J Pediatr (Rio J). 2019;95(5):503–505

Jornal de Pediatria
www.jped.com.br

EDITORIAL

Endothelial dysfunction and cardiovascular disease in childhood obesity☆,☆☆

Disfunção endotelial e doença cardiovascular na obesidade infantil

Michael Freemark

Duke University Medical Center, Pediatric Endocrinology and Diabetes, Durham, United States

It is a popular misconception that myocardial infarction and stroke are acute events that strike suddenly and unexpectedly in middle aged and elderly adults. Yet the Bogalusa, Muscatine, Young Finns, and PDAY studies clearly demonstrate that atherosclerosis is a chronic, progressive disease that begins in childhood.[1] Identification of high-risk children and institution of preventive measures at an early age are therefore imperative.

Critical determinants of atherosclerosis in adolescence and adulthood include obesity, hyperlipidemia, hypertension, glucose intolerance, smoking, sedentary activity, and a family history of early cardiovascular disease and stroke. The earliest structural lesions of atherosclerosis, fatty streaks, can be detected even in young children. Accumulation of lipid-laden macrophages, monocytes, and T cells is followed by platelet aggregation, vascular smooth muscle cell proliferation, and the formation of a lesion capped by smooth muscle and collagen known as a fibrous plaque. But prior to the emergence of fatty streaks and plaques there are changes in endothelial function manifest as heightened permeability to lipoproteins, up-regulation of leukocyte adhesion molecules, and translocation of leukocytes into the arterial wall.[2] These are associated with functional changes in micro- and macro-vascular compliance and reactivity that are associated, at least in adults, with mortality from cardiovascular disease.[3]

As assessed by reductions in flow-mediated dilation of the brachial artery and flow-mediated hyperemia of peripheral vessels, endothelial dysfunction has been demonstrated in children and adolescents with obesity and insulin resistance.[4] Poorly understood, however, are the roles of diet and physical activity in the control of vascular function in obese and lean young people.

The study by Penha et al.[5] examined the relationship between physical activity in prepubertal children and vascular function as measured by venous occlusion plethysmography. This method assesses changes in limb volume following venous occlusion. An acute increase in limb volume during venous outflow obstruction reflects arterial blood inflow, which depends on the capacity of the major arterial conduit vessels to overcome resistance of small arterioles; an inadequate rise in limb volume during venous occlusion reflects higher resistance, or lower vasodilatory capacity, of small resistance vessels. Thus, the technique is an indirect measure of the vasoreactivity of the microcirculation.

DOI of original article:
https://doi.org/10.1016/j.jped.2018.04.010

☆ Please cite this article as: Freemark M. Endothelial dysfunction and cardiovascular disease in childhood obesity. J Pediatr (Rio J). 2019;95:503–5.

☆☆ See paper by Penha et al. in pages 531–7.

E-mail: michael.freemark@duke.edu

https://doi.org/10.1016/j.jped.2018.07.004

The authors found a reduced hyperemic response to venous occlusion in overweight and obese children, in association with measures of adiposity (% body fat and hyperleptinemia). Interestingly, there was no relationship between arterial vascular reactivity and physical fitness or habitual physical activity, as assessed by questionnaire and a speed-shuttle endurance run. Run performance did correlate negatively with body fat and waist circumference; whether a decrease in physical fitness is a cause or consequence (or both) of adiposity is currently unclear.[1]

The authors did not explore the mechanisms by which obesity reduces microvascular reactivity in prepubertal children. A defect in vascular relaxation may signify a deficit of nitrous oxide (NO) generation by vascular endothelial cells or an impaired response of vascular smooth muscle cells to NO or other endogenous vasodilatory substances.[6,7] Endothelial synthesis of NO is controlled in part by insulin and various other hormones and cytokines. In lean subjects, insulin promotes vasodilatation by increasing the expression of NO synthase (eNOS) in endothelial cells; this action is mediated by *tyrosine* phosphorylation of insulin receptor substrates 1 and 2 and activation of phosphoinositide 3-kinase (PI-3 kinase) and Akt. In obesity and other states associated with insulin resistance, *serine* phosphorylation of insulin receptor substrates inhibits activation of PI-3 kinase and Akt and impedes NO generation; under these conditions, insulin promotes *vasoconstriction* through mitogen-activated protein kinase (MAPK)-mediated induction of endothelin-1.[6,7] The overweight subjects in this study were insulin resistant, as determined by hypoadiponectinemia and increases in HOMA-IR and the ratio of triglycerides to HDL. Nevertheless, the hyperemic response did not correlate with measures of insulin sensitivity.

In parallel with its effects on insulin sensitivity, obesity can impair endothelial function through visceral and perivascular fat accretion and vascular inflammation: obesity-induced hypertrophy of visceral and perivascular white adipocytes is accompanied by free fatty acidemia, macrophage infiltration, and generation of inflammatory cytokines and reactive oxygen species. In concert, these promote tissue inflammation, reduce vascular NO availability, and inhibit the smooth muscle cell vasodilatory response to NO.[6–8] Other factors contributing to loss of vascular compliance in obesity include activation of the sympathetic nervous system by hyperleptinemia,[6–8] induction of renin-angiotensin-aldosterone activity via heightened white adipocyte angiotensinogen production,[6–9] and loss of capillary perfusion associated with hypoadiponectinemia.[6–10]

What is the significance of endothelial dysfunction in overweight and obese children? Loss of endothelial vasodilatation likely contributes to hypertension, a common co-morbidity in obese subjects, and to the development of obesity-related glomerulosclerosis.[7] Of equal or more concern, experimental evidence suggests that endothelial dysfunction might limit cerebral blood flow and predispose to cognitive dysfunction.[7]

The relationship between endothelial dysfunction in prepubertal children and adult cardiovascular disease is less clear. No studies to date clearly demonstrate that prepubertal endothelial dysfunction predisposes to myocardial infarction or stroke. On the other hand, obesity during childhood and adolescence increases the risks for coronary artery disease if excess fat deposition persists into adulthood. A large (n = 2.3 million), longitudinal study[11] of Israeli adolescents found that obesity at mean age 17.3 years was associated with a 4.9-fold increase in the risk of coronary artery disease and a 4.1-fold increase in cardiovascular deaths by ages 47–57 years. Lower (but statistically significant) risks of future acute coronary events (10% increase for every 1-unit increase in BMIz) were noted in a study of 7–13-year-old Danish children.[12] Finally, a meta-analysis[13] showed that a 1-SD increase in BMI in childhood and adolescence (ages 7–18 years) predicts a 14–30% increase in the risk of adult coronary heart disease.

Nevertheless, the association of carotid intimal thickening with childhood obesity was abolished after adjustment for adult obesity in the Bogalusa, Muscatine and Young Finns studies.[1] Moreover, cardiovascular mortality was not increased in adult Swedes who were obese in childhood but not during adolescence or adult life.[14] Thus, endothelial dysfunction in children and obesity-related risks for cardiovascular morbidity and mortality are potentially reversible.

What measures might be taken to reverse the endothelial dysfunction in obese children? Weight loss is known to promote NO generation, and a combination of diet and aerobic exercise training improves *macro*-vascular endothelial function in obese children in as little as 6–8 weeks[15,16]; more prolonged interventions may be needed to improve *micro*-vascular endothelial function.[17] It is thought that surges in limb blood flow during bouts of physical activity may facilitate a rise in endothelial NO production and/or activity. Both aerobic and resistance training are effective[18]; however, the benefits of exercise on vascular function appear to be lost if training ceases.[15]

Dietary and exercise counseling may not suffice for subjects with more severe metabolic dysfunction; in such cases, the addition of a pharmacologic agent may prove salutary. For example, an emerging literature suggests that metformin can enhance endothelial function in adults with severe insulin resistance, type 2 diabetes mellitus, and the polycystic ovary syndrome.[19] The drug may therefore provide cardiovascular as well as glycemic benefits to adolescents with prediabetes or overt glucose intolerance. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) improve endothelial-dependent vasodilation in adults with renal disease[9,20] and may be useful in obese children and adolescents with hypertension and/or microalbuminuria.

Critical gaps remain in our understanding of the development and pathogenesis of vascular dysfunction and atherogenesis in children. Long-term studies of dietary and exercise interventions in overweight and obese subjects will enhance our ability to prevent long-term vascular complications and increase quality of life.

Conflicts of interest

The author declares no conflicts of interest.

References

1. Freemark M. Childhood obesity in the modern age: global trends, determinants, complications and costs. In: Freemark

MS, editor. Pediatric obesity: etiology, pathogenesis, and treatment. New York: Springer International Publishing AG, Humana Press; 2018. p. 3–24.
2. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med. 1999;340:115–26.
3. Kajikawa M, Maruhashi T, Hida E, Iwamoto Y, Matsumoto T, Iwamoto A, et al. Combination of flow-mediated vasodilation and nitroglycerine-induced vasodilation is more effective for prediction of cardiovascular events. Hypertension. 2016;67:1045–52.
4. Tomsa A, Klinepeter Bartz S, Krishnamurthy R, Krishnamurthy R, Bacha F. Endothelial function in youth: a biomarker modulated by adiposity-related insulin resistance. J Pediatr. 2016;178:171–7.
5. Penha JT, Gazolla FM, Carvalho CN, Madeira IR, Rodrigues-Junior F, Machado EA, et al. Physical fitness and activity, metabolic profile, adipokines and endothelial function in children. J Pediatr (Rio J). 2019;95:531–7.
6. Wasserman DH, Wang TJ, Brown NJ. The vasculature in prediabetes. Circ Res. 2018;122:1135–50.
7. Sorop O, Olver TD, van de Wouw J, Heinonen I, van Duin RW, Duncker DJ, et al. The microcirculation: a key player in obesity-associated cardiovascular disease. Cardiovasc Res. 2017;113:1035–45.
8. Engin A. Endothelial dysfunction in obesity. Adv Exp Med Biol. 2017;960:345–79.
9. Cabandugama PK, Gardner MJ, Sowers JR. The renin angiotensin aldosterone system in obesity and hypertension: roles in the cardiorenal metabolic syndrome. Med Clin North Am. 2017;101:129–37.
10. Zhao L, Fu Z, Liu Z. Adiponectin and insulin cross talk: the microvascular connection. Trends Cardiovasc Med. 2014;24:319–24.
11. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. N Engl J Med. 2016;374:2430–40.
12. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med. 2007;357:2329–37.
13. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev. 2016;17:56–67.
14. Ohlsson C, Bygdell M, Sondén A, Rosengren A, Kindblom JM. Association between excessive BMI increase during puberty and risk of cardiovascular mortality in adult men: a population-based cohort study. Lancet Diabetes Endocrinol. 2016;4:1017–24.
15. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. Circulation. 2004;109:1981–6.
16. Kelly AS, Wetzsteon RJ, Kaiser DR, Steinberger J, Bank AJ, Dengel DR. Inflammation, insulin, and endothelial function in overweight children and adolescents: the role of exercise. J Pediatr. 2004;145:731–6.
17. Bruyndonckx L, Hoymans VY, De Guchtenaere A, Van Helvoirt M, Van Craenenbroeck EM, Frederix G, et al. Diet, exercise, and endothelial function in obese adolescents. Pediatrics. 2015;135:e653–61.
18. Ashor AW, Lara J, Siervo M, Celis-Morales C, Oggioni C, Jakovljevic DG, et al. Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. Sports Med. 2015;45:279–96.
19. Triggle CR, Ding H. Metformin is not just an antihyperglycaemic drug but also has protective effects on the vascular endothelium. Acta Physiol (Oxf). 2017;219:138–51.
20. Patarroyo Aponte MM, Francis GS. Effect of Angiotensin-converting enzyme inhibitors and Angiotensin receptor antagonists in atherosclerosis prevention. Curr Cardiol Rep. 2012;14:433–42.