SciMedCentral

Annals of Pediatrics & Child Health

Review Article

Metabolic Syndrome in Pediatrics: The Role of Lipid Partitioning

Romy Kursawe*

Department of Pediatrics, Yale University School of Medicine, USA

***Corresponding author**

Romy Kursawe, Department of Pediatrics, Yale University School of Medicine, 330 Cedar Street, P.O. Box 208064, CT 06520, New Haven, Connecticut, 06520, USA, Tel: 203 785-6972; Fax: 203 785-6421; E-mail: romy.kursawe@yale.edu

Submitted: 20 November 2013

Accepted: 06 January 2014

Published: 07 January 2014

Keywords

- Metabolic syndrome
- Pediatrics
- Childhood obesity
- Cardiovascular diseases

Abstract

The ever growing prevalence of childhood obesity is being accompanied by an increase in the pediatric population of diseases once believed to be exclusive of the adulthood such as the metabolic syndrome (MS). The MS has been defined as the link between insulin resistance, hypertension, dyslipidemia, impaired glucose tolerance and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular diseases in adults. In the past years it however became clear that a subgroup of obese patients is metabolically healthy with insulin sensitivity similar to healthy lean individuals, and lower liver fat content than the majority of metabolically 'unhealthy' obese patients. Recent studies investigating lipid partitioning among specific fat depots revealed that protection against ectopic fat deposition in liver, muscle and heart, as well as protection against adipose tissue dysfunction and inflammation, seem to be contributing to the healthy obese phenotype.

INTRODUCTION

The prevalence of childhood obesity has been increasing in the last four decades with an estimated sixty millions of children being overweight worldwide by 2020 [1]. The worldwide epidemic of childhood obesity is responsible for the occurrence in pediatrics of disorders once mainly found in adults, such as the Metabolic Syndrome (MS). Described by Gerald Reaven, the MS has been defined as "a link between insulin resistance, hypertension, dyslipidemia, impaired glucose tolerance and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular diseases in adults" [2]. MS in children is commonly defined as the co-occurrence of three or more of the following features: severe obesity (usually with a waist circumference higher than the 90th sex and age specific percentile), dyslipidemia (increase of triglycerides and decrease of HDL), hypertension and alterations of glucose metabolism such as impaired glucose tolerance (IGT) and type 2 diabetes (T2D) [3]. The key factor in the pathogenesis of MS is insulin resistance, with its major cause being obesity, in addition to a genetic background, low physical activity, specific dietary habits and the ethnic background. Weiss et al. have well demonstrated how the increase of insulin resistance parallels the increase of the risk of MS in obese children and adolescents [4]. The main pathogenic feature of insulin resistance is the lipid accumulation in organs and tissues that usually do not store lipids (ectopic fat accumulation) such as the liver, pancreas and, the skeletal muscle [4]. The lipid accumulation interferes with the normal insulin signalling cascade and makes the tissues resistant to the insulin action. Interestingly the resistance to insulin seems to be limited to the glucose metabolism. Therefore, under these conditions while hyperinsulinemia is not able to suppress hepatic glucose production, it turns the liver into a "fat-producing-factory" with all of its negative downstream effects, including the genesis of hypertriglyceridemia [4]. Also, the fat cells resistance to insulin action causes an increase in lipolysis with a consequent increase in dismissing lipids in the plasma [4]. This causes a massive accumulation of lipids into the liver, which results in hepatic steatosis and higher triglycerides production. From a molecular point of view the link between lipid accumulation and insulin resistance seems to be represented mostly by diacylglycerol (DAG) [5,6]. Increased lipids in the hepatocytes (but also in the skeletal muscle) has been shown to increase in the cells the amount of DAG, a signaling intermediate that activate members of the protein kinase C (PKC) family, thus altering insulin signaling [6]. As consequence of insulin resistance the pancreas needs to increase its insulin production to maintain normal value of glycemia, promoting, in this way, the lipid accumulation, further worsening insulin resistance and generating a vicious cycle.

Is obesity sufficient for identifying children at risk for MS?

Data from multiracial cohorts of obese children showed that the severity of obesity and the prevalence of metabolic syndrome are strongly associated [4]. Interestingly, obesity is not synonymous of insulin resistance as some obese adolescents may be very insulin sensitive and show a healthy metabolic

phenotype [7]. This so called "metabolically healthy obesity" most likely represents the extremes of continuous relationship between increased BMI and deteriorations of components of the metabolic syndrome such as blood pressure, fasting insulin levels, HDL cholesterol and TG levels, which has been recently described in children [8]. In adults it has been shown that about 50% of obese individuals can be classified as metabolically healthy using % body fat to determine obesity, and 34% when using BMI [9]. In children (4-18 years of age), a recent study by Weghuber et al. [10] showed that only 16% can be regarded as metabolically healthy, while about 36% fulfilled the criteria for metabolic syndrome. The metabolically healthy phenotype is characterized by lower waist circumference, visceral fat content, and significantly decreased nuchal SAT at a given proportion of body fat, and showed increased peripheral insulin sensitivity, a less pronounced pro-inflammatory status, lower malondialdehyde concentration (as surrogate parameter of oxidative stress), higher liver function parameters and higher total adiponectin. Interestingly, uric acid best predicted the distinction between obese subjects with or without metabolic syndrome [10].

The fat distribution plays an important role in influencing the occurrence of metabolic complications consequent to obesity. Visceral fat accumulation, in fact, is strongly associated with MS in childhood [11] and coronary artery disease (CAD) later in life [12] and is the best clinical predictor of visceral fat accumulation [13]. Although reference values for waist circumference in children do exist for Canada [14], Italy [15], UK [16], and US [11] and cut-off points beyond which there is an increase of the prevalence of CAD risk factors have been provided [11], this measure is not commonly used in children, probably because no organization has endorsed waist circumference cut-off for children. The importance of measuring waist circumference is corroborated by studies in children and adolescents showing that subjects with high waist circumference values are more likely to have elevated CAD risk factors, compared with those with low waist circumference, within a given BMI category [12]; this means that waist circumference may be, for such an extent, considered a more reliable measure for predicting MS than BMI alone. In fact, as in adults [17-20], in children an increased waist circumference has been correlated with abnormal systolic and diastolic blood pressure and elevated levels of serum cholesterol, LDL, triglycerides, insulin as well as with lower HDL concentrations [21-23]. The association between the clustering of cardiovascular risk factors and waist circumference is not only a reflection of the obesity degree, but it has a pathophysiological background, given that visceral adiposity is one of the main risk factors for the development of insulin resistance, diabetes mellitus, hypertension, and cardiovascular disease [24]. The mechanisms involved in these common clinical associations are not completely known, but include the impaired suppression of hepatic glucose production [25], the increased portal release of free fatty acids, the increased visceral production of glycerol [26], and the abnormal production of adipose tissue-derived hormones and cytokines, such as tumor necrosis factor (TNF)-alpha, leptin and adiponectin [27,28].

Association between Lipid partitioning and Metabolic Syndrome

The term 'lipid partitioning' refers to the distribution of body fat in organs (some of which are insulin-responsive tissues) and compartments. The majority of excess fat is stored in its conventional subcutaneous depot, yet other potential storage sites exist as well, such as the intra-abdominal (visceral) fat compartment and insulin-responsive tissues such as muscle, liver, the pancreas and large blood vessels. Lipid partitioning has been proven to be a better determinant for insulin resistance then obesity alone. The distribution of body fat varies between men and women, men start to accumulate fat in the visceral depot far earlier than women, as well as between different ethnicities, with African Americans having increased subcutaneous fat storage capacity [29]. Therefore, a more healthy phenotype of obesity is an increased subcutaneous versus visceral abdominal fat ratio and a higher gluteal-femoral than abdominal fat distribution - the so called pear-shape. The pattern of lipid storage not only has local, direct autocrine effects on signal transduction pathways, but also determines the secretion profile of specific adipocytokines and inflammatory cytokines, thus affecting metabolism in distant organs via an endocrine effect [30,31]. The combined effect of these factors determines the sensitivity of insulin-mediated pathways within insulin-responsive organs (such as muscle and liver) and impacts the vascular system by affecting endothelial function.

We showed in multiple studies that an unhealthy abdominal lipid partitioning with low subcutaneous and high visceral fat storage is associated with ectopic fat in muscle and liver, resulting in insulin resistance in youth (Figure 1) [7,32,33]. Taksali et al. described a potential non-favorable pattern of lipid partitioning with excess intra-abdominal fat in relation to abdominal subcutaneous fat [32]. Obese children with a high visceral-to-subcutaneous fat ratio are not more obese (by BMI or by percent body fat) in comparison to those with a lower ratio, but have a greater degree of insulin resistance and an adverse metabolic phenotype manifesting as more severe dyslipidemia, systolic blood pressure and dysglycemia [32,33]. A potential explanation for this phenomenon is that the intra-abdominal fat deposits drain directly into the liver where a postulated increase free fatty acid flux accumulates. While intra-abdominal fat does have a greater sensitivity to adrenergic stimulation and a lower sensitivity to

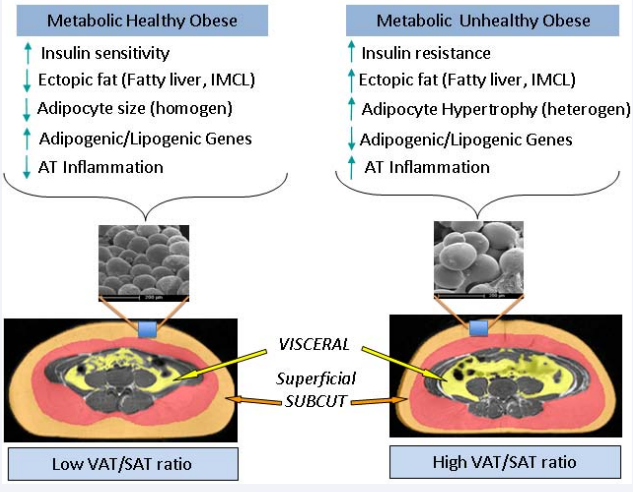

Figure 1 Major differences between the 2 phenotypes of obese adolescents.

insulin *in vitro*, the contribution of this deposit to circulating free fatty acid concentration seems to be in proportion to its absolute quantity, therefore, its adverse effects may be related to other factors [34]. Differences in the abundance of lipid droplet proteins that regulate the storage and breakdown of triglycerides in the fat cell could play a key role. It has been suggested that when energy accumulates in adipocytes, the perilipin border of the fat vacuole breaks down, causing the adipocyte to demise [35]. Cell death then causes a recruitment of macrophages via tissue-derived chemokines, especially in the visceral compartment. The accumulation of these macrophages results in increased secretion of inflammatory cytokines, initiating a proinflammatory milieu, which possibly drives the development of systemic insulin resistance, altered glucose metabolism and endothelial dysfunction [35]. Obesity has been shown to be associated with subclinical inflammation in adolescents and more so in those who met the criteria of the metabolic syndrome. Analyses of subcutaneous and visceral adipose tissue depots from insulin sensitive and resistant patients indicate that the insulin sensitive and resistant patients differ with respect to AMP-activated protein kinase (AMPK) activity and oxidative stress in all of their fat depots [36] and in the expression of genes related to inflammation, mitochondrial function, SIRT1/Nampt, and many others [36-39] in selected depots. Key abnormalities appear to be impaired triglyceride storage and increased lipolysis by lipid droplets, mitochondrial dysfunction, inflammation, and increases in oxidative and endoplasmic reticulum stress [39,40]. Many of these abnormalities could be related to increased synthesis and release of chemokines from the adipocytes or more likely adjacent vascular cells that attract monocytes (CD68), T (CD4) and B lymphocytes, and neutrophils (MPO) from circulating blood [41]. The resultant increases in the release of free fatty acid (FFA), reactive oxygen species (ROS), and inflammatory cytokines and the decreased release of adiponectin from the adipocyte are thought to act on peripheral tissues to cause such disorders as type 2 diabetes, atherosclerosis, and NAFLD. In subcutaneous abdominal fat, the indicated changes may also be associated with decreased capillarity [37] and impaired O_2 consumption and increased synthesis of type VI collagen [37, 42], all of which could limit adipose tissue expansion.

The Adipose tissue in the MS

Several pathophysiological explanations for the metabolic syndrome have been proposed involving insulin resistance, chronic inflammation and ectopic fat accumulation following adipose tissue saturation [37]. However, current concepts create several paradoxes, including limited cardiovascular risk reduction with intensive glucose control in diabetics [43], therapies resulting in weight gain (PPAR agonists) [44]. A newer prospective is the functional failure of the adipose tissue as an organ unable to buffer postprandial lipids [45].

The functions described for white adipose tissue from classical physiology are: heat insulation, mechanical cushioning, and storage site for fat in the form of triglycerides. However, this view has been dramatically changed with the recognition of the adipose tissue as a key endocrine organ. Adipose tissue secretes active endocrine, paracrine and autocrine substances in response to different stimulus. Some of them are mainly released by the adipose tissue (i.e., leptin) while others are shared with other systems (i.e., tumor necrosis factor-alpha; TNF-α) thus interweaving its function in systemic whole-organism regulations. The current hypotheses consider that adipose tissue switches between two states: i) avidly draining free fatty acids that come mainly from triglyceride rich lipoproteins during the postprandial period and ii) gently releasing them during the fasting period [45]. Switching between one state and the other is most probably regulated by a multifactorial system including substrate and hormone levels, but also the functional state of the adipose tissue itself. A failure of the adipose tissue function in taking up dietary fat (being permanently switched to releasing free fatty acids) might lead to an excess of lipid flux towards other tissues, during the postprandial period and even during the fasting period, and to a decreased clearance of triglyceride rich lipoprotein particles [46]. The functional capacity of the adipose tissue varies among subjects explaining the incomplete overlapping among the metabolic syndrome and obesity and these differences may be explained by the different genetic background. In fact, Variations at multiple gene loci seem to be partially responsible for these inter-individual differences. Two candidate genes regulating lipid partitioning are the adiponectin (APM1) and the perilipin (PLIN) gene [47].

Numerous investigators have shown increased circulating biomarkers of inflammation in metabolic syndrome, thus providing support for the syndrome's proinflammatory state. However, there is a paucity of data on subcutaneous adipose tissue (SAT) biology in the pathogenesis of metabolic syndrome [48]. The subcutaneous fat - which comprises ~80% of adipose tissue - is readily accessible to study and has been shown to be metabolically correlated to indices of insulin resistance as well as to visceral adipose tissue (VAT) [49-52]. In addition to intra-abdominal fat, investigators have shown that the amount of SAT positively correlates with increasing metabolic syndrome factor scores and negatively correlates with circulating adiponectin levels [53]. Other investigators have also reported that SAT is significantly associated with MS and increases with the increasing number of MS features, independent of age and sex [54]. Furthermore, inflammatory cells and processes, such as macrophage infiltration, appear to be important in adipose tissue inflammation. Specifically, investigators have examined abdominal SAT from obese subjects and reported that an inflamed adipose phenotype characterized by tissue macrophage accumulation in crown-like structures is associated with systemic hyperinsulinemia and insulin resistance and impaired endothelium-dependent flow-mediated vasodilation [55]. Macrophage retention in fat has been also linked to up-regulated tissue CD68 and tumor necrosis factor-alpha (TNF-α) mRNA expressions in addition to increased plasma high-sensitivity C-reactive protein (CRP) concentrations.

The Liver in the MS

Recent studies in obese adolescents demonstrated that increased ALT levels are associated with deterioration in insulin sensitivity and glucose tolerance, as well as with increasing FFA and triglyceride levels [56]. Also, the relationship between fatty liver and glucose dysregulation has been demonstrated in a multiethnic group of 118 obese adolescents, where

independently of obesity the severity of fatty liver was associated with the presence of pre-diabetes (IGT and IFG/IGT) [57]. In fact, paralleling the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment in beta-cell function as indicated by the fall in the disposition index [57]. Further studies showed that the pronounced dyslipidemic profile associated with fatty liver in pediatrics is characterized by large VLDL, small dense LDL, and decreased large HDL concentrations [58]. A study from D'Adamo et al. has highlighted the role of hepatic fat content in modulating insulin sensitivity [59]. The authors studied two groups of subjects with similar visceral fat and IMCL: one group without and the other one with hepatic steatosis and showed that obese individuals with steatosis had increased muscular and hepatic insulin resistance [59]. More recently in a longitudinal study we observed that baseline hepatic fat content correlates with 2 hours glucose and insulin sensitivity and secretion at follow-up [60]. These data clearly indicate that the deleterious effect of intra-hepatic fat accumulation influences the insulin sensitivity at a multi-organ level playing a bigger role than the other ectopic compartments [60]. In general, obese children and adolescents with hepatic steatosis tend to show an adverse metabolic pattern as characterized by dyslipidemia and adverse changes in glucose metabolism.

Nonalcoholic Fatty Liver Disease (NAFLD) has become the most common cause of liver disease in pediatrics [61] and encompasses a range of disease severity spanning from the simple steatosis to non-alcoholic steatohepatitis (NASH) [62], which has been shown to progress to cirrhosis in children [63]. We have recently shown that liver damage correlates with insulin resistance in obese children [64]. In particular, the levels of the caspase-cleaved CK18 fragment (CK-18), a robust biomarker of liver damage, are inversely correlated with insulin sensitivity, meaning that not only the amount of intra-hepatic fat, but also the degree of steatohepatitis may affect insulin sensitivity [64]. Interestingly this association is present in Caucasian and Hispanic obese children and adolescents, but not in African Americans. In the latter population there seems to be dissociation between the degree of liver injury and insulin sensitivity [64]. This data is consistent with the data shown by Guerrero et al showing a clear dissociation between the amount of liver fat and the degree of insulin sensitivity in African Americans [65]. The cause of this difference among ethnic groups is not known, but it is likely that the genetic background and the interaction between gene variants and nutrients may be a major determinant of such differences.

The most credited model for the pathogenesis of NAFLD, is the ''two-hit'' theory, where the first hit is represented by the insulin resistance, responsible for the abnormalities in lipid storage and lipolysis therefore leading to an increased fatty acids flux from adipose tissue to the liver and to subsequent accumulation of triglycerides into the hepatocytes [66]. While, the "second hit" might be represented by the oxidative stress, which activates inflammatory the inflammatory cascade and generates reactive oxygen species such as hydroxyl radicals and superoxide anions, which react with the excess lipid to form peroxides [67]. The synthesis of triglycerides in the liver is nutritionally regulated and has two main routes: adipose tissue lipolysis and hepatic de novo lipogenesis (DNL), which account respectively for about 60% and 25% of hepatic fat accumulation, only a little fraction of the liver fat comes directly from the chylomicron remnants [66]. In fact, insulin resistant individuals have a reduced ability to suppress free fatty acids flux from the adipose tissue. Therefore the increased amount of FFA from adipose tissue lipolysis causes an increased formation of triglycerides in the liver but also an increase of De Novo Lipogenesis (DNL), due to the abundant availability of substrate and the up-regulation of key lipogenic genes. The formation of triglycerides from simple carbohydrates requires multiple metabolic pathways, including glycolysis and pyruvate oxidation to generate acetyl-CoA for fatty acid synthesis, NADPH generation to supply the reductive power, packaging of fatty acids into a glycerophosphate backbone, and finally, lipoprotein packaging to export triglycerides. Under fasting conditions, the contribution of *DNL* to triglycerides is small in humans [66]. When liver is saturated with glycogen (roughly 5% of liver mass), any additional glucose taken up by hepatocytes is shunted into pathways leading to the synthesis of fatty acids, which will be esterified in triglycerides and exported to adipose tissue as VLDL [66]. It has been shown in obese adults that hepatic *DNL* contributes to hepatic triglycerides accumulation, which represents the hallmark of hepatic steatosis, and to an elevation of fasting VLDL [66]. Once the ability of the liver to form TGs from FFA is saturated, the accumulation in the hepatocytes of FFA probably triggers the inflammation and oxidative pathways responsible for the progression of the disease from simple NAFLD to NASH. In fact, the products of peroxidation may injure cells directly by interfering with membrane function or stimulate fibrosis by hepatic stellate cells. In particular, oxidative stress is associated with an increased production of reactive oxygen species (ROS) and pro-inflammatory cytokines [68,69]. One of the effects of ROS is to cause lipid peroxidation of some lipids, such as the polyunsaturated fatty acids (PUFA) generating metabolites that are deleterious for the hepatocyte [68]. The lipid peroxidation leads to the activation of Kupffer cells with the production of inflammatory cytokines such as the TNF-alpha and to the activation of stellate cells, which in turn will favor neutrophils chemotaxis as well as liver fibrosis [67]. A large body of evidence suggests that the quality of dietary fat can influence the development of NAFLD [70,71]. In particular, recent literature provides clues that the dietary imbalance between omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFA) leads to development of NAFLD [72]. Individuals with NAFLD, in fact, have been shown to have a lower dietary intake of n-3 PUFA than healthy controls and an increase in the n-6/n-3 ratio consume in the diet [72,73]. Consistent with these data, lipidomic studies have shown that the intra-hepatic fat in subjects with steatohepatitis is composed by an excess n-6 PUFA [74]. Also, we have recently shown that the excess of oxidized lipids derived from the Linoleic Acid (the precursor of the omega 6 PUFA) is associated with both liver injury and insulin secretion [75]. The pathogenetic mechanism linking these compounds to liver damage may be related to their effect on the PPAR-alpha a potent modulator of lipid transport and oxidation. Also the PUFA metabolites such as eicosanoids or oxidized fatty acids have one to two orders of magnitude greater affinity for PPAR-alpha and are consequently far more potent transcriptional activators of PPAR-alpha-dependent genes than their ancestry compounds [76]. Therefore, in a liver rich of n-6 PUFA the continuous

production of oxidized fatty acids perpetuates and enhances the intracellular oxidative stress leading to a sterile inflammation. Also, some data suggest that oxidized species deriving from the omega-6 PUFA may play a role in the impaired insulin secretion observed in subjects with fatty liver [75]. This phenomenon may be mainly due to the fact that the increase omega-6 PUFA in the beta cell affects the glucose, amino acids and GLP-1 stimulated insulin secretion and renders the beta cell strongly susceptible to cytokine induced cell death.

CONCLUSION

Taken together, obesity in children is not a consistent clinical entity. Up to 30% of obese patients are metabolically healthy, while the majority of obese individuals develop metabolic diseases including type 2 diabetes, dyslipidemia and CVDs. Healthy obese individuals will therefore not significantly improve their obesity-related metabolic risk by weight-loss interventions. Since the prevalence for the metabolic syndrome is rising in children we need to better define the individuals at risk and in need for early lifestyle and pharmacological interventions. Waist circumference may be considered a more reliable clinical measure for predicting MS in children than BMI alone. The information that can be provided by waist circumference measurement in children, together with the recent changes in body fat distribution should provide the impetus for its measurement to be standardised and routinely taken in clinical and epidemiological settings. In addition to established threshold-based definitions of the metabolic syndrome and its single components, new biomarker (uric acid) and fat measurements (nuchal SAT thickness) that emerge as clinically relevant determinants of the respective obesity phenotype should be further studied. Treatment strategies targeting the lipid partitioning between visceral and subcutaneous abdominal adipose tissue, as well as fat accumulation in liver, should be focused on to reverse the unhealthy into healthy obese phenotype.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (NIH) (R01-HD40787, R01-HD28016, and by CTSA Grant Number UL1 RR0249139 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH roadmap for Medical Research. Its contents are solely the responsibility of the author and do not necessarily represent the official view of NIH.

REFERENCES

1. de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010; 92: 1257-1264.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37: 1595-1607.
3. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. Lancet. 2007; 369: 2059-2061.
4. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004; 350: 2362-2374.
5. Galbo T, Shulman GI. Lipid-induced hepatic insulin resistance. Aging (Albany NY). 2013; 5: 582-583.
6. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet. 2010; 375: 2267-2277.
7. Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, et al. The "obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab. 2005; 90: 3731-3737.
8. Bell LM, Byrne S, Thompson A, Ratnam N, Blair E, Bulsara M, et al. Increasing body mass index z-score is continuously associated with complications of overweight in children, even in the healthy weight range. J Clin Endocrinol Metab. 2007; 92: 517-522.
9. Shea JL, Randell EW, Sun G. The prevalence of metabolically healthy obese subjects defined by BMI and dual-energy X-ray absorptiometry. Obesity (Silver Spring). 2011; 19: 624-630.
10. D. Weghuber, S. Zelzer, I. Stelzer, K. Paulmichl, D. Kammerhofer, W. Schnedl, D. Molnar, H. Mangge, High risk vs. "metabolically healthy" phenotype in juvenile obesity - neck subcutaneous adipose tissue and serum uric acid are clinically relevant. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2013; 121: 384-390.
11. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr. 2004; 145: 439-44.
12. Janssen I, Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, et al. Combined influence of body mass index and waist circumference on coronary artery disease risk factors among children and adolescents. Pediatrics. 2005; 115: 1623-1630.
13. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol. 1994; 73: 460-8.
14. Katzmarzyk PT. Waist circumference percentiles for Canadian youth 11-18y of age. Eur J Clin Nutr. 2004; 58: 1011-1015.
15. Zannolli R, Morgese G. Waist percentiles: a simple test for atherogenic disease? Acta Paediatr. 1996; 85: 1368-1369.
16. McCarthy HD, Jarrett KV, Crawley HF. The development of waist circumference percentiles in British children aged 5.0-16.9 y. Eur J Clin Nutr. 2001; 55: 902-907.
17. Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. Int J Obes Relat Metab Disord. 2001; 25: 652-61.
18. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med. 2002; 162: 2074-2079.
19. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. Am J Clin Nutr. 2002; 75: 683-8.
20. Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Waist circumference vs body mass index for prediction of disease risk in postmenopausal women. Int J Obes Relat Metab Disord. 2001; 25: 1183-1188.
21. Maffeis C, Pietrobelli A, Grezzani A, Provera S, Tatò L. Waist

circumference and cardiovascular risk factors in prepubertal children. Obes Res. 2001; 9: 179-187.

22. Freedman DS, Serdula MK, Srinivasan SR, Berenson GS. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. Am J Clin Nutr. 1999; 69: 308-317.

23. Savva SC, Tornaritis M, Savva ME, Kourides Y, Panagi A, Silikiotou N, et al. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. Int J Obes Relat Metab Disord. 2000; 24: 1453-8.

24. Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. Diabetes Care. 1999; 22: 1808-1812.

25. O'Shaughnessy IM, Myers TJ, Stepniakowski K, Nazzaro P, Kelly TM, Hoffmann RG, et al. Glucose metabolism in abdominally obese hypertensive and normotensive subjects. Hypertension. 1995; 26: 186-192.

26. Williamson JR, Kreisberg RA, Felts PW. Mechanism for the stimulation of gluconeogenesis by fatty acids in perfused rat liver. Proc Natl Acad Sci U S A. 1966; 56: 247-254.

27. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001; 409: 307-312.

28. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science. 1996; 271: 665-8.

29. Jensen MD. Adipose tissue and fatty acid metabolism in humans. J R Soc Med. 2002; 95 Suppl 42: 3-7.

30. Weiss R. Fat distribution and storage: how much, where, and how? Eur J Endocrinol. 2007; 157 Suppl 1: S39-45.

31. Santoro N, Weiss R. Metabolic syndrome in youth: current insights and novel serum biomarkers. Biomark Med. 2012; 6: 719-727.

32. Taksali SE, Caprio S, Dziura J, Dufour S, Calí AM, Goodman TR, et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes. 2008; 57: 367-371.

33. Kursawe R, Eszlinger M, Narayan D, Liu T, Bazuine M, Cali AM, et al. Cellularity and adipogenic profile of the abdominal subcutaneous adipose tissue from obese adolescents: association with insulin resistance and hepatic steatosis. Diabetes. 2010; 59: 2288-96.

34. Koutsari C, Jensen MD. Thematic review series: patient-oriented research. Free fatty acid metabolism in human obesity. J Lipid Res. 2006; 47: 1643-1650.

35. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005; 96: 939-949.

36. Xu XJ, Gauthier MS, Hess DT, Apovian CM, Cacicedo JM, Gokce N, et al. Insulin sensitive and resistant obesity in humans: AMPK activity, oxidative stress, and depot-specific changes in gene expression in adipose tissue. J Lipid Res. 2012; 53: 792-801.

37. Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, et al. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. Circulation. 2011; 124: 67-76.

38. Gillum MP, Kotas ME, Erion DM, Kursawe R, Chatterjee P, Nead KT, et al. SirT1 regulates adipose tissue inflammation. Diabetes. 2011; 60: 3235-3245.

39. Hardy OT, Perugini RA, Nicoloro SM, Gallagher-Dorval K, Puri V, Straubhaar J, Czech MP. Body mass index-independent inflammation in omental adipose tissue associated with insulin resistance in morbid obesity. Surg Obes Relat Dis. 2011; 7: 60-7.

40. Gregor MF, Yang L, Fabbrini E, Mohammed BS, Eagon JC, Hotamisligil GS, et al. Endoplasmic reticulum stress is reduced in tissues of obese subjects after weight loss. Diabetes. 2009; 58: 693-700.

41. Anderson EK, Gutierrez DA, Hasty AH. Adipose tissue recruitment of leukocytes. Curr Opin Lipidol. 2010; 21: 172-177.

42. Pasarica M, Gowronska-Kozak B, Burk D, Remedios I, Hymel D, Gimble J, et al. Adipose tissue collagen VI in obesity. J Clin Endocrinol Metab. 2009; 94: 5155-5162.

43. No authors listed] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352: 854-865.

44. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med. 2003; 115 Suppl 8A: 42S-48S.

45. Frayn KN. Adipose tissue as a buffer for daily lipid flux. Diabetologia. 2002; 45: 1201-1210.

46. Kolovou GD, Anagnostopoulou KK, Pavlidis AN, Salpea KD, Iraklianou SA, Tsarpalis K, et al. Postprandial lipemia in men with metabolic syndrome, hypertensives and healthy subjects. Lipids Health Dis. 2005; 4: 21.

47. Corella D, Qi L, Tai ES, Deurenberg-Yap M, Tan CE, Chew SK, et al. Perilipin gene variation determines higher susceptibility to insulin resistance in Asian women when consuming a high-saturated fat, low-carbohydrate diet. Diabetes Care. 2006; 29: 1313-1319.

48. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? Diabetes Care. 2009; 32: 1068-1075.

49. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes. 1997; 46: 1579-1585.

50. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest. 1995; 96: 88-98.

51. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes. 1996; 45: 1684-1693.

52. Ferreira I, Henry RM, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD. et al. The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. Arch Intern Med. 2005; 165: 875-82.

53. Salmenniemi U, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen K, et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation. 2004; 110: 3842-8.

54. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes. 2004; 53: 2087-94..

55. Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, et al. Adipose macrophage infiltration is associated with insulin resistance

and vascular endothelial dysfunction in obese subjects. Arterioscler Thromb Vasc Biol. 2008; 28: 1654-9.

56. Burgert TS, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, et al. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. J Clin Endocrinol Metab. 2006; 91: 4287-94.

57. Cali AM, De Oliveira AM, Kim H, Chen S, Reyes-Mugica M, Escalera S, et al. Glucose dysregulation and hepatic steatosis in obese adolescents: is there a link? Hepatology. 2009; 49: 1896-1903.

58. D'Adamo E, Northrup V, Weiss R, Santoro N, Pierpont B, Savoye M, et al. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. Am J Clin Nutr. 2010; 92: 500-508.

59. D'Adamo E, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, et al. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. Diabetes Care. 2010; 33: 1817-1822.

60. Kim G, Giannini C, Pierpont B, Feldstein AE, Santoro N, Kursawe R, et al. Longitudinal effects of MRI-measured hepatic steatosis on biomarkers of glucose homeostasis and hepatic apoptosis in obese youth. Diabetes Care. 2013; 36: 130-136.

61. Schwimmer JB, Deutsch R, Rauch JB, Behling C, Newbury R, Lavine JE. Obesity, insulin resistance, and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. J Pediatr. 2003; 143: 500-5.

62. Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology. 2011; 53: 1874-82.

63. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut. 2009; 58: 1538-1544.

64. Santoro N, Feldstein AE, Enoksson E, Pierpont B, Kursawe R, Kim G, et al. The association between hepatic fat content and liver injury in obese children and adolescents: effects of ethnicity, insulin resistance, and common gene variants. Diabetes Care. 2013; 36: 1353-1360.

65. Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? Hepatology. 2009; 49: 791-801.

66. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005; 115: 1343-1351.

67. Feldstein AE, Bailey SM. Emerging role of redox dysregulation in alcoholic and nonalcoholic fatty liver disease. Antioxid Redox Signal. 2011; 15: 421-424.

68. Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. Am J Gastroenterol. 2004; 99: 1497-1502.

69. Yesilova Z, Yaman H, Oktenli C, Ozcan A, Uygun A, Cakir E, et al. Systemic markers of lipid peroxidation and antioxidants in patients with nonalcoholic Fatty liver disease. Am J Gastroenterol. 2005; 100: 850-855.

70. Cortez-Pinto H, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME. How different is the dietary pattern in non-alcoholic steatohepatitis patients? Clin Nutr. 2006; 25: 816-823.

71. Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. Nutrition. 2007; 23: 46-52.

72. Araya J, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, et al. Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. Clin Sci (Lond). 2004; 106: 635-43.

73. Li Y, Chen D. The optimal dose of omega-3 supplementation for non-alcoholic fatty liver disease. J Hepatol. 2012; 57: 468-469.

74. Puri P, Baillie RA, Wiest MM, Mirshahi F, Choudhury J, Cheung O, et al. A lipidomic analysis of nonalcoholic fatty liver disease. Hepatology. 2007; 46: 1081-1090.

75. Santoro N, Caprio S, Giannini C, Kim G, Kursawe R, Pierpont B, et al. Oxidized Fatty Acids: A Potential Pathogenic Link Between Fatty Liver and Type 2 Diabetes in Obese Adolescents? Antioxid Redox Signal. 2013; .

76. Krey G, Braissant O, L'Horset F, Kalkhoven E, Perroud M, Parker MG, et al. Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. Mol Endocrinol. 1997; 11: 779-91.

Cite this article

Kursawe R (2014) Metabolic Syndrome in Pediatrics: The Role of Lipid Partitioning. Ann Pediatr Child Health 2(1): 1007.