | <0.0001 |
| HDL cholesterol, mg/dl | 37.8 | 8.8 | 50.7 | 21 | <0.0001 |
| Fasting glucose, mg/dl | 80.5 | 9.6 | 80.4 | 8.8 | 0.9 |
| Glucose at 120 min, mg/dl | 119.8 | 25.2 | 107.4 | 18.8 | <0.0001 |
| Fasting insulin, µUI/ml | 32.1 | 21.7 | 23.4 | 16.8 | <0.0001 |

BMI-SDS = BMI standard deviation scores; WHtR = waist-to-height ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL cholesterol = high-density lipoprotein cholesterol.

[a]Analysis of covariance has been used to evaluate differences between means; age, gender, BMI-SDS, pubertal stage, and height when necessary, were used as covariates.

## Discussion

In the present study we have shown in a large cohort of Italian obese children that high WHtR, a positive family history for T2D, and AN are associated with a high risk of suffering from metabolic syndrome and prediabetes.

Each of the three clinical markers studied has been demonstrated to be associated with an increased risk of metabolic syndrome and prediabetes/diabetes. Moreover, each of these markers is simple to obtain during a first clinical examination.

Visceral fat accumulation has been shown to be strongly associated with metabolic syndrome in childhood [14], and waist circumference has been recognized as the best clinical indirect index of visceral fat accumulation [15, 16]. The importance of measuring waist circumference is corroborated by pediatric studies showing that, within a given BMI category, subjects with a large waist circumference have a higher cardiovascular risk than those with a lower waist circumference [14]. Unfortunately, although reference values for waist circumference in children do exist for some countries such as Canada [17], Italy [18], UK [19], and USA [12], the clinical use of waist circumference in children is limited by the lack of an inter-

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**Table 3.** Odds ratio to have metabolic syndrome or prediabetes in subjects with one, two or three clinical features considered[a]

| | OR | 95% CI | p |
|---|---|---|---|
| *Metabolic syndrome* | | | |
| T2D family history | 1.26 | 0.94–1.69 | 0.13 |
| AN | 1.81 | 1.24–2.66 | 0.002 |
| High WHtR (>0.60) | 2.24 | 1.68–2.3 | <0.0001 |
| T2D family history and AN | 1.80 | 1.05–3.10 | 0.03 |
| T2D family history and high WHtR | 2.47 | 1.64–3.72 | <0.0001 |
| AN and high WHtR | 3.34 | 1.91–5.84 | <0.0001 |
| T2D family history, AN, and high WHtR | 3.60 | 1.6–8.12 | 0.002 |
| *Prediabetes* | | | |
| T2D family history | 2.36 | 1.19–4.64 | 0.01 |
| AN | 1.83 | 0.90–3.69 | 0.09 |
| High WHtR (>0.60) | 2.32 | 1.24–4.34 | 0.009 |
| T2D family history and AN | 3,94 | 1.13–13.8 | 0.03 |
| T2D family history and high WHtR | 4.71 | 1.73–12.8 | 0.002 |
| AN and high WHtR | 2.12 | 0.77–5.82 | 0.1 |
| T2D family history, AN, and high WHtR | 1.65 | 0.43–6.35 | 0.5 |

T2D = Type 2 diabetes; AN = acanthosis nigricans; WHtR = waist-to-height ratio.

[a]A logistic regression analysis was used to calculate the odds of detecting subjects with metabolic syndrome and prediabetes; age, gender, BMI and pubertal stage were included among the independent variables.

**Table 4.** Odds ratio to have dyslipidemia or hypertension in obese subjects with one, two or three clinical features considered[a]

| | OR | 95% CI | p |
|---|---|---|---|
| *Dyslipidemia* | | | |
| T2D family history | 1.18 | 0.92–1.53 | 0.2 |
| AN | 1.87 | 1.35–2.59 | 0.0002 |
| High WHtR (>0.60) | 2.02 | 1.57–2.60 | <0.0001 |
| T2D family history and AN | 1.88 | 1.17–3.01 | 0.009 |
| T2D family history and high WHtR | 2.06 | 1.45–2.92 | <0.0001 |
| AN and High WHtR | 2.75 | 1.76–4.3 | <0.0001 |
| T2D family history, AN and high WHtR | 2.60 | 1.37–4.95 | 0.004 |
| *Hypertension* | | | |
| T2D family history | 1.16 | 0.85–1.59 | 0.35 |
| AN | 1.31 | 0.88–1.95 | 0.19 |
| High WHtR (>0.60) | 2.24 | 1.63–3.07 | <0.0001 |
| T2D family history and AN | 1.41 | 0.79–2.54 | 0.24 |
| T2D family history and high WHtR | 2.21 | 1.45–3.38 | 0.0002 |
| AN and High WHtR | 2.32 | 1.33–4.03 | 0.003 |
| T2D family history, AN and high WHtR | 2.13 | 0.99–4.58 | 0.05 |

T2D = Type 2 diabetes; AN = acanthosis nigricans; WHtR = waist-to-height ratio.

[a]A logistic regression analysis was used to calculate the odds of detecting subjects with dyslipidemia and hypertension; age, gender, BMI and pubertal stage were included among the independent variables.

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nationally accepted classification which gives age-specific waist circumference cut-offs and by the lack of population-based reference values in most countries. To overcome these limitations, the use of the WHtR has recently been proposed [20–26]. We here reported that a WHtR higher than 0.60 is associated with a statistically significant increased risk of metabolic syndrome, prediabetes, hypertension, and dyslipidemia. The association between the clustering of cardiovascular and metabolic risk factors and abdominal fat is not only a reflection of the obesity degree, but also has a physiopathological background, given that visceral adiposity is one of the main risk factors for the development of insulin resistance, T2D, and cardiovascular disease [27, 28].

The second feature used to detect obese children at high risk to show metabolic syndrome and prediabetes was the family history of T2D. The genetic background underlying the occurrence of metabolic syndrome and T2D has been progressively uncovered, and the heritability of insulin resistance and as well as the components of metabolic syndrome has been shown [29–31]. Interestingly, we observed that a family history for T2D is associated with IFG and IGT, but not with the metabolic syndrome. This may be explained by dissecting the metabolic components leading to T2D. Insulin resistance and beta cell deficiency are the main contributors to the pathogenetic mechanisms leading to T2D. While insulin resistance is probably the link between the glucose metabolism and the metabolic syndrome, the failure of beta cells, which ultimately results in T2D, is only responsible for the derangement of glucose metabolism and is highly heritable. Thus, the association between family history of T2D and IFG/IGT only reflects the high heritability of beta cell function, which does not seem to play a role in the development of metabolic syndrome.

On the other hand, AN, which is a strong clinical marker of insulin resistance, seems to be strong predictor for metabolic syndrome, too. In fact, in our study AN was strongly associated with a higher risk of metabolic syndrome and dyslipidemia. Although the mechanisms driving this association are not known, some hypotheses have been made. The most accredited hypothesis is that AN is a direct consequence of insulin resistance. It has been shown that the increase in circulating serum insulin levels causes an increased stimulation of insulin and insulin-like growth factor 1 receptors [32–34] causing a progressive pigmentation of the skin and the development of papillomatous plaques that characterizes AN [35, 36]. Given the strong relationship between insulin resistance and AN, a higher prevalence of AN in obese children could be expected during adolescence, a period characterized by a naturally increased insulin-resistant state. However, we did not find any difference in AN prevalence between prepubertal and pubertal obese children. Moreover, when the analyses evaluating the risk for metabolic syndrome and prediabetes were run, the pubertal stage was used as covariate, meaning that the effect of AN on metabolic status is independent of puberty as well as of age, sex, and obesity degree.

Analyzing the data concerning glucose homeostasis, we have noticed that blood glucose level at 120 min after OGTT was significantly higher in children with metabolic syndrome than in children without. On the contrary, fasting blood glucose was not different in these two groups of children, but fasting insulin was significantly higher in children with metabolic syndrome than in children without. The first finding (i.e., the difference of blood glucose after OGTT) may be probably due the fact that subjects with IGT are more prone to show the features of metabolic syndrome, thus being included in this category and driving the difference for 2-hour glucose. The observation of similar fasting blood glucose but higher fasting insulin in metabolic syndrome children just reflects the increased insulin resistance of these children and is in agreement with the leading role of increased insulin resistance in the pathogenesis of metabolic syndrome.

We acknowledge that this study has some limitations: The lack of a longitudinal assessment of the diabetes and cardiovascular disease risks does not allow to quantify the long-term

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cardiometabolic risk, and the lack of a control population of age- and gender-matched lean children does not allow to extend these findings to the general population. Nevertheless, this study also has some strengths. First of all, it is the first study assessing the clinical implication of the co-occurrence of AN, high WHtR, and a family history ofT2D.

In conclusion, we showed that children with AN, high WHtR or a family history of T2D or a combination of these have a high risk of showing a disadvantageous cardiovascular and metabolic profile. The risk progressively increases with the number of clinically relevant findings. This finding suggests that three simple actions, i.e., looking at the patient, asking about the T2D family history and measuring the waist circumference and height, may represent a useful tool in the hand of pediatricians in order to identify children at risk for obesity complications and to decide on the further course of clinical investigations and interventions in these patients.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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