Editorial

The skinny on metabolic syndrome in adolescents

Sridevi Devaraj[1], **Ishwarlal Jialal**[2,3]

[1]Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA; [2]Children's Hospital of Oakland Research Institute, Oakland, CA, USA; [3]UC Davis Medical Center, Sacramento, CA, USA

Correspondence to: Ishwarlal Jialal, MD, PhD. Director, Laboratory for Atherosclerosis and Metabolic Research, UC Davis Medical Center, Sacramento, CA 95817, USA. Email: ijialal@ucdavis.edu.

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The metabolic syndrome (MetS) captures a cluster of cardio-metabolic risk factors that have been shown to predict the development of both cardiovascular disease and type 2 diabetes. With international consensus we have now arrived at a harmonized definition of MetS in adults globally (1). However, there are still several definitions of MetS in children; all definitions include an obesity element (waist circumference or BMI or BMI percentile or z-score), two "dyslipidemia" elements (elevated triglycerides and low HDL-cholesterol), elevated blood pressure, and a component representing glucose metabolism (impaired fasting glucose or impaired glucose tolerance). A recent review reported that the prevalence of MetS in overweight children was around 12% and in obese children, 29% (2).

In the paper by Lee *et al.* (3), the authors examined data from the Centers for Disease Control and Prevention (CDC) NHANES [1999–2012] of 5,117 adolescents aged 12 to 19 years. MetS was defined as having at least three of the following: BMI z-score ≥1.645, fasting glucose ≥100 mg/dL, fasting triglycerides ≥110 mg/dL, HDL ≤40 mg/dL, and systolic or diastolic BP exceeding the 90th percentile for height, age, and gender. The authors have been strong proponents of the MetS z-score to calculate MetS severity and used this to examine severity of MetS in this data set. MetS severity was calculated by using the Pediatric MetS z-score (http://mets.health-outcomes-policy.ufl.edu/calculator). In addition, they examined dietary intake from a 24-hour food recall and physical activity was assessed as minutes per week of moderate to vigorous physical recreational activity per day. The overall prevalence of ATP-III MetS over this time period was 9.83%. Importantly, the authors found no significant changes in the prevalence of MetS or obesity in adolescents from 1999 to 2012. However, they report temporal trends of decreasing MetS severity score and fasting triglyceride measurements. There were further temporal trends of increasing BMI z-score and HDL-cholesterol. No significant trends in overall fasting glucose and mean systolic BP measurements were recorded. The decreasing trends in the proportion of children with high fasting triglycerides and low HDL prevalence was negated by the increasing BMI z scores and thus prevalence of MetS did not decrease over this time period.

The BMI z-score used in the definition of MetS or the MetS severity score does not define the role of obesity in insulin resistance. Waist circumference has been demonstrated to be an independent predictor of insulin resistance and intra-abdominal fat independent of BMI in obese adolescents. The authors do not explain their choice of BMI over waist circumference, the original criteria proposed by ATPIII. With regards to the lipid component, it is well known that the dyslipidemia in MetS is exemplified by high TG and low HDL-cholesterol. There were decreasing trends in the proportion of children with high fasting triglycerides and low HDL-cholesterol prevalence which could explain the decrease in the MetS severity score, however, it is concerning that there was a concomitant temporal increase in the BMI z-score, and this could explain the lack of decrease in MetS prevalence in these adolescent children. Nonetheless increase in MetS severity score by this group has been validated by showing the score to predict both increased future risk for CVD and diabetes (4,5) by following up children with mean age 13 years in the Princeton Lipid Research Clinic study with subsequent follow-up as adults mean age 38 years in the Princeton Follow-up study and finally at age 50 years in the Princeton

Health Update study. Whilst this needs to be confirmed by other groups, an explanation for the decrease in the MetS z-score without a commensurate decrease in prevalence merits further comment.

Inflammation appears to play a key role in the development of insulin resistance and future atherogenesis in patients with MetS (6,7). With respect to inflammation, several studies have recognized the role of visceral fat-derived pro-inflammatory cytokines and adipokines (such as decreased adiponectin) in promoting insulin resistance in obese adolescents. The prototypic marker of inflammation, C-reactive protein is associated with adiposity, fasting insulin, dyslipidemia, and blood pressure in pre-pubertal children. C-reactive protein, interleukin-6 and tumor necrosis factor-α have been shown to be increased in adolescents with the MetS. Thus, reduced levels of adiponectin and increased inflammatory cytokines seem to be evolving factors accompanying the classic components of the syndrome. They previously reported significant correlations with hsCRP, insulin resistance and uric acid (3-5). Since MetS is associated with increased oxidative stress (8) then one needs to explain this increased severity score with increasing uric acid since functioning as a water soluble antioxidant one would anticipate lower levels unless its role in MetS has nothing to do with oxidative stress. Will adding CRP, fasting insulin and Adiponectin as measures of inflammation and insulin resistance help further enhance this z-score?

Overall, the authors also reported temporal trends of decreasing total calorie consumption, decreasing carbohydrate consumption, and increasing unsaturated fat consumption. Mean calorie consumption was positively associated with fasting triglyceride levels and inversely associated with BMI z-score and HDL. Carbohydrate intake was directly associated with fasting triglyceride and inversely associated with HDL levels. Unsaturated fat intake was inversely associated with fasting triglyceride and directly associated with HDL levels while saturated fat intake was directly associated with HDL.

Whilst intake of fibric acid derivatives could explain the decreasing triglycerides and increasing HDL-C it appears that none of the patients were on hypolipidemic or hypoglycemic drugs. The increased HDL and decreased triglyceride could well be attributed to decreased refined carbohydrate intake and increased unsaturated fat intake (9-11). However, they do not report on subclasses such as N-3-PUFA, N-6PUFA fatty acids and monounsaturated fatty acid intake. Thus it is not possible to tease out which fatty acids resulted in the lowering of triglycerides and increase in HDL-cholesterol. Furthermore no mention is made of trans-fatty acid intake. Thus, it is possible that a combination of decreased refined carbohydrates and increased polyunsaturated/monounsaturated fat in the diet could have resulted in the increased HDL cholesterol and lowering of triglycerides. Furthermore, the paradox of total calorie consumption inversely correlating with BMI z-score is not explained. Surprisingly they do not report any association of physical activity with the MetS severity score but did point out that physical activity data was only available in a consistent format from 2007 and not 1999. Hence their findings with physical activity need to be interpreted with caution.

These data emphasize a few points: the importance of monitoring MetS in adolescents, the importance of adopting healthy dietary choices (such as increasing monounsaturated fat, omega 3 in the diet, decreasing total calorie consumption, and decreasing refined carbohydrate intake, and fructose containing products) and increasing physical activity in adolescents, as well as determining other contributors to insulin resistance and obesity, such as C-reactive protein and adiponectin. All of these modalities will contribute to decreased prevalence and severity of MetS and enhance the health of the future generation. Most importantly this MetS z-score appears to more relevant to children and needs to be validated by other investigators to enter into mainstream of clinical practice. In adult patients with increasing features of MetS cardio-metabolic risk factors are associated with increased biomarkers of inflammation, oxidative stress and insulin resistance (8,12,13). It still remains that therapeutic lifestyle changes of improved diet and exercise will enhance the health of the future generation and serve to decrease the incidence of MetS and its sequelae. Gupta (14) also emphasizes the "addiction" to technology (television watching, video games, computers and cell phones etc.) that contributes to the loss in crucial outdoor physical activity and the phenomena of skipping breakfast. In conclusion if we want to make a significant effort to reduce this mammoth burden in these young children then we need a concerted effort from government, parents, school administrators, public health officials and care providers to stem this dangerous tsunami.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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