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New Predictors of the Metabolic Syndrome in Children—Role of Adipocytokines

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ABSTRACT: There is ample discussion of the relevance of the metabolic syndrome, the definition criteria, and predictive power. Nevertheless, along with the increasing prevalence of childhood obesity, the prevalence of the metabolic syndrome in obese children is reported at 30%, irrespective of the definition applied. Because children are otherwise relatively free of co-morbidities, they constitute an interesting population in which to study the sequence of events of obesity-related pathology. The adipocytokines appear to be important in this respect. Leptin was initially suggested as a promising "antiobesity" hormone. New concepts indicate that, in humans, leptin and its soluble receptor may be more important in states of energy deficiency rather than a predictor of the metabolic syndrome. Adiponectin, on the other hand, is not only related to obesity and insulin resistance, but appears to be the strongest predictor for metabolic syndrome, even in children. In newborns and infants, both adipocytokines occur in high concentrations, even though this cannot completely explain the increased risk for ensuing metabolic disease later in life. Finally, low-grade systemic inflammation may underlie the clustering of metabolic risk factors, but their role in children remains to be specified. Overall factors from the adipose tissue may constitute not only markers but also mediators of metabolic sequelae of obesity. **(*Pediatr Res* 61: 640–645, 2007)**

The metabolic syndrome in children is not only a scientifically and clinically relevant issue but also a controversial and complex issue with many questions not satisfactorily answered, such as, "What is the metabolic syndrome?" "How is the situation in children?" "How can we predict it?" and "Does the adipose tissue contribute to it?"

TERMS AND DEFINITION OF THE METABOLIC SYNDROME

The term and concept of the metabolic syndrome was first introduced by Reaven in 1988 (1), when he noticed, from the analysis of experimental, clinical, and epidemiologic studies, the simultaneous occurrence of hyperinsulinemia with several other cardiovascular risk factors in the same patient and that this clustering results in a markedly higher cardiovascular morbidity. He already assumed that there might be one common underlying mechanism for those risk factors—insulin resistance. Certainly, obesity seems to be another strong predisposing factor for all those components. The concept of the metabolic syndrome was then defined and institutionalized and was widely applied in clinical medicine (2–4). However, recent re-evaluation lead to a critical appraisal of the term and questioned the concept of the metabolic syndrome. In a joint statement of the American Diabetes Association and the European Association of the Study of Diabetes, the clarity and accuracy of the existing definition was questioned (5). Some criteria used are ambiguous or incomplete, and it has not been proven that the predictive value of the "syndrome" over the predictive value of the single components themselves is actually higher. In addition, ongoing research has identified more components that would be worthwhile to consider, including cytokines and adipocytokines.

Nevertheless, there is no doubt that there is a clustering of risk factors that correlate with each other and are associated with cardiovascular disease, and certainly obesity and insulin resistance constitute major risk factors.

THE METABOLIC SYNDROME IN CHILDREN

The metabolic syndrome has been regarded as a syndrome of multi-morbid adults. In pediatric medicine, we increasingly see obese children and adolescents with impaired glucose tolerance, hypertensive blood pressure levels, dyslipidemia, and hyperuricemia. Hence, no matter what definition is applied, there is a portion of obese children at high risk for cardiovascular disease. These may be regarded as extreme cases, but they are no longer sporadic examples. The increase in the prevalence of obesity in children is well known (6,7). This phenomenon is demonstrated by the dynamic long-term alterations in BMI centiles. Comparing BMI centiles 15 y apart, there was a clear rise in the 97th centile over time, whereas the 3rd and 50th centiles remained stable over the

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Abbreviations: SGA, small for gestational age; **AGA,** adequate for gestational age; **SDS,** standard deviation score; **NASH,** nonalcoholic steatohepatitis; **sOB-R,** soluble leptin receptor; **CrP,** C-reactive protein

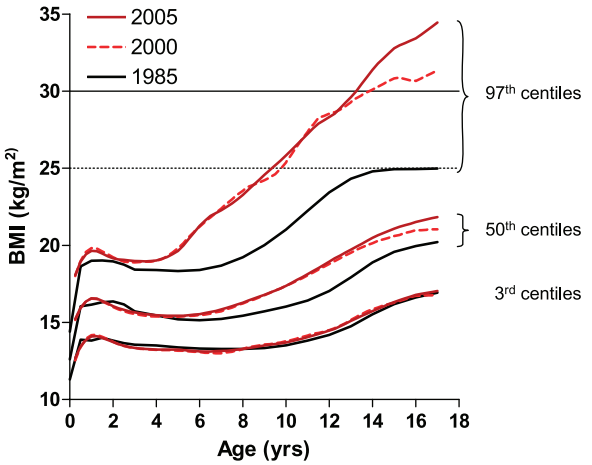

Figure 1. Secular trends in BMI centiles over two centuries in central Germany. BMI centiles of girls in the year 1985 (Hesse) are compared with the years 2000 (n = 30,029) and 2005 (n = 68,527) (CrescNet). The divergence of the 97th centile begins at preschool age, about 3–6 y, whereas the 3rd and 50th centiles remain stable over the years.

same period of time (Fig. 1). This indicates not only that more children become obese, but, in addition, that the degree of obesity increases (8,9). The 97th centile crosses the adult cut-off of 25 kg/m^2 at an age range of about 10 y, and by 14 y 97th centile exceeds 30 kg/m^2.

With the increasing prevalence of obesity, we will have to and already do face the consequences of obesity at a much younger age. In our cohort of obese children, we saw a high prevalence of metabolic pathology. One third had signs of insulin resistance that correlated with BMI, and many had dyslipidemia (Table 1). This is in agreement with many other studies, such as by Sinha (10), and is also seen in other German Caucasian cohorts (11,12).

Another important component is blood pressure and hypertension, which is not currently well investigated in children. In a large cross-sectional study of about 2500 children, we identified a mild but continuous increase in the prevalence of hypertensive blood pressure levels that sharply raised when children became overweight (13). It also appears that cardiovascular risk factors cluster in children, as shown in other studies, which similarly observed that about one third of overweight and obese children had classical cardiovascular risk factors such as dyslipidemia and particularly BMI dependent hypertension (14). There are few studies that aimed to define the metabolic syndrome in children, which is probably even more difficult than in adults since the selection and the cut-offs of the parameters are even more arbitrary. These studies uniformly show that the metabolic syndrome is a disorder highly prevalent in the pediatric population (Table 2) (15–18). Hence, almost all sequelae of obesity-related disorders develop already in childhood (Fig. 2).

Table 1. *Incidence of metabolic disorders in obese Caucasian children of central Germany*

Parameter	Patients with pathology (%)	BMI, r	BMI SDS, r
Impaired glucose tolerance	18.3	0.12*	NS
Hyperinsulinemia			
Peak insulin >1000 pmol/L	40.4	0.24†	0.11*
Fasting insulin >158 pmol/L	11.0	0.45†	0.19†
Insulin resistance HOMA-IR >3.0	33.6	0.46†	0.18†
Hyperuricemia	25.4	0.52†	0.18†
Hypertriglyceridemia	22.5	NS	NS
Hypercholesterinemia	12.1	NS	0.13‡
Elevated liver enzymes	16.1	0.18†	NS

Data are shown for n = 307 consecutive obese children (BMI SDS ≥1.88 SDS) of the University Hospital for Children and Adolescents Leipzig, Germany. Pearson's correlation coefficient for n = 398 oGTTs was calculated, referring to BMI and BMI SDS indicating the degree of obesity.* $p < 0.05$; † $p < 0.0001$; ‡ $p < 0.01$.

HOMA-IR, homeostasis model assessment-insulin resistance; OGGTs, oral glucose tolerance test.

NONALCOHOLIC STEATOHEPATITIS (NASH)—A NEW COMPONENT OF THE METABOLIC SYNDROME?

In addition to these classical components of the metabolic syndrome, there is increasing concern about the emergence of NASH in obese children. Nonalcoholic fatty liver disease was found in 55% (19) to 77% of obese children with about 24% already suffering from NASH (20). Recent studies suggest that insulin resistance and oxidative stress are important in the pathogenesis of NASH and that NASH may hence be considered as the hepatic manifestation of the metabolic syndrome (21). As in adults, NASH in children may progress to cirrhosis associated in later life in about 20% and 30–40% of patients with NASH cirrhosis will experience liver-related death (22). Hence, this condition deserves consideration in the work-up for co-morbidities in obese children. Currently, there is, however, no recommendation on pharmacological intervention in children. Because both long-term studies on the clinical course and treatment options are lacking, life-style (dietary) intervention is of high importance (23).

PREDICTORS FOR THE METABOLIC SYNDROME IN CHILDREN—FACTORS FROM ADIPOSE TISSUE

Considering this early increase in obesity prevalence and that the fact that children are otherwise relatively free of co-morbidities and usually treatment naïve, they constitute an interesting and valuable population to study the sequence of events leading to obesity-related pathology. Particularly, research into the mechanisms and mediators of obesity-related sequelae has greatly expanded over the last years and, in this respect, factors released from adipose tissue appear to be particularly important. These compounds, such as inflammatory components and cytokines, fatty acids and, of course, the adipocytokines, exert biologic actions beyond the adipose tissue and many directly influence peripheral metabolic, vascular and endocrine processes (24,25).

Leptin. Leptin was the first of the classical adipocytokines detected (26). It was initially very promising, with actions to reduce food intake and to increase energy expenditure and thereby reduce body weight in rodents, as has extensively been reviewed elsewhere (27). In humans, the effects of leptin in obese people were disappointing (28). However, there are new interesting aspects emerging, particularly the effect of leptin on vasculature and endothelial cells by interaction with

Table 2. *Overview of the incidence of metabolic syndrome in children in representative studies*

	Weiss *et al.* (2004)	de Ferranti *et al.* (2004)	Lambert *et al.* (2004)	Butte *et al.* (2005)
Definition criteria for metabolic syndrome				
Obesity	BMI >97th centile	Waist >75th centile	BMI >85th centile	Waist >90th centile
Triglycerides	>95th centile	>1.1 mmol/L	>75th centile	>90th centile
HDL cholesterol	<5th centile	<1.3 mmol/L	<25th centile	<10th centile
Blood pressure	>95th centile	>90th centile	>75th centile	>90th centile
Glucose metab. Fasting glucose IGT	≥7.8 mmol/L	≥6.1 mmol/L	≥6.1 mmol/L	>100 mg/dL
Prevalence of metabolic syndrome in the study population				
Prevalence (degree of obesity)	38.7% (moderate), 49.7% (morbid)	31.2%	11.5%	20% (overweight), 30% (BMI ≥99th centile)
No. (ethnic population)	439 obese (mixed)	1960 obese (mixed)	2244 normal (normal)	1030 (319 families)(Hispanic); 34% overweight, 57% obese
Reference	(15)	(18)	(17)	(77)

Definition criteria for metabolic syndrome are shown in the upper part of the table. Metabolic syndrome was defined as having three or more of the components. Cut-off levels for the respective studies are given. IGT, impaired glucose tolerance.

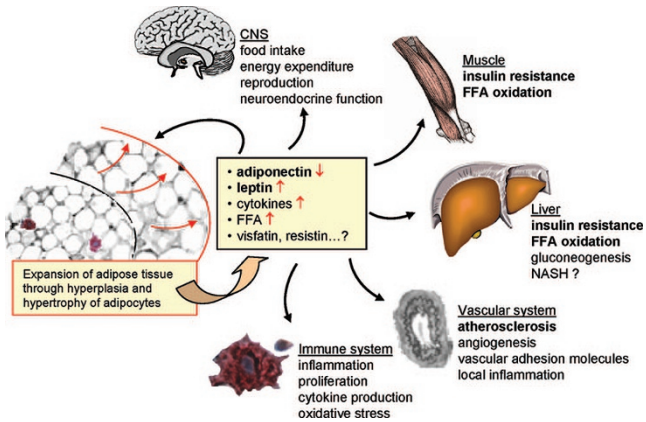

Figure 2. Contribution of adipocytokines to components of the metabolic syndrome. The schematic overview illustrates interactions of adipocytokines (which are not listed completely) with peripheral and central metabolic processes. Some effects of leptin and adiponectin are specified in Table 3 and are reviewed elsewhere.

Table 3. *Effects of leptin and adiponectin on metabolic, cardiovascular, and immune function*

Leptin		Adiponectin
(↓)	Insulin sensitivity	↑
↓	Food intake	→
↓	Body weight	→
↑	Dyslipidemia	↓
↑	Energy expenditure	
↑	Cell proliferation	↓
↑	(Vascular) inflammation	↓
↑	Endothelial adhesion molecules	↓
Angiogenesis ↑		Antiatherogenic
Thermogenesis ↑		
SNS activity ↑		
Reproduction ↓		

pathways of oxidative stress, nuclear factor-κB, endothelin, and others, which is also relevant in humans as reviewed elsewhere (29). It is well known that leptin levels correlate closely with BMI in both adults and children. In addition, there are associations of leptin with metabolic parameters such as insulin resistance indices (HOMA-IR) or lipids. This may, however, be mainly attributable to the underlying association with fat mass.

Another player in the leptin system is the sOB-R, which may play an important role in the regulation and modulation of leptin action. We identified specific binding of leptin to its soluble receptor in human plasma and confirmed that this is the major leptin binding protein in human serum (30). To evaluate the biologic and cellular relevance of leptin binding to its soluble receptor, we applied a system of hematopoietic cells transfected with full-length human leptin receptor, in which leptin exerted a pronounced and dose-dependent proliferative response (31). If sOB-R was added to the system, the proliferation exerted by leptin was blocked when sOB-R was present in excess (31). To evaluate the physiologic and pathophysiological relevance of these complexes in children, we first analyzed normal children and saw that the sOB-R decreased with age, whereas leptin strongly increased during puberty (32). Expectedly, obese children had higher leptin levels compared with lean children. In contrast to this, the sOB-R serum levels were significantly lower in the obese children (33). There are, however, situations in which the molar excess of sOB-R over leptin is remarkably high. We identified high sOB-R excess in neonates in the phase of postnatal weight loss (34) in children with manifestation of type 1 diabetes, where it decreased when the metabolism was corrected by giving insulin (35). These are situations of high energy demand and/or energy deficiency. More direct evidence for this notion was provided by a recent study in malnourished children that presented with high ratios of sOB-R over leptin that declined after re-feeding (36). Hence, one may hypothesize that this regulation of leptin by the sOB-R, possibly the whole leptin system, is more important in states of energy deficiency rather than being a predictor of the metabolic syndrome (37).

Adiponectin. Much more promising with respect to counteracting the metabolic syndrome is the adipocytokine adiponectin. Adiponectin is an adipocytokine that is exclusively expressed by adipocytes and circulates in very high concentrations in human serum. In contrast to most other adipocytokines, it exerts profound beneficial actions in that it has antiatherogenic, antidiabetogenic, and anti-inflammatory/-proliferative effects and thereby protects against the development of type 2 diabetes and cardiovascular disease (38,39).

It is decreased in obesity and these decreased adiponectin levels are associated with parameters of the metabolic syndrome in adults (29). Because it is also known that men have significantly lower adiponectin than women, we evaluated the course of adiponectin during pubertal development. In boys, there was a remarkable decline in adiponectin levels with the progression of puberty that eventually resulted in significantly lower adiponectin levels in boys compared with girls after completion of puberty (40). Thus, gender and pubertal stage need to be considered when comparing adiponectin levels between lean and obese children. Not surprisingly, adiponectin levels were markedly decreased in obese children. In a stepwise multiple regression analysis aimed to identify independent predictors in obese children, adiponectin levels closely correlated with parameters of insulin resistance, dyslipidemia, and the proinsulin:insulin ratio that override the effects of BMI and pubertal development seen in the lean children (40–42). Particularly, the high-molecular-weight complex reflects metabolic abnormalities associated with childhood obesity (43).

In addition to metabolic parameters, adiponectin was also negatively associated with intima media thickness in children, which is an early indicator of developing and existing vascular damage (44). Hence, in all these studies there is a clear association of low adiponectin levels with cardiovascular risk factors. In studies investigating whether adiponectin actually predicts the presence or occurrence of metabolic syndrome in children, adiponectin levels lower than the median were actual the strongest predictor of metabolic syndrome, with an odds ratio of 10 (45,46). Thus, adiponectin is obviously a very early predictor of metabolic syndrome in children.

Considering this important role of adiponectin, the regulation of adiponectin expression becomes interesting. Adiponectin is exclusively expressed by adipocytes; still, the expression and serum levels are decreased in obesity (29). It is also known that obesity results not only from hypertrophy but also from hyperplasia of adipose through the recruitment and differentiation of preadipocytes (47). While preadipocytes do not express adiponectin, expression was induced increasingly with differentiation of the adipocytes and protein expression was confirmed to be specific for mature adipocytes (48). The exposure of adipocytes to serum during the course of differentiation and acutely to mature adipocytes led to a profound suppression of adiponectin indicating a strong humoral components exist in human serum that suppress adiponectin expression. This or these components are present in the serum of lean as well as obese patients and are of high molecular weight (48). As an important metabolic regulator, adiponectin itself is controlled in conditions of metabolic stress (49) and by a number of hormones and factors involved in regulation of metabolic and/or immune function. Insulin decreases adiponectin levels in humans and in rodents, both *in vivo* and *in vitro* (50). Thiazolidindiones, as potent PPARγ agonists, increase the expression of adiponectin (51,52). Most other factors with significant impact on adiponectin regulation do exert inhibitory effects (50), as there are catecholamines, glucocorticoids (53), cytokines [IL-6 and tumor necrosis factor (TNF)-α] (53), prolactin (54), growth hormone (54), and androgens (40,55).

Inflammatory cytokines. Finally, in recent years, research has elucidated that low-grade systemic inflammation may underlie, at least in part, the clustering of cardiovascular risk factors (56,57). Through the production and secretion of cytokines, the adipose tissue may hence contribute to that low-grade inflammatory state (56,57).

It is well acknowledged in adults that the high-sensitive CrP is a good marker for low-grade inflammation that is elevated in obesity in relation to cardiovascular risk profiles (58). In obese children, many studies do also show an elevation of CrP. However, in contrast to adults, most studies in children do not conclusively confirm that CrP is associated with insulin resistance or metabolic risk if corrected for BMI, possibly except for lipid status (59–62). The situation is similar with other adipocytokines. TNF-α, IL-6, and resistin are produced by adipose tissue (or adipose resident macrophages), and some, such as IL-6, in amounts relevant for serum levels (63). Accordingly, there is also an elevation of the proinflammatory cytokine IL-6 in obese children (64). For TNF-α, the situation is less clear cut, with studies showing a positive association with body fat and others showing a decrease in obese prepubertal children (65,66). Serum levels of resistin do not appear to be much changed in obesity in children (67). Overall, the BMI independent predictive value for metabolic risk factors really remains to be shown for children.

ADIPOCYTOKINES IN RELATION TO BIRTH WEIGHT

Reduced fetal growth is independently associated with an increased risk of the development of cardiovascular diseases, the insulin-resistance syndrome, or one of its components (68). Comparing the prevalence of the metabolic syndrome between young adults formerly having been SGA or AGA revealed a significant difference for all components, with metabolic syndrome observed in 2.3% of the SGA group and in 4 per 1000 of the AGA group (69). The pathophysiologic mechanisms of this association are incompletely understood, though current hypotheses point to derangements in the fetal development process of adiposity that is responsible for postnatal growth and the later development of insulin resistance.

The adipocytokine adiponectin as well as leptin are clearly detectable in breast milk and are also produced by placental and/or fetal tissue (70). Thus, the fetus and the infant are exposed to these factors, which is reflected by high serum concentrations of adiponectin and leptin in cord blood and peripheral serum (34,71,72). In the first months and years of life, these initially high adiponectin and leptin serum concentrations decline (34,73). There are no significant gender differences in the adipocytokine levels in newborns. As expected, cord blood and peripheral serum leptin levels are related to birth weight in several studies (74). However, as outlined above, these increased leptin levels are exceeded several-fold by sOB-R, which may preserve the fetus and/or

infant from deleterious energy waste in a state of energy deficit (34).

In contrast to adults, in children adiponectin correlated positively with birth weight (71,75). Considering that adiponectin expression increases with the differentiation of adipocytes (48), this relationship may reflect the amount of developing adipose tissue. This may also explain why adiponectin levels are lower in SGA compared with AGA newborns (72,76). The contribution of circulating adiponectin to the increased risk for developing insulin resistance and diabetes in formerly SGA children is, however, not clear, and is obviously difficult to evaluate due to the array of confounding factors over time.

In summary, there is a worrying increase of obesity-related co-morbidities in children beginning from a relatively young age, even leading to the full complex of "metabolic syndrome," which is, however, difficult to define. Factors from the adipose tissue may constitute not only markers but also mediators of metabolic sequelae of obesity.

Adiponectin, so far, appears to be the strongest predictor from the adipose tissue for developing or existing metabolic syndrome, even in children, whereas the role for leptin, the initial classical adipocytokine, may be more important in states of energy deficiency than in energy excess and metabolic syndrome. Other cytokines are markers of low-grade systemic inflammation, but their role in children remains to be further specified. Children constitute a valuable study population in which to evaluate the sequence of events in obesity-related pathophysiology and, therefore, to identify causal relationships.

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