Metabolic syndrome in children (Review)

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Abstract. Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors, including central obesity, insulin resistance, glucose intolerance, dyslipidemia and increased blood pressure. The prevalence of MetS is on the increase worldwide owing to the epidemic of overweight and obesity. The risk of prevalence of MetS greatly increases during adulthood for those children exposed to cardiometabolic risk factors in their early lives. MetS has also been associated with liver fat accumulation in children. Elevated levels of plasma alanine aminotransferase and γ-glutamyl transferase have been associated with liver fat accumulation. The present review aimed to expand knowledge on the clustering of cardiometabolic risk factors responsible for the widespread occurrence of metabolic disease in children.

Contents

1. Introduction

Metabolic syndrome (MetS) is a cluster of cardio metabolic risk factors, including central obesity, insulin resistance, glucose intolerance, dyslipidemia and raised blood pressure (1,2). The prevalence of MetS is on the increase worldwide due to the epidemic of overweight and obesity (3). Children with MetS have an increased risk of adulthood MetS, type 2 diabetes and cardiovascular disease (CVD) (4,5). MetS also predicts type 2 diabetes, CVD and all-cause mortality in adults (6,7). Thus, gaining a better understanding of the pathophysiology and determinants of this risk factor clustering as early as childhood is crucial.

In previous studies conducted on children continuous variables were used for the components of MetS and a continuous cardiometabolic risk score was calculated instead of using a definition based on dichotomous variables (8,9). Despite abundant research on MetS using a continuous cardiometabolic risk score or factor analysis, to the best of our knowledge, there are no previous studies in which the cardiometabolic risk score has been validated by confirmatory factor analysis (CFA) in different age groups. Furthermore, few studies have investigated the long-term health consequences of a high cardiometabolic risk score (10). In addition to traditional cardiometabolic risk factors, several other metabolic disorders, such as liver fat accumulation, have been associated with MetS in children (11). The epidemic of pediatric overweight and obesity has markedly increased the number of children affected/diagnosed with non-alcoholic fatty liver disease (NAFLD) (12,13). The plasma concentrations of liver enzymes, such as alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) are potentially useful tools in the screening of pediatric NAFLD (14). The present review focused on the recent aspects of MetSs in young infants.

2. Genetic factors responsible for MetS

Several genome-wide scans performed in families with clustering of cardio metabolic risk factors have strongly supported an inherited component to MetS (15,16). In a study of 357 children and 378 parents, children who had at least one parent with MetS, defined by the Adult Treatment Panel III criteria, had higher levels of obesity and insulin resistance than children in whom neither parent had MetS (17). Additionally, the Bogalusa Heart Study has shown that offspring of parents with early coronary heart disease were overweight beginning in childhood and developed an adverse cardiovascular risk factor profile at an increased rate (18). Other family and twin studies have identified a strong familial aggregation for cardio=metabolic risk factors (19).

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3. Low physical activity, sedentary behavior and poor cardiorespiratory fitness

The current epidemic of overweight and MetS is mainly due to an imbalance between energy intake and energy expenditure. Low levels of physical activity increase the risk of MetS, type 2 diabetes, CVD and all-cause mortality in adults (20). The prevalence of these diseases may be controlled by the elevation of physical activity and cardiorespiratory fitness (21). Low levels of physical activity and cardiorespiratory fitness have been associated with increased levels of independent and clustered metabolic risk factors among adolescents and children (22,23). A sedentary lifestyle has also caused a decrease in cardiorespiratory and musculoskeletal fitness. Although, the independent role and relative importance of physical activity and sedentary lifestyle in the development of childhood overweight is well known, MetS and associated adverse health consequences, as well as underlying biological mechanisms remain to be determined.

4. Dietary factors and MetS

The role of diet in the development of MetS is not well understood. Western dietary patterns and the consumption of meat and fried foods have been directly related to the risk of MetS, whereas the consumption of whole-grain products, fruit, vegetables and dairy products have been inversely associated with MetS (24). Weight loss has been observed to be effective in the treatment of the components of MetS, including excessive body adiposity, insulin resistance, dyslipidemia and elevated blood pressure (25). The Finnish Diabetes Prevention Study revealed that even modest weight loss reduced the prevalence of MetS in 522 middle-aged overweight men and women with impaired glucose tolerance (26). The Diabetes Prevention Program in the USA showed that an intensive lifestyle intervention reduced the incidence of MetS by 41% in 3,000 adults (27). Results from the Physical Activity and Nutrition in Children (PANIC) Study suggested that promoting regular consumption of main meals, decreasing the consumption of sugar-sweetened beverages and low-fat margarine and increasing the consumption of vegetable oils should be emphasized to reduce metabolic risk among children (28).

5. Other factors

Other potential risk factors underlying MetS include epigenetic factors as well as the overnutrition of the fetus resulting in increased birth weight and low birth weight associated with rapid catch-up growth (29). Exposure of the fetus to gestational diabetes of the mother increases the risk of MetS (30). Cigarette smoking and excess alcohol consumption have been connected with increased cardiometabolic risk (31). A poor socioeconomic status and psychosocial background have also been associated with MetS (32). Furthermore, health-related policies such as the focus on early prevention, plays a fundamental role in reducing overweight and obesity and related clustering of cardiometabolic risk factors.

6. Insulin resistance and hyperglycemia

Insulin resistance is increased in overweight and obese individuals and is often seen as the core feature of MetS (33). The main physiological effects of insulin include an increase in skeletal muscle glucose uptake and suppression of hepatic glucose production and adipose tissue lipolysis. Insulin resistance is a general term meaning that insulin does not exert its normal effects in insulin-sensitive target tissues, such as skeletal muscle and adipose tissue (34). As previously discussed, insulin resistance in adipose tissue manifests itself as the inability to suppress lipolysis, which leads to an influx of FFAs to the liver, skeletal muscle and other organs leading to insulin resistance in these tissues (35). The large number of adipokines secreted by adipose tissue modulates insulin sensitivity. Insulin resistance in the liver increases gluconeogenesis and decreases glycogen synthesis resulting in fasting hyperglycemia (36).

The majority of peripheral glucose uptake and further metabolism occurs in the skeletal muscle. Increased plasma FFA levels disrupt the glucose-fatty acid cycle and insulin-mediated glucose uptake in the muscle. However, in non-diabetic state, this resistance is compensated by increased insulin secretion from the pancreatic β-cells. If pancreatic insulin secretion fails, insulin resistance in skeletal muscle increases hyperglycemia. The more insulin resistance the body experiences, the more insulin is secreted to prevent decompensation of glucose tolerance (37). If the compensatory mechanisms fail, the subsequent hyperglycemia and glucotoxicity may exacerbate the insulin resistance and islet β-cell insulin secretion. Insulin resistance further worsens the low-grade inflammatory state, induces endothelial dysfunction in the arteries and elevates blood pressure. In addition, insulin resistance decreases signaling in the hypothalamus which leads to increased food intake and weight gain (38).

7. Dyslipidemia

It is currently unknown whether insulin resistance induces dyslipidemia or whether these risk factors are associated via a common underlying cause. Increased hepatic FA intake stimulated by insulin resistance leads to the increased production of VLDL-triglycerides and apolipoprotein B. Apolipoprotein B is a marker of triglyceride-rich lipoproteins and retards triglyceride clearance (39). Increased liver fat content is associated with the overproduction of VLDL from the liver due to a lack of insulin-induced suppression of VLDL production (40). In addition to the overproduction of VLDL by the liver, alterations in lipoprotein lipase activity have been associated with MetS. Circulating HDL cholesterol levels are decreased owing to overconsumption, while the density of low-density lipoprotein (LDL) increases in MetS. The small dense LDL is potentially atherogenic owing to its low affinity to the LDL receptor and long retention time in the circulation (41).

8. Elevated blood pressure

The role of blood pressure in the pathophysiology of MetS is not fully understood but several mechanisms have been suggested. Obesity has been associated with increased

sympathetic tone, which raises blood pressure. Furthermore, insulin and leptin appear to increase sympathetic nervous activity. In the setting of insulin resistance, the vasodilatory effect of insulin can be lost, resulting in endothelial dysfunction and vasoconstriction (42). Hyperinsulinemia leads to increased sodium absorption in the kidneys, which increases blood volume and thereby blood pressure (43). It has also been hypothesized that LDL cholesterol and triglycerides may damage the endothelium, impair nitric oxide release and cause endothelial dysfunction. This hypothesis suggests that dyslipidemia causes hypertension by mechanisms only partly related to obesity and insulin resistance (44,45).

9. Consequences of MetS

Type 2 diabetes and its complications. MetS is associated with a marked increase in the risk for type 2 diabetes, which is characterized by chronically elevated blood glucose concentrations resulting from insulin resistance and reduced insulin secretion (46). A typical situation is relative insulin deficiency due to the inability of body to adequately compensate for insulin resistance. Type 2 diabetes is a heterogeneous disease and its clinical expression requires genetic and environmental factors (47). Nevertheless, most patients have insulin resistance and MetS prior to the onset of type 2 diabetes. Overweight, obesity, insulin resistance and dyslipidemia in 75-85% of patients precede the progression of type 2 diabetes (48). The risk of CVD events is much higher in patients with type 2 diabetes than in non-diabetic subjects (49). Other common complications of type 2 diabetes included retinopathy, nephropathy and neuropathy, which also predict CVD (50). In recent years, the prevalence of type 2 diabetes in children as well as adolescents has been on the increase (51).

PNPLA3 gene variant and liver adiposity. Studies conducted on obese adults and children have suggested that the *PNPLA3* gene I148M variant is related to the severity of hepatic steatosis and the presence of NASH and fibrosis. The *PNPLA3* 148M allele has not been generally associated with the components of MetS, such as measures of body adiposity, as well as lipid and glucose metabolism (52). However, the results of previous studies in children have suggested that the 148M allele carriers have lower plasma levels of HDL cholesterol and a lower BMI than the non-carriers (53). It has been suggested that the increased amount of body fat may act as a stressor on the *PNPLA3* 148M carriers thereby influencing the susceptibility to increased circulating liver enzymes. Investigators hypothesized that the lack of association with ALT plasma levels may have been due to small sample sizes. Thus, an inreased number of studies are needed to gain a better understanding of the biological functions and pathogenetic mechanisms of this genetic variant with regard to liver adiposity.

Atherosclerosis and atherosclerotic CVDs. In adults, MetS has been strongly associated with subclinical atherosclerosis, as estimated by carotid artery intima-media thickness (IMT) and atherosclerotic lesions using non-invasive ultrasonography (54,55). Previous findings have shown that cardiometabolic risk factors in childhood predict increased adult carotid IMT (53) as well as decreased carotid artery elasticity (56,57).

MetS is associated with increased risk for CVD in the next 5-10 years and the lifetime risk is undoubtedly higher (58). MetS has also been associated with increased risk of acute ischemic stroke or transient ischemic attack. Individuals with MetS but without diabetes had a 1.5-fold higher risk of ischemic stroke or transient ischemic attack compared with patients without MetS. This risk was higher in women than in men (59). In the KIHD study, middle-aged men without any previous history of CVD were followed up for 11 years, and those with MetS were three to four times more likely to succumb to coronary heart disease, about three times more likely to succumb to CVD and about two times more likely to succumb to all these causes. Despite the predictive value of MetS for type 2 diabetes, CVD and all-cause mortality in adults, it remains unclear whether MetS has prognostic value over its individual components (60). Furthermore, MetS is not an absolute risk indicator, because it does not contain many of the factors that determine absolute risk, for example, age, gender, cigarette smoking and LDL cholesterol levels.

10. Other manifestations of MetS

Other well-known manifestations of MetS include polycystic ovarian syndrome in women and obstructive sleep apnea. Polycystic ovarian syndrome is characterized by anovulation, androgen excess and insulin resistance (61). Women with polycystic ovarian syndrome have been found to have increased risk for developing type 2 diabetes and CVD. The pathophysiology of polycystic ovarian syndrome is unclear, but the ovary, hypothalamic-pituitary axis and insulin are likely to play a major role in MetS (62). Obstructive sleep apnea has been associated with excess body fat content, insulin resistance and other features of MetS (63,64). Individuals with obstructive sleep apnea are at increased risk for CVD morbidity and mortality (65). Several other disorders and symptoms such as dementia, depression, osteoarthritis, pulmonary embolism, gallbladder disease, asthma and many types of cancer have been associated with overweight and obesity (66).

11. Conclusion

It can be concluded from the above citations that MetS is a serious disorder associated with multiple diseased states. Extensive research is needed in the therapeutic as well as diagnostic areas for the improvement of affected pediatric patients.

References

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM and Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120: 1640-1645, 2009.

2. Kassi E1, Pervanidou P, Kaltsas G and Chrousos G: Metabolic syndrome: definitions and controversies. BMC Med 9: 48, 2011. doi: 10.1186/1741-7015-9-48.
3. Flegal KM, Carroll MD, Kit BK and Ogden CL: Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 307: 491-497, 2012.
4. Morrison JA, Friedman LA and Gray-McGuire C: Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: The Princeton Lipid Research Clinics Follow-up Study. Pediatrics 120: 340-345, 2007.
5. Morrison JA, Friedman LA, Wang P and Glueck CJ: Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr 152: 201-206, 2008.
6. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM and Heiss G: The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 28: 385-390, 2005.
7. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J and Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288: 2709-2716, 2002.
8. Eisenmann JC, Laurson KR, DuBose KD, Smith BK and Donnelly JE: Construct validity of a continuous metabolic syndrome score in children. Diabetol Metab Syndr 2: 8, 2010.
9. Pandit D, Chiplonkar S, Khadilkar A, Kinare A and Khadilkar V: Efficacy of a continuous metabolic syndrome score in Indian children for detecting subclinical atherosclerotic risk. Int J Obes 35: 1318-1324, 2011.
10. Hillier TA, Rousseau A, Lange C, Lépinay P, Cailleau M, Novak M, Calliez E, Ducimetière P and Balkau B; D.E.S.I.R. Cohort: Practical way to assess metabolic syndrome using a continuous score obtained from principal components analysis. Diabetologia 49: 1528-1535, 2006.
11. Boyraz M, Hatipoglu N, Sari E, Akcay A, Taskin N, Ulucan K, Akcay T: Non-alcoholic fatty liver disease in obese children and the relationship between metabolic syndrome criteria. Obes Res Clin Pract 8: e356-e363, 2014.
12. Widhalm K and Ghods E: Nonalcoholic fatty liver disease: a challenge for pediatricians. Int J Obes 34: 1451-1467, 2010.
13. Giorgio V, Prono F, Graziano F and Nobili V: Pediatric non alcoholic fatty liver disease: old and new concepts on development, progression, metabolic insight and potential treatment targets. BMC Pediatr 13: 40, 2013. doi: 10.1186/1471-2431-13-40.
14. Rodríguez G, Gallego S, Breidenassel C, Moreno LA and Gottrand F: Is liver transaminases assessment an appropriate tool for the screening of non-alcoholic fatty liver disease in at risk obese children and adolescents? Nutr Hosp 25: 712-717, 2010.
15. Sale MM, Woods J and Freedman BI: Genetic determinants of the metabolic syndrome. Curr Hypertens Rep 8: 16-22, 2006.
16. Terán-García M and Bouchard C: Genetics of the metabolic syndrome. Appl Physiol Nutr Metab 32: 89-114, 2007.
17. Pankow JS, Jacobs DR Jr, Steinberger J, Moran A and Sinaiko AR: Insulin resistance and cardiovascular disease risk factors in children of parents with the insulin resistance (metabolic) syndrome. Diabetes Care 27: 775-780, 2004.
18. Bao W, Srinivasan SR, Valdez R, Greenlund KJ, Wattigney WA and Berenson GS: Longitudinal changes in cardiovascular risk from childhood to young adulthood in offspring of parents with coronary artery disease: The Bogalusa Heart Study. JAMA 278: 1749-1754, 1997.
19. Pietiläinen KH, Bergholm R, Rissanen A, Kaprio J, Häkkinen AM, Sattar N and Yki-Järvinen H: Effects of acquired obesity on endothelial function in monozygotic twins. Obesity (Silver Spring) 14: 826-837, 2006.
20. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S and Willich SN: Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil 15: 239-246, 2008.
21. Pereira S and Pereira D: Metabolic syndrome and physical activity. Acta Med Port 24: 785-790, 2011 (In Portuguese).
22. Rauner A, Mess F and Woll A: The relationship between physical activity, physical fitness and overweight in adolescents: a systematic review of studies published in or after 2000. BMC Pediatr 13: 19, 2013. doi: 10.1186/1471-2431-13-19.
23. Väistö J, Eloranta AM, Viitasalo A, Tompuri T, Lintu N, Karjalainen P, Lampinen EK, Ågren J, Laaksonen DE, Lakka HM, *et al*: Physical activity and sedentary behaviour in relation to cardiometabolic risk in children: cross-sectional findings from the Physical Activity and Nutrition in Children (PANIC) Study. Int J Behav Nutr Phys Act 11: 55, 2014. doi: 10.1186/1479-5868-11-55.
24. Lutsey PL, Steffen LM and Stevens J: Dietary intake and the development of the metabolic syndrome: The atherosclerosis risk in communities study. Circulation 117: 754-761, 2008.
25. Pasanisi F, Contaldo F, de Simone G and Mancini M: Benefits of sustained moderate weight loss in obesity. Nutr Metab Cardiovasc Dis 11: 401-406, 2001.
26. Ilanne-Parikka P, Eriksson JG, Lindström J, Peltonen M, Aunola S, Hämäläinen H, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Lahtela J, *et al*; Finnish Diabetes Prevention Study Group: Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. Diabetes Care 31: 805-807, 2008.
27. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S and Fowler S; Diabetes Prevention Program Research Group: The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: The Diabetes Prevention Program randomized trial. Ann Intern Med 142: 611-619, 2005.
28. Eloranta AM, Lindi V, Schwab U, Kiiskinen S, Venäläinen T, Lakka HM, Laaksonen DE and Lakka TA: Dietary factors associated with metabolic risk score in Finnish children aged 6-8 years: the PANIC study. Eur J Nutr 53: 1431-1439, 2014.
29. Sookoian S and Pirola CJ: Epigenetics of insulin resistance: an emerging field in translational medicine. Curr Diab Rep 13: 229-237, 2013.
30. Burguet A: Long-term outcome in children of mothers with gestational diabetes. Diabetes Metab 36: 682-694, 2010.
31. Yu M, Xu CX, Zhu HH, Hu RY, Zhang J, Wang H, He QF, Su DT, Zhao M, Wang LX, *et al*: Associations of cigarette smoking and alcohol consumption with metabolic syndrome in a male Chinese population: a cross-sectional study. J Epidemiol 24: 361-369, 2014.
32. Tamashiro KL: Metabolic syndrome: links to social stress and socioeconomic status. Ann N Y Acad Sci 1231: 46-55, 2011.
33. Abbasi F, Brown BW Jr, Lamendola C, McLaughlin T and Reaven GM: Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 40: 937-943, 2002.
34. Laakso M and Kuusisto J: Insulin resistance and hyperglycaemia in cardiovascular disease development. Nat Rev Endocrinol 10: 293-302, 2014.
35. DeFronzo RA and Tripathy D: Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 32 (Suppl 2): S157-S163, 2009.
36. Michael MD, Kulkarni RN, Postic C, Previs SF, Shulman GI, Magnuson MA and Kahn CR: Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. Mol Cell 6: 87-97, 2000.
37. Yki-Järvinen H: Glucose toxicity. Endocr Rev 13: 415-431, 1992.
38. Begg DP and Woods SC: The endocrinology of food intake. Nat Rev Endocrinol 9: 584-597, 2013.
39. Olivieri O, Bassi A, Stranieri C, Trabetti E, Martinelli N, Pizzolo F, Girelli D, Friso S, Pignatti PF and Corrocher R: Apolipoprotein C-III, metabolic syndrome, and risk of coronary artery disease. J Lipid Res 44: 2374-2381, 2003.
40. Borén J, Taskinen MR, Olofsson SO and Levin M: Ectopic lipid storage and insulin resistance: a harmful relationship. J Intern Med 274: 25-40, 2013.
41. Packard CJ, Demant T, Stewart JP, Bedford D, Caslake MJ, Schwertfeger G, Bedynek A, Shepherd J and Seidel D: Apolipoprotein B metabolism and the distribution of VLDL and LDL subfractions. J Lipid Res 41: 305-318, 2000.
42. Tooke JE and Hannemann MM: Adverse endothelial function and the insulin resistance syndrome. J Intern Med 247: 425-431, 2000.
43. Salonen JT, Lakka TA, Lakka HM, Valkonen VP, Everson SA and Kaplan GA: Hyperinsulinemia is associated with the incidence of hypertension and dyslipidemia in middle-aged men. Diabetes 47: 270-275, 1998.
44. Vogel RA: Cholesterol lowering and endothelial function. Am J Med 107: 479-487, 1999.
45. Laaksonen DE, Niskanen L, Nyyssönen K, Lakka TA, Laukkanen JA and Salonen JT: Dyslipidaemia as a predictor of hypertension in middle-aged men. Eur Heart J 29: 2561-2568, 2008.

46. Comar JF, de Oliveira DS, Bracht L, Kemmelmeier FS, Peralta RM and Bracht A: The metabolic responses to L-glutamine of livers from rats with diabetes types 1 and 2. PLOS ONE 11: e160067, 2016.
47. Lebovitz HE: Type 2 diabetes: An overview. Clin Chem 45: 1339-1345, 1999.
48. Kawada T: Serum granzyme-B, insulin resistance, metabolic syndrome and cardiovascular risk: Statistical validity for risk assessment. Eur J Obstet Gynecol Reprod Biol: Jul 30, 2016 (Epub ahead of print).
49. Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K and Laakso M: Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care 27: 2898-2904, 2004.
50. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K and Laakso M: Proteinuria and metabolic syndrome as predictors of cardiovascular death in non-diabetic and type 2 diabetic men and women. Diabetologia 49: 56-65, 2006.
51. Reinehr T: Type 2 diabetes mellitus in children and adolescents. World J Diabetes 4: 270-281, 2013.
52. Giudice EM, Grandone A, Cirillo G, Santoro N, Amato A, Brienza C, Savarese P, Marzuillo P and Perrone L: The association of PNPLA3 variants with liver enzymes in childhood obesity is driven by the interaction with abdominal fat. PLoS One 6: e27933, 2011.
53. Goran MI, Walker R, Le KA, Mahurkar S, Vikman S, Davis JN, Spruijt-Metz D, Weigensberg MJ and Allayee H: Effects of PNPLA3 on liver fat and metabolic profile in Hispanic children and adolescents. Diabetes 59: 3127-3130, 2010.
54. McNeill AM, Rosamond WD, Girman CJ, Heiss G, Golden SH, Duncan BB, East HE and Ballantyne C: Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). Am J Cardiol 94: 1249-1254, 2004.
55. Ash-Bernal R and Peterson LR: The cardiometabolic syndrome and cardiovascular disease. J Cardiometab Syndr 1: 25-28, 2006.
56. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, *et al*: Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 290: 2277-2283, 2003.
57. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS and Raitakari OT: Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: The Cardiovascular Risk in Young Finns Study. Circulation 112: 1486-1493, 2005.
58. Wong ND, Sciammarella MG, Polk D, Gallagher A, Miranda-Peats L, Whitcomb B, Hachamovitch R, Friedman JD, Hayes S and Berman DS: The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. J Am Coll Cardiol 41: 1547-1553, 2003.
59. Koren-Morag N, Goldbourt U and Tanne D: Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. Stroke 36: 1366-1371, 2005.
60. Grundy SM: Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 47: 1093-1100, 2006.
61. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R and Welt CK; Endocrine Society: Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 98: 4565-4592, 2013.
62. Legro RSA: A 27-year-old woman with a diagnosis of polycystic ovary syndrome. JAMA 297: 509-519, 2007.
63. Drager LF, Togeiro SM, Polotsky VY and Lorenzi-Filho G: Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol 62: 569-576, 2013.
64. Schulz R, Eisele HJ, Reichenberger F and Seeger W: Obstructive sleep apnoea and metabolic syndrome. Pneumologie 62: 88-91, 2008 (In German).
65. Hamilton GS, Solin P and Naughton MT: Obstructive sleep apnoea and cardiovascular disease. Intern Med J 34: 420-426, 2004.
66. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL and Anis AH: The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 9: 88, 2009. doi: 10.1186/1471-2458-9-88.