Original Article

Linear growth and prevalence of the different components of the metabolic syndrome (MetS) in young obese nondiabetic children (below 5 years) in comparison to older obese children (6-12 years)

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Abstract. *Background and aim:* In Qatar, the prevalence of metabolic syndrome (MetS) in children and adults is increasing in parallel with the markedly increasing trends in obesity rates. *Objective:* The aim of our study was to assess the prevalence of different components of MetS, measure plasma atherogenic indexes (AIP), and to evaluate linear growth in young obese nondiabetic children (< 5 years) in comparison to older obese children (6-12 years). *Methods:* We analysed the anthropometric and biochemical profile of 135 random sample obese children who attended to the Paediatric Clinic of Hamad Medical Centre (HGH) in Doha (Qatar) from January 2018 to December 2019. *Results*: A large proportion of children presented with obesity, around the age of 5 years, were obese at the end of their first year of life (63.8%) and more were obese at the 2 years of age (82.6%). Significantly rapid gain in weight and linear growth occurred during the first 6 months of postnatal life. Moreover, some metabolic risk factors and high AIP occurred more frequently in older obese children compared to young obese children. *Conclusions:* This study documented the early occurrence of different components of the MetS in young obese children and the progressive increase of their prevalence in older prepubertal children. Most of obese children who presented at or below 5 years of age had significant obesity and rapid linear growth during the first two years (infancy). These two findings pointed out to the necessity to impose early detection and preventive measures on a national scale. (www.actabiomedica.it)

Key words: obesity, young children, metabolic syndrome (MetS), body mass index, catch-up growth

Introduction

The worldwide prevalence of childhood overweight and obesity has increased in recent decades (1). Emerging evidence indicates that a large proportion of children who have obesity before puberty can develop obesity in early adulthood, with early-life fat deposition associated with later risk of adult obesity and cardiovascular diseases (CVD) (2,3).

The metabolic syndrome (MetS) is a cluster of the most dangerous risk factors for developing type 2 diabetes mellitus (T2DM) and CVD. Recent studies have shown that it develops during childhood and is highly prevalent among children and adolescents who suffer from obesity. The key elements of the MetS are central obesity, high blood pressure, dyslipidemia and hyperglycemia. Its early identification is very important to facilitate preventive action (4,5).

In two studies comparing obese and overweight children with nonobese children (aged 8-16 years) revealed that obese and overweight children showed significantly higher levels of insulin and blood pressure (BP), and lower high-density lipoprotein (HDL)-cholesterol than normal weight children. The CDC

criteria yielded similar results, although with fewer differences between obese and overweight children. Compared with normal-weight children (the reference group), the odds ratios for all of the CVD risk factors were greater than one. Moreover, obese children were 10 times more likely to have hypertension than normal-weight children (6,7).

Before 2008, in Qatar, there were not reported cases of children with T2DM. In the following years, the incidence of T2DM has increased from 1.82 per 100,000 in 2012 to 2.7 per 100,000 in 2016, with an incidence of T2DM equal to 2.9/100,000 per year (8).

Considering the current high prevalence of obesity in children living in Qatar, as well as the increasing incidence of T2DM, it becomes essential to plan measures for prevention of MetS in early in life. Each component of the syndrome should be identified as early as possible to prevent metabolic and cardiovascular diseases (9).

Atherogenic index of plasma (AIP) is a novel and better biomarker associated with obesity and composed of triglycerides and high-density lipoprotein cholesterol. It has been used to quantify blood lipid levels and commonly used as optimal indicator of dyslipidemia and associated diseases (e.g., cardiovascular diseases) (10). However, no published study has yet examined the association between AIP and obesity in young children.

Our study aimed to assess the prevalence of the different components of MetS and measure the AIP in a random sample of obese young children below the age of 5 years and in older children (6-12 years) living in Qatar. In addition, the relation between their anthropometric data in relation to parents was assessed.

Study design and participants

A retrospective study was conducted among 69 children below the age of 5 years and 66 children between 5 and 12 years, who were randomly selected from a group of 500 obese children referred from the primary centres to the Pediatric Obesity Clinic, Endocrinology and Nutrition of Hamad General Hospital, Doha (Qarar). The study protocol was approved by the Institutional review Board (IRB) of Hamad Medical Centre. Children with dysmorphic syndromes and/or endocrinological disorders were excluded from the study.
Data recorded included: age, gender, weight and height, body mass index (BMI), systolic and diastolic blood pressures, lipid profile, glycated hemoglobin (A_{1C}), and alanine transferase level (ALT). The data were compared to normal lab data for the same age group of subjects. For the diagnosis of MetS, the Weiss definition for children and adolescents was used as reference (5).

Abnormalities in the fasting levels of triglycerides and HDL cholesterol were adjusted for age, and sex (> 95th percentile for triglycerides; < 5th percentile for HDL cholesterol) (11). Impaired glucose tolerance (IGT) was defined as a glucose level greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at two hours after OGTT (12).

Like adults, the enrolled children and adolescents were classified as having the MetS if they met three or more of the following criteria for age and sex: BMI above the 97th percentile (Z score: ≥ 2.0), triglyceride level above the 95th percentile, HDL cholesterol level below the 5th percentile, systolic or diastolic blood pressure above the 95th percentile, and IGT. The degree of insulin resistance (IR) was determined with the use of a homeostatic model (homeostatic model assessment-insulin resistance; HOMA-IR) (13).

Clinical assessment

Obese children were selected when their BMI Z-score was above +2. Each child's weight and height were collected using a standardized technique from birth to the last clinic visit and length/height Z score (LAZ and HAZ) and BMI-for-age Z-scores calculated based on the WHO reference (14).

Blood pressure was measured in all children by trained nurses using the same device (DinamapR oscillometric method). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in a sitting position on the right arm after a 10 min rest. Two measurements were taken for each child and the average of the two was calculated. Hypertension was defined as average SBP and/or DBP ≥ 95th percentile for age, sex and height (15).

Dietary assessment was performed by expert dietitians (qualitative and quantitative assessment using the 24h recall method) of obese young children (3- 5 years) at presentation and at each follow up visit.

Biochemical analysis

In a fasting state, plasma total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), excess triglycerides, and fasting glucose were measured applying enzymatic assays using an automated analyser (Olympus AU5400; Olympus Diagnostics, Nyon, Switzerland). Additionally, insulin was determined by electrochemiluminescence with a modular auto-analyser (Cobas 8000, e602 module; Roche Diagnostics, Basel, Switzerland).

HOMA-IR was calculated as the product of the fasting plasma insulin level (mU/L) and the fasting plasma glucose level (mmol/L), divided by 22.5. High LDL-C was defined as >130 mg/dL (16); low HDL-C as <40 mg/dL (17); high triglyceride level as >110 mg/dL (17); high glucose as >110 mg/dL (17); and high fasting insulin as >15 mU/L (18)

Because HOMA-IR cut-off points for diagnosis of IR have not been defined for children and adolescents, values >3.6 were considered as high (19). Hypertension, low HDL-C, high TAG, high glucose and high insulin were included in analysing the clustering of metabolic risk factors (20).

Statistical analysis

Data were presented as mean ± standard error of the mean (SE). Non-paired t test was used to compare anthropometric data of children when data were normally distributed, and Wilcoxon test was used when the data were not normally distributed. The prevalence of each component of MetS was presented in percent and two proportions Z test was used to compare proportions between the two study groups. Linear regression equation was used to find correlations between variables. Significance was accepted when p value was <0.05.

Results

Anthropometric data:

In 10.4 % of children the birth weight was > 4 kg. None of the obese children had weight for length SDS (WLZ) > 2. Moreover, 24.6% of children were SGA (< 10th percentile for age). The proportion of postnatal obesity (BMI-Z > 2) in children who presented with obesity at < 5 years of age is reported in table 1. The progressive increase of BMI-Z from birth to 5 years of age (Figure 1) was associated with a progressive increase in LAZ/HAZ (Figure 2). In addition, the WAZ changes in 12 children born SGA showed rapid and progressive gain in their WAZ during the 5 years of postnatal life which was maximum during the first year of life (gain around 4 SD) (Figure3).

Table 1. Proportion of postnatal obesity (BMI-Z > 2) in children who presented with obesity at 5 years of age or below (n= 69)

BMIZ >2	Percent (%)	Mean ± SD
Obese at 5 years	100	4.3 ± 1.5
Obese at 2 years	82.6	3.47 ± 1.6
Obese at 1 year	63.8	2.41 ± 1.3
Obese at 6 months	47.8	1.24± 1.2

When we analyzed children who had rapid weight catch-up (WAZ gain > 0.67SD), 72% and 45% of obese

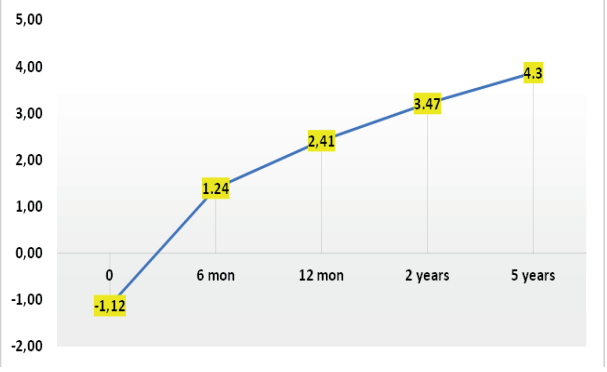

Figure 1. BMI-Z changes during childhood in obese children presented at 5 years of age

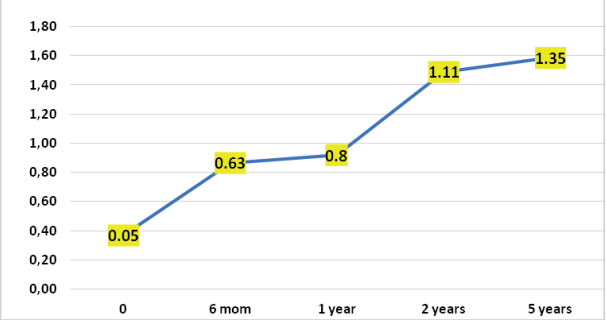

Figure 2. Length/Height Z score changes during childhood in obese children presented at 5 years of age

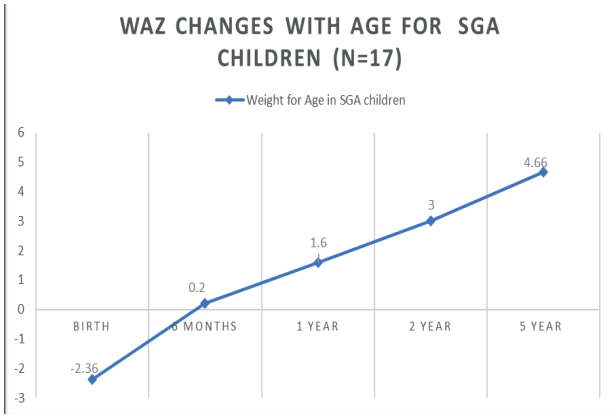

Figure 3. WAZ changes with age for SGA term infants (N=17)

children at 5 years of age who were born AGA had significant weight catch-up (> 0.67 SD) during their first 6 months and 12 months of postnatal life, respectively. 43% and 24% of children who had obesity at 5 years of age had significant stature catch-up (> 0.67 SD) during their first 6 months and 12 months of postnatal life, respectively. Comparing the anthropometric data of young versus old obese children showed that both groups had tendency to be relatively tall (Table 2).

Dietary assessment

Dietary assessment of obese young children (3- 5 years) was performed by expert dietitians (qualitative and quantitative assessment using the 24-h recall method) at presentation and at each follow up visit. Results showed significantly increased intake of calories (67% ± 7%) above the recommended for age. In addition, they were consuming a significantly high proportion of their total caloric intake from simple sugars in the form of sweets, candies, sweetened juices, soft drinks, and snacks with meals, as well as from refined carbohydrate (mainly rice, pasta, potatoes, and white bread). Moreover, they had higher intake of fried foods with saturated oils (butter and margarine) and marked intake deficiency of vegetables, greens, and fruits. The intake of protein (meat, poultry, fish, and egg) was adequate in most of the cases. There was also a clear imbalance in the form of an increased quota of carbohydrates, excessive intake of simple carbohydrates (2-fold), saturated fats (1.5-fold), and a deficiency of dietary fibres.

Table 2. Anthropometric data for obese young children (at or < 5 years) and old children (6-12 years)

Parameters	Children < 5 years	Children 6 -12 years
BMI (Mean ± SE)	29 ± 0.98	30.4 ± 0.72
BMI-Z (Mean ± SE)	4.3 ± 0.18	3.6 ± 0.1
Ht-SDS (Mean ± SE)	1.3 ± 0.16	1.1 ± 0.14

Metabolic syndrome components, comparison between young and old obese children:

The prevalence of different biochemical parameters of MetS and AIP index are presented in table 4. A high HOMA-IR with fasting hyperinsulinemia (> 15 mU/L), and high AIP index, HbA_{1C} and ALT concentrations occurred more frequently in older obese children compared to young obese children, but the difference was not statistically significant.

The prevalence of obesity and overweight in their fathers and mothers was very high (70% and 60% in obese young children and 82% and 96% in obese old children, respectively).

Correlations

BMI-Z at 5 years was correlated significantly with BMI-Z at 2 years (r= - 0.65, p: <0.01) (Table 5). HbA_{1C} was correlated with fasting insulin (r = 0.65, p= 0.006) and LDL level (r = 0.48, p: 0.01) and negatively with HDL (r = - 0.41, p: 0.03). Fasting insulin level was correlated with triglyceride level (r = 0.45, p < 0.01). BMI-Z correlated with HbA_{1C} (r = 0.82, p < 0.001) (Figure 4) and LDL (r = 0.38, p: 0.02). HDL level correlated negatively with triglyceride level (r = -0.607, P < 0.01), and HbA_{1C} (r = - 0.41, p: 0.002). Fasting insulin level was correlated significantly with ALT (r = 0.76, p: < 0.001) (Figure 5). Moreover, ALT was correlated significantly with cholesterol and LDL levels and negatively with HDL level (Table 6).

Discussion

Forty-one percent of Qatari Nationals (39.5% in men, 43.2% in women) are obese (BMI ≥30 kg/m^2) and 70.1% (71.8% in men, 68.3% in women) are

Table 4. Metabolic risk factors among obese children < 5 years versus those between 6 -12 years.

Variables	<5 years	6-12 years	P value
	%	%	
Number	69	66	
HbA1c > 5.7%	20%	29%	0.51
LDL > 2.7 mmol/L	0 %	8.0%	0.2
HDL < 1.03 mmol/L	20%	20.8%	0.97
TG >1.7 mmol/L	6.7%	8.0%	0.65
Cholesterol > 4.5 mmol/L	10%	20.8%	0.25
ALT > 35 IU/L	10%	25.0%	0.23
Fasting insulin > 15 mU/L	53.3%	72.0%	0.26
IFG > 5.6 mmol/L	23.3%	17.9%	0.29
HOMA IR >2	76.6%	92.7	0.07
HOMA IR > 3.6	55.5%	71.4%	0.17
Hypertension BP >95th centile for age and sex	23.3%	12.5%	0.23
Atherogenic index of plasma (AIP > - 0.23)	55.5%	76.7%	0.06
Parents with obesity and overweight (%)	Fathers 50% obese Mothers 30% obese Fathers 20% overweight Mothers 30% overweight	Fathers 64% obese Mothers 52% obese Fathers 18% overweight Mothers 44% overweight	

Table 5. Correlations between BMI-SDS during infancy and childhood.

	BMI-Z score at 6 months	BMI-Z score at 1 year	BMI-Z score at 2 years	BMI -Z score at 5 years
BMI-Z score at 6 mo.	1.00			
BMI-Z score at 1 yr.	0.50*	1.00		
BMI-Z score at 2 yr.	0.46*	0.41*	1.00	
BMI-Z score at 5 yr.	0.31	0.36*	0.65*	1.00
*p <0.05				

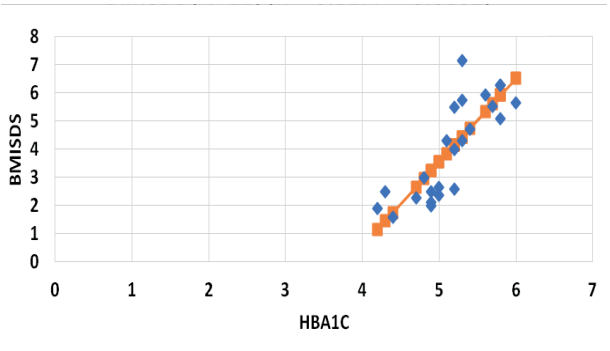

Figure 4. Correlation between HbA_{1c} and BMI-SDS (N =22; r = 0.82, p:<0.0001)

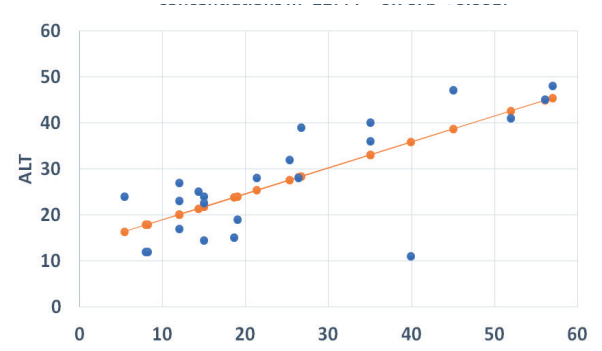

Figure 5. Correlation between fasting insulin and ALT concentrations (N =22; r= 0.76, p:< 0.001)

Table 6. Correlations between different metabolic components in obese children < 5 years of age.

	ALT	LDL	HDL	TG	Cholesterol	AIP
ALT	**1.00**					
LDL	**0.52***	**1.00**				
HDL	**-0.04**	**0.42**	**1.00**			
TG	**0.23**	**-0.01**	**-0.01**	**1.00**		
Cholesterol	**0.498***	**0.87***	**-0.52**	**0.45***	**1.00**	
AIP	**0.24**	**-0.12**	**-0.51**	**0.84***	**0.18**	**1.00**

***p <0.05**

overweight (BMI ≥ 25 kg/m^2). A childhood obesity rate study conducted in Qatar, randomly selected 315 primary school children, and identified that 32% of boys and 33% of girls were overweight or obese (21).

Childhood adiposity is of great concern because of its adverse consequences, for both short- and long-term health (22). The prevalence of diabetes and hypertension in young adults aged between 20-29 years is 8.9% and 9.8 %, respectively. The 2012 STEPS report suggested that for Qatari Nationals, the prevalence of having three or more cardiovascular risk factors was 44.9 % in subjects aged 18-64 years. (23)

In the present study, a large proportion of children with obesity around the age of 5 years were obese at the end of their first year of life (63.8%) and more were obese at the 2 years of age (82.6%). None of them was obese at birth (WAZ > 2) but 24.6 % were born SGA. Significantly rapid gain in weight (WAZ increased by > 0.67 SD) and linear growth (LSDS increased by 0.67 SD) occurred during the first 6 months of postnatal life. BMI-SDS at 5 years was correlated significantly with BMI-SDS at 1 year (r = 0.36, p: 0.04) and at 2 years (r = - 0.6, p: <0.01) (Table 5).

In support to our findings, a prospective, observational, cohort study of gestational diet, pregnancy outcomes, and offspring health (Project Viva) measured length and weight of 559 children at birth and 6 months. Results showed that more-rapid increases in weight for length in the first 6 months of life were associated with sharply increased risk of obesity at 3 years of age (24).

Another cohort study investigated the degree of weight gain across the gestational spectrum in 1971 children enrolled at birth and followed up to the age 7 years. The authors found that a rapid weight gain during infancy was associated with an increased risk of overweight or obesity at age 2–7 years in a dose-response fashion among all children except for early preterm births. These findings suggest that monitoring and ensuring optimal weight gain across the entire gestational spectrum, beginning from birth, represents the first step towards primary prevention of childhood obesity (25).

Diet in early childhood may be an important target for prevention of childhood obesity, but nevertheless, there are not many studies that examined overall diet of preschool children in relation to later body composition (26,27).

Few studies performed in school age children have reported an association between higher scores on a 'snacking' dietary pattern, or high fat and low fiber intake and higher risk for developing obesity. Similarly, they suggested a link between higher diet quality scores and a lower risk for obesity (28-31).

Studies on dietary patterns in relation to obesity among young children are scarce (32). Diet composition appears to be an important factor promoting and/or worsening IR. Elevated consumption of animal protein, particularly in early life, as well as diets rich in saturated, trans, and n-6 polyunsaturated fatty acids, and diets with a high carbohydrate to fat ratio, besides a high glycaemic and low-fiber diet also appear to exacerbate adiposity and IR (33).

Dietary assessment performed by expert dietitians (qualitative and quantitative assessment using the 24-h recall method) of our obese young children (3- 5 years) at presentation and follow up, showed significantly increased quantity of caloric intake (67 ± 7%) above the recommended for age. In addition, they were consuming a significantly high proportion of their total ca-

loric intake from simple sugars in the form of sweets, candies, sweetened juices, and soft drinks (as snacks and with food) and from complex refined carbohydrate intake (mainly rice, pasta, potatoes, and white bread). They had higher intake of fried food with saturated oils (butter and margarine) but marked deficiency of intake of vegetables, greens, and fruits. Their intake of protein (meat, poultry, fish, and egg) was adequate in most of the cases.

In support to our findings, Voortman et al. (34), explored the associations between dietary patterns in children at the age of 1 year and fat mass index (FMI), and fat-free mass index (FFMI) in large population-based cohort study in young children, and found that children who had a high intake of fruit, vegetables, grains, and vegetable oils starting at their first year of life had a higher FFMI at 6 years. The food pattern, which was characterized by high intake of refined grains, meat, potatoes, fish, soups and sauces, and sugar-containing beverages, was associated with a higher FMI and higher body fat percentage.

In our study, we observed the occurrence of different components of the MetS (hypertension, dysglycemia, high triglyceride and cholesterol) in obese children as early as 5 years of age with 5.8 % of our cohort fulfilled the definition. Comparatively high HOMA-IR associated to fasting hyperinsulinemia, high atherogenic index, and high HbA_{1C}, cholesterol and ALT concentrations occurred more frequently in older obese children compared to young obese children. These data support the concept of progression of IR state that headed to dysglycemia and deterioration of the metabolic components with age in obese children.

In support of this concept, a review of 63 studies (49 220 children above the age of 5 years in highly developed countries) reported a worsening of risk parameters for CVD in overweight and obese participants. Compared with normal weight children, systolic blood pressure was higher by 4.54 mm Hg in overweight children, and by 7.49 mm Hg in obese children. Obesity adversely affected concentrations of all blood lipids; total cholesterol and triglycerides were 0.15 mmol/L and 0.26 mmol/L higher in obese children, respectively. Fasting insulin and IR were significantly higher in obese participants but not in overweight participants (35).

Standards for IR in children have not been established. IR is believed to have both genetic and environmental factors implicated in its aetiology. This genetic component is supported by the extremely high prevalence of obesity and overweight in the parents of our young and old children with obesity. The genetic component seems to be polygenic in nature, and several genes have been suggested as potential candidates (36). However, several other factors can influence insulin sensitivity, such as fat mass, ethnicity, gender, perinatal factors, puberty, sedentary lifestyle, and diet (37). Apart from the genetic influence, approximately 55% of the variance in insulin sensitivity in children can be explained by total adiposity, after adjusting for other confounders, such as age, gender, ethnicity, and pubertal stage (38).

Different mechanisms have been suggested to link adiposity to IR. Adipocytes produce non-esterified fatty acids, which inhibit carbohydrate metabolism via substrate competition and impaired intracellular insulin signalling. Adiponectin (a cytokines produced by adipose tissue) with an important insulin-sensitizing effect associated with anti-atherogenetic properties. Its level is decreased in obese children and has been implicated in the pathogenesis of IR and MetS (39-42).

Adipose tissue also produces tumour necrosis factor-αand interleukin-6 (IL-6), both are inflammatory factor, which can alter insulin action at different levels in the intracellular pathway. IL-6 stimulates the hepatic production of C-reactive protein, and this can explain the state of inflammation associated with obesity that could mediate, at least partially, obesity-related IR. Moreover, studies have observed that obesity causes high levels of leptin, which acts as a pro-inflammatory cytokine and amplifies the process of IR (43-45).

In our study, seventeen children born SGA showed a rapid and progressive gain in their WAZ during the 5 years of postnatal life which was maximum during the first year of life. Several other reports have recognized the positive association between LBW and later obesity in children. It appears that LBW reflects nutritional deprivation in utero and consequently, these infants when receive high protein /caloric formula will gain weight more rapidly in order to make up their

lack of growth (catch up growth). This could lead to increased susceptibility to childhood obesity and metabolic abnormalities (46,47).

Moreover, obesity, particularly increased abdominal visceral adiposity, and non-alcoholic fatty liver disease (NAFLD) are associated with IR in children. The higher prevalence of increased ALT (>35 U/L) in 25% of our older obese children and 10% of young obese children and the significant correlation between ALT and fasting insulin level supported this view. Studies using the clamp methodology demonstrate that NAFLD is associated with hepatic and peripheral IR. The relation between IR and NAFLD seems to be, in part, driven by abdominal fat content (48,49).

In our children, ALT was correlated significantly with LDL and cholesterol levels and negatively with HDL levels. In another study, serum ALT level was positively correlated with serum triglyceride, plasma fasting glucose and BMI, while a negative correlation was present with serum HDL (50). Nevertheless, in our young obese children, positive non-significant correlations were found between ALT level and BMI and WAZ (51).

It has been recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition that all obese children older than 3 years should have an abdominal ultrasounds and hepatic function tests to search for NAFLD. In addition, the American Academy of Pediatrics recommends that a metabolic assessment including fasting glucose and lipids and blood pressure measurement should be offered to obese children and adolescents regardless of other conditions (52).

In summary, it is alarming that IR, hyperinsulinemia and the occurrence of different metabolic abnormalities occur in obese children at an early age. It is also clear that these changes are persistent and progressive with age, as long as obesity continues. These changes and complications might be furtherly exacerbated by the influence of puberty, due to the physiological decrease in insulin sensitivity associated with normal pubertal development.

Our findings recommend that monitoring and ensuring optimal weight gain beginning from birth, during infancy and early childhood represents a first step towards primary prevention of childhood obesity and cardiometabolic complications. Moreover, in clinical practice, traditional metabolic variables included in the definitions of MetS should be assessed in all obese children.

Conflict of interest: No potential conflict of interest relevant to this article was reported.

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