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METABOLISM (R PASQUALI, SECTION EDITOR)

Metabolic Issues in Adolescence

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Abstract The prevention, diagnosis and treatment of obesity-induced metabolic conditions are cornerstones of the management of overweight and obesity in adolescents. This paper reviews important new evidence in the field of the metabolic issues concerning the obese adolescent, with particular focus on epidemiological and clinical aspects. Current concepts and controversies regarding metabolic syndrome (MS), MS components and novel metabolic markers will be discussed, as well as two other conditions that increase the metabolic and cardiovascular risk in obese adolescents: polycystic ovary syndrome and non alcoholic fatty liver disease.

Keywords Obese adolescents · Metabolic syndrome in adolescence · NAFLD · PCOS · Novel serum biomarkers · Metabolic issues

Introduction

Early onset obesity, which has reached pandemic proportion, is associated with increased morbidity and mortality and therefore with a shorter life expectancy [1, 2•]. Most of the health threatening consequences of juvenile obesity are due to metabolic disturbances induced by an excessive accumulation of fat which leads to chronic diseases like type 2 diabetes (T2DM), hypertension and cardiovascular disease (CVD) [1, 2•]. Thus, the prevention, diagnosis and treatment of obesity-induced metabolic conditions are cornerstones of the management of overweight and obesity in adolescents [3]. This paper reviews important new evidence in the field of the metabolic issues concerning the obese adolescent, with particular focus on epidemiological and clinical aspects. Current concepts and controversies regarding metabolic syndrome (MS), MS components and novel metabolic markers will be discussed, as well as two other conditions that increase the metabolic and cardiovascular risk in the obese adolescents: polycystic ovary syndrome (PCOS) and non alcoholic fatty liver disease (NAFLD).

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Metabolic Syndrome and Beyond

In adolescents as in adults MS is generally defined as the association of obesity or central obesity with at least two other cardiovascular risk factors among high blood systolic and/or diastolic blood pressure, high triglycerides (TG) and low high density lipoprotein cholesterol (HDL-C) [4, 5•, 6•, 7]. There are several controversies that have been fuelling the scientific debate on adolescent MS for years [5•, 6•, 7].

First of all, due to the lack of sufficient longitudinal data linking early metabolic parameters with long term hard metabolic and cardiovascular end-points, such as T2DM and CVD, a real consensus on the definition of MS for children and adolescents has never been achieved [5•, 6•]. Several definitions with different cut-off values for the diverse parameters have been proposed, leading to very large different prevalence estimates and diagnosis inconsistency when tested in the same populations and often proving diagnosis instability during adolescence [7–9]. Furthermore, none of the current definitions of MS for children and adolescents take into account novel important markers that would probably help predict long term metabolic and cardiovascular outcomes besides traditional MS components [6•]. Finally, and most importantly, there is increasing concern about the legitimacy of MS itself as a physiopathological and clinical entity [4, 5•,

6•]. From the physiopathological point of view, the legitimacy of MS would imply the existence of unifying mechanisms underlying the single metabolic impairments clustered in the MS definition. Insulin resistance (IR), driven by obesity-related ectopic and visceral fat accumulation, inflammation, impaired micro RNAs profile and some dietary habits, fetal programming, etc…, has been traditionally considered a major "unifying" cause of MS [4, 5•]. In fact IR correlates not only with impaired glucose uptake and storage or oxidation, but also with impaired TG storage and increased lipolytic activity in adipose tissue, with a consequential increase in the hepatic very low density lipoproteins (VLDL) synthesis and decrease in overall VLDL clearance [10–13]. Moreover, peripheral IR is a cause of hypertension [14]. In fact hyperinsulinemia and peripheral IR increase renal sodium resorption and decrease endothelial production of nitric oxygen (NO), respectively [15, 16]. However, several other mechanisms are emerging in both animal models and humans as physiopathological bases of one or more metabolic alterations typical of MS [4, 5•]. Thus pathologic pathways explaining single metabolic impairments can be redundant and differently expressed at the single individual level, according to genetic and lifestyle variability, and can play roles of variable importance in the diverse metabolic disturbances. Consequently, the components of MS do not completely share a pathogenesis. So for example adipokines, whose profile is altered in hypertrophic, inflamed adipose tissue, not only play a role in insulin signalling but also have several direct effects on glucose and lipid metabolism and on endothelial function, and are also associated with the β-cell damage underlying the development of glucose intolerance/diabetes [5•, 17, 18]; the activation of the renin-angiotensin-aldosterone system typical of metabolically unhealthy obesity plays a direct role in the development of hypertension and contributes to inflammation via reactive oxygen species (ROS) production and macrophage activation, with consequent worsening of IR [4, 19, 20]; chronic hyperactivity of hypothalamic-pituitary-adrenal axis (HPA) and 11 β -hydroxysteroid dehydrogenase type 1 (11-β-HSD1) are also directly linked to hypertension and IR [4, 5•, 21] and there is recent evidence that high-normal ACTH and cortisol may be associated with specific cardiovascular risk factors in pediatric obesity [22]; certain facultative obesity-related dietary behaviors can directly affect specific MS components and also worsen IR: this is the case of over-consumption of fructose, which directly increases TG and uric acid (UA) synthesis, but also decreases insulin sensitivity via ROS production [5•, 23, 24]; and so on. Factor analyses in adolescent populations have failed to support the notion that MS is a 1-factor cluster of metabolic disturbances, thus contributing to confute the idea of MS as a unique physiopathological entity [25, 26].

From the clinical point of view, there is still debate about the utility of MS as cardiovascular predictor in children and adolescents, as it has not been definitively established whether MS, which does not seem to be justifiable as physiopathological entity, has at least a legitimate role as a clinical tool to identify adolescents with the highest metabolic and cardiovascular risk [6•]. Although in general population longitudinal studies have not shown that MS during childhood and adolescence is any more useful than body mass index (BMI) in predicting subclinical atherosclerosis [27••], cross sectional studies on obese adolescents have shown that obese individuals with single components of MS, such as hypertension or impaired glucose tolerance (IGT), have higher carotid intima-media thickness (cIMT) than obese counterparts with no impairment [28]. Moreover, a short term longitudinal study of obese Latino children and adolescents showed that persistent MS was associated with higher cIMT compared to subjects without MS [29], thus providing evidence that screening obese youth for the presence of MS could have some clinical advantage. However, a recent cross sectional study including 461 overweight adolescents reported that the presence of MS is a poor predictor of increased cIMT compared to the sum of the quantitative components of MS. This strongly suggests that "in clinical practice, treatment of overweight adolescents should be based on weighing cardiovascular risk factors themselves, rather than on the dichotomous variable MS" [30]. So for example, an obese adolescent with severe isolated hypertension should raise more concern than an obese peer displaying MS due to modest impairment of several metabolic components.

Based on these considerations, the following part of this section focuses on recent evidence about the single metabolic/cardiovascular impairments traditionally screened in obese youth, with special attention to the clinical implications of severe impairments, and will briefly mention some novel potential metabolic markers recently explored by research in the field.

Disturbances of Glucose Homeostasis

As in adults, obesity-related disturbances of glucose homeostasis in adolescence are impaired fasting glucose (IFG), that is confirmed fasting plasma glucose (FPG) of 100 – 125 mg/dl, IGT, that is 2-h plasma glucose after an oral glucose tolerance test (OGTT), of 140 – 199 mg/dl, and T2DM, that is casual or 2-h plasma glucose ≥ 200 mg/dl in an overweight or obese child or adolescent with a family history of T2DM, substantial residual insulin secretory capacity at diagnosis, insidious onset of disease, signs of IR and absence of diabetic autoimmunity [31].

Even if T2DM is rare in children and adolescents, its rate is growing in parallel with the obesity epidemic and, especially in Asian populations, among ethnic minorities and adolescents, it accounts for an increasing proportion of the overall diagnoses of diabetes in youth (10-40 % in U.S. and EU, more

than 50 % in Asian populations, and up to 76 % in Native Americans) [31]. Little evidence exists on predictors of T2DM development in obese adolescents. Traditional pre-diabetic conditions (IFG and IGT) are not fully accurate predictors of future T2DM, as explained in the paragraphs on IFG and IGT. Preliminary data from a pilot longitudinal study show that HbA1c in non diabetic obese adolescents may be a predictor of short term onset of T2DM [32]. Notably, longitudinal cohorts have shown that all MS components are associated with adult T2DM and the combination of four or more MS components during childhood or adolescence is strongly predictive of T2DM during young adulthood, though this criterion has poor sensitivity [33, 34••]. Hypertension and high TG retained from childhood to adulthood have recently come out to be strongly predictive of adult T2DM [35•].

As regards the recommended screening strategies for T2DM, according to the American Academy of Pediatrics (AAP) all adolescents evaluated for obesity should undergo a FPG test [3]. FPG has recently shown a good accuracy in detecting OGTT-confirmed cases of T2DM in obese children and adolescents, in contrast to the 6.5 % HbA1c cut-off proposed by the American Diabetes Association (ADA) as a screening tool for T2DM, which has shown low sensitivity in detecting T2DM cases diagnosed by FPG or OGTT [32, 36].

An extensive discussion of the current recommendations for the management of T2DM in youth is beyond the purpose of this review. However, it is important to point out that the AAP guidelines for the management of T2DM have recently been published and have introduced an important modification in regards to the International Society for Pediatric and Adolescent Diabetes /International Diabetes Federation (ISPAD/IDF) guidelines, that is the recommendation to start immediately a combined pharmacological/behavioral therapy in all patients, avoiding the first non pharmacological step based on lifestyle changes alone, which, in contrast has been recommended by the ISPAD/IDF Consensus for all asymptomatic patients with HbA1c<7 % and blood glucose<130 and 180 mg/dl in fasting and post-prandial conditions respectively [31, 37]. This novel recommendation relies on the evidence of poor compliance to lifestyle changes in youth and is reinforced by recent evidence of very rapid deterioration of β-cell function in obese youth after diagnosis of T2DM [37, 38]. The "Treatment Options for Type 2 Diabetes in Adolescents and Youth" (TODAY) study, a recent three arms randomized clinical trial involving 699 obese adolescents with T2DM, showed that metformin combined with a lifestyle intervention program is less effective than metformin combined with rosiglitazone in reducing the rate of deterioration of glucose control, suggesting that monotherapy with metformin may not be sufficient to stop the deterioration of β-cell function [39••]. Even if the AAP guidelines acknowledge this, they do not recommend any other oral medication besides metformin, due to the lack of FDA approval of rosiglitazone for children and adolescents [37].

Isolated IGT is considered a pre-diabetic condition [31], even if short term longitudinal studies have shown that it is a strong predictor of T2DM only in African American severely obese adolescents and not in white obese adolescents, who tend to convert from IGT to normal glucose tolerance in most cases [40, 41]. However, IGT during childhood and adolescence is a cardiovascular risk factor per se, independent of the development of diabetes, as it is associated with an increased rate of CVD in adults [42] and it has recently been shown to be associated with increased cIMT in youth [30]. IGT is quite rare (3–14 %) in non selected pediatric populations with common overweight/obesity [43], so that the large scale OGTT has a low yield in diagnosing IGT in these populations and current clinical research is attempting to find out effective screening tools to select obese youth most likely to present IGT, for whom OGTT would be justified. The ADA criteria for selecting children to test for T2DM and criteria specifically designed for screening obese children for IGT in European populations [44, 45] have recently shown sub-optimal accuracy in identifying IGT when tested in different populations [46]. Recently fasting TG>103 mg/dl has been proposed as a criterion for selecting obese youth at risk of IGT in a Canadian population [46]. A few months later our group has validated this criterion in a large pooled population of Italian children and adolescents, and has proposed an implemented tool combining TG and FPG to select youth at risk for IGT. The combination of TG ≥ 100 mg/dl and FPG ≥ 80 mg/dl had 69 % sensitivity and 78 % specificity in selecting youth with IGT, which is the highest accuracy ever achieved by a published screening tool for IGT in youth [43]. This screening strategy should be validated abroad before being recommended in the management of obese youth [43].

IFG, that affects 2-5 % of obese children and adolescents, is also considered a pre-diabetic condition [31, 43, 46]. However, long term prospective studies on population-based cohorts of pre-adolescents and adolescents failed to demonstrate any association between baseline IFG and T2DM in young adulthood [27••, 31]. On the other hand, a recent longitudinal study in another population based cohort of children and adolescents showed that IFG was the strongest independent predictor of adult IFG/T2DM among parental history of T2DM, IFG and cigarette smoking after adjustment for BMI [34••]. Another study in pre-adolescent and adolescent girls showed that IFG was a strong independent predictor of IFG/T2DM at 24 years of age, along with weight gain, MS, and high insulinemia [47]. Further longitudinal studies especially designed for populations of obese adolescents at baseline would probably be helpful to clarify the exact significance of isolated IFG in obese individuals during adolescence.

Combined IFG and IGT is a condition characterized by profound impairment of both insulin sensitivity and secretion, whose pathophysiology in obese youth largely overlaps with that of overt T2DM [48]. Thus, although longitudinal studies

exploring the exact short and long term predictive utility of this condition are lacking, it should be considered a strong risk factor for the development of T2DM.

As in adults a 1-h glucose>155 mg/dl during an OGTT in obese children and adolescents showed that it was associated with impaired glucose disposition and insulin secretion, thus being a candidate predictor of T2DM for future longitudinal studies [49].

Finally, it is important to point out that measuring or at least estimating insulin sensitivity and secretion in obese adolescents is not currently recommended because of the lack of reliable and feasible surrogate measures and of clinically significant thresholds [50, 51].

Lipid Abnormalities

Age and gender specific cut-offs for normal lipid values have been recommended by the latest AAP guidelines on lipid screening and cardiovascular health in childhood [52]. There is a substantial lack of data on the role of lipid profile during adolescence in the development of future cardiovascular or metabolic disease, both in general and in obese populations [52]. However, data from the three pediatric cohorts Fels Longitudinal Study, Muscatine Study and Princeton Follow-up Study, as well as from the Bogalusa Heart Study and the Young Finns Study, have shown that TG in childhood or adolescence are associated with both MS and T2DM in adulthood, with sensitivity and specificity depending on the adopted cut-offs [27••, 33, 34••, 35•]. In multiple analyses, TG proved to be associated with adult MS independently of BMI [53].

Of note, in a cohort of 909 5-19-year-old children and adolescents followed up for a period of 22-30 years, TG> 110 mg/dl was the only independent categorical risk factor for CVD during young adulthood [34••], further reinforcing the importance of TG as a cardiovascular risk factor during childhood and adolescence. It may be surprising that low density lipoprotein cholesterol (LDL-C) has not come out to be a predictor of CVD. This is likely to be due to the fact that a cut-off of 110 mg/dl has been adopted to define abnormality, which is probably too low to be predictive of CVD. Higher levels of LDL-C, typical of polygenic or familial hypercholesterolemia, are much less common but are associated with a significantly greater risk of CVD [28] and although they may account for a small percentage of early events compared to the much more common TG>110 mg/dl, they must be regarded as a severe risk factor, especially in obese adolescents [52, 54–56]. In fact, it is recommended that the presence of obesity be considered an important aggravating cardiovascular risk while managing adolescent patients with TG and/or cholesterol abnormalities [52, 55, 56]. An exhaustive discussion of therapeutic options for lipid abnormalities in adolescence is beyond the purpose of this review and the reader is invited to read specific guidelines on this issue [52, 55–57]. It is however important to stress that therapy should be tailored to the individual patient, based on his/her age, family history of early CVD, degree of lipid abnormality and the presence of other important cardiovascular risk factors and is based on lifestyle changes and drugs, mainly statins [52, 55, 56]. The presence of obesity is one of the factors contributing to making the decision to start pharmacological therapy [52, 55, 56]. Adolescent obesity and dietary fat, besides being independent aggravating cardiovascular risk factors, also affect directly the atherogenic effect of LDL-C as they favor small atherogenic rather than larger less atherogenic LDL-C particles, similarly to what has been observed in adults [58, 59]. HDL-C is another traditional metabolic and cardiovascular risk factor, although most longitudinal studies taking into account BMI and other traditional risk factors have failed to demonstrate an independent association between HDL-C and adult cIMT, T2DM, MS or CVD [27••, 34••, 53]. Recent data suggest that the TG/HDL-C ratio, which correlates with small, dense LDL-C, may be helpful in selecting children and obese adolescents at the greatest cardiovascular risk. In fact, the TG/HDL-C ratio was associated with arterial stiffness in children and young adults, even when only obese subjects were taken into consideration [60]. Moreover, the TG/HDL-C ratio was associated with worse values of other metabolic parameters in children and adolescents and children with a ratio of ≥ 2 showed a two to threefold higher risk of high alanine transaminase (ALT) levels and concentric left ventricular hypertrophy than those with a lower ratio, regardless of confounders [61•].

Hypertension

Obesity is an important driver of primary hypertension in adolescents [62–64]. The AAP have provided guidelines for the diagnosis and management of hypertension [65]. The prevalence of hypertension is estimated to be about 5 % in adolescents but obese adolescent boys have almost a ten-fold higher risk to be hypertensive and obese girls a more than double risk [63]. Hypertension during childhood and adolescence predicts adult hypertension [34••]. Moreover, in childhood and adolescence hypertension is strongly associated with higher cIMT [28], is associated with greater arterial stiffness [66] and is also a long term predictor of adult cIMT [27••]. Finally, hypertension is a metabolic risk factor, as it predicts adult MS and T2DM [27••, 53]. Recently, besides weight status and lifestyle, UA and sodium intake have proved to be modifiable risk factors for hypertension in youth [67, 68•, 69, 70•]. Sodium intake interacts with obesity to increase the risk of pre-hypertension/hypertension among pre-adolescents and adolescents [67]. See the following paragraph for deeper discussion on uric acid and hypertension.

Increased attention has been focused on the pharmacological treatment of primary hypertension in adolescence [71, 72]. It has been reported that almost two thirds of hypertensive adolescents in the U.S. are prescribed drugs by their primary care physician only [72] and a large national survey on German obese children and adolescents has reported that drug treatment of hypertension was rarely performed and the criteria for drug treatment recommended in the European Guidelines [73] are rarely taken into account [71]. Thus, future efforts to sensitize pediatricians toward the diagnosis and treatment of adolescent hypertension are warranted, especially within the overall management of obesity.

Novel Potential Serum Biomarkers

Because traditional metabolic and cardiovascular risk factors have only moderate accuracy in predicting metabolic and cardiovascular morbidity and mortality, for several years a large amount of research has been focusing on novel metabolic and cardiovascular markers as potential preventive and therapeutic targets [74–77]. This is true also for children and adolescents. Retinol-binding protein 4 (RBP4), a well established risk factor for IR, metabolic impairments and atherogenesis in adults, have also proved to be associated with IR and adiposity-related comorbidities in obese adolescents [78–80]. Similarly, the adipokine adiponectin, whose pleiotropic metabolic effects have been extensively described in both children and adults, could be another interesting biomarker for the risk assessment and the follow-up of obese adolescents as well as an intriguing therapeutic target [78]. Pigment epithelium growth factor (PEDF), an adipose tissue-derived glycoprotein, is another potential metabolic and cardiovascular marker, whose prognostic and clinical role in obese adolescents needs to be defined by future studies [78]. Among routinely dosed biochemical markers, UA is gaining increasing attention as a metabolic and cardiovascular predictor as well as a therapeutic target for the prevention of cardiovascular morbidity [81]. UA induces vascular, adipocyte and hepatic oxidative stress as well as rennin-angiotensin-aldosterone system activation and NO synthase inhibition, thus contributing to IR, hypertension and MS [82]. In adults, UA is a well established predictor of MS, T2DM and CVD and elegant experiments in animal models have shown that fructose-induced MS components are prevented by urate-lowering drugs [81, 82]. UA has been shown to play a role in adolescent primary hypertension in epidemiological surveys and in small trials assessing the efficacy of allopurinol as an antihypertensive drug [70•, 83]. Recently, urate lowering drugs have been successfully used to treat pre-hypertension in obese adolescents [68•]. Moreover, longitudinal data have recently shown that UA is an independent predictor of all metabolic syndrome components in adolescents [84]. Thus, UA is likely to be an interesting risk marker and therapeutic target in obese adolescents, especially in those with hypertension.

PCOS

PCOS is a well-established metabolic and cardiovascular risk factor in adult women. In fact, 70 % of women with PCOS have IR and T2DM beyond that predicted by BMI alone [85•] and PCOS is associated with a dramatic acceleration of the typical transition from IGT to overt T2DM [85•]. Hyperandrogenism has been shown to have a direct cause-effect link with the development of T2DM [86, 87]. The diagnosis of PCOS and hyperandrogenism is challenging in adolescence, due to the physiological endocrine perturbations typical of this period, which make it difficult to distinguish transient para-physiological impairments of the hypothalamus-pituitary-gonadal axis from frankly pathological conditions [88•]. However, it has been proposed recently that the Androgen Excess –PCOS Society criteria for the diagnosis of PCOS in adults (clinical and/or biochemical hyperandrogenism + ovulatory disfunction + polycystic ovary) may be adequate for adolescent girls as well [89].

Adolescent girls with PCOS have significantly higher rates of perturbations of glucose metabolism, mainly IGT [89–91], and are at increased risk of hypertension [92] and MS [89, 93], compared to their healthy counterparts. IR and metabolic perturbations are more prevalent in obese than in non obese girls with PCOS [89, 91, 92] and increased androgens in obese girls with PCOS have been associated with increased cIMT [28]. Longitudinally, PCOS at 14 years has been shown to be associated with MS and class III obesity at 24 years [94]. Thus, obese girls with PCOS should be considered at particularly high metabolic risk and it is advisable that all obese girls with irregular menses be extensively evaluated in search of PCOS and metabolic co-morbidities like IGT, hypertension and other MS components. IR is an important pathogenic determinant of PCOS [88•], so that as in adults therapeutic options for adolescent girls with PCOS include not only oral contraceptive pills and anti-androgens, but also lifestyle interventions and insulin sensitizer drugs, mainly metformin [85•]. There is a lack of long-term data on the efficacy and safety of diverse therapeutic regimens in lean and obese adolescents with PCOS and there are few short term intervention studies, so that a clear evidenced-based consensus on this issue is not available [85•], as it is highlighted in an extensive review on this topic [85•].

NAFLD:

NAFLD is strongly associated with visceral obesity and is defined as bioptic hepatic fat infiltration>5 % of hepatocytes

in the absence of excessive alcohol intake, or viral or autoimmune or drug-induced liver disease [95••]. The prevalence of NAFLD in obese adolescents is dramatically high (up to 80 %) in obesogenic countries [95••]. The natural history of NAFLD is still uncertain, but a small, although still not well defined, percentage of children and adolescents with NAFLD develop cirrhosis and hepatocellular carcinoma, as consequences of NAFLD-induced non alcoholic steatohepatitis (NASH). Genetic variants and ethnicity have been robustly associated with NASH and NASH severity [95••] and there is intense ongoing research to find out non invasive and cost-effective markers of NASH, due to the inaccuracy of hepatic enzymes ALT and AST [95••]. Recently, an algorithm based on the pediatric NAFLD fibrosis index (age, waist circumference and TG) and the enhanced liver fibrosis (ELF) test (hyaluronic acid, amino terminal propeptide of type III collagen and TIMP1) has been proposed to accurately assess liver fibrosis in youth with NAFLD [95••]. Hepatic ultrasonography with transient elastography has also been successfully used to assess hepatic fibrosis in children and adolescents [95••].

Even in absence of liver injury, NAFLD in obese adolescents is clinically significant per se. In fact, evidence is accumulating that NAFLD is associated with a worse metabolic and cardiovascular profile among obese youth. Insulin sensitivity is more seriously compromised and traditional metabolic impairments are more prevalent in obese adolescents with NAFLD than in non-affected subjects [96]. Interestingly, NAFLD has been recently associated with cIMT in obese adolescents, independently of classical metabolic confounders (lipid profile, BMI, etc…) [96, 97]. According to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), liver biopsy, the gold standard for the diagnosis of NAFLD, cannot be adopted as a first approach to assess the presence of NAFLD in children and adolescents [95••]. Anthropometric and biochemical markers have moderate accuracy in selecting obese adolescents with NAFLD [98, 99]. The ESPGHAN recommends that NAFLD be suspected in all of the overweight/obese adolescents with increased waist circumference, especially in presence of positive family history. In these adolescents, abdominal ultrasound and liver function tests should be performed, followed by exclusion of other liver diseases [95••]. A consensus on the treatment of NAFLD is still lacking. Lifestyle changes and omega-3 supplementation have shown a good short term efficacy in obese children and adolescents [95••]. Gut microbiota and antioxidant vitamins have recently been proposed as further potential targets to treat NAFLD and NASH [95••, 100]. According to the experts in the field, a multi-targeted therapy could be the most effective approach for treating youth with NAFLD [95••].

Conclusion

An increasing amount of evidence has been unravelling the pathogenesis, the clinical presentation and the prognosis of several traditional or recently described metabolic disturbances associated with adolescent obesity, so that the classical concept of MS is no longer satisfactory to assess and possibly rectify metabolic and cardiovascular risk in adolescent obese patients. Currently, recognized and routinely assessed obesity-related metabolic disturbances in adolescence, include not only traditional MS components, but also NAFLD/NASH and, in girls, hyperandrogenism and PCOS. In the near future, metabolic evaluation of an obese adolescent will most likely include other modifiable metabolic and cardiovascular predictors, such as hyperuricemia and other disturbances.

Compliance with Ethics Guidelines

Conflict of Interest Anita Morandi and Claudio Maffeis declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance,
- •• Of major importance

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