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Review

Childhood obesity: a life-long health risk

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Childhood obesity has become major health concern for physicians, parents, and health agencies around the world. Childhood obesity is associated with an increased risk for other diseases not only during youth but also later in life, including diabetes, arterial hypertension, coronary artery disease, and fatty liver disease. Importantly, obesity accelerates atherosclerosis progression already in children and young adults. With regard to pathophysiological changes in the vasculature, the striking similarities between physiological changes related to aging and obesity-related abnormalities are compatible with the concept that obesity causes "premature" vascular aging. This article reviews factors underlying the accelerated vascular disease development due to obesity. It also highlights the importance of recognizing childhood obesity as a disease condition and its permissive role in aggravating the development of other diseases. The importance of childhood obesity for disease susceptibility later in life, and the need for prevention and treatment are also discussed.

Keywords: atherosclerosis; non-alcoholic steatohepatitis; diabetes; insulin resistance; stroke; myocardial infarction; physical exercise; cardiovascular risk; hypertension; vascular programming

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Childhood obesity: a health problem gone global

Childhood obesity has been of medical interest for more than 150 years[1, 2]. Until the middle of the 20th century the prevalence of obesity in the general population of the United States was relatively moderate[3]. However, in the last two decades the prevalence has risen to epidemic proportions[4–6]. In fact, 34.4 percent of the population of the United States are now considered overweight (and not obese) and 33.9 percent are considered to be obese[7], affecting more than 200 million people. Similarly, the number of children diagnosed with obesity and/or obesity-related diabetes has been continuously increasing over the past 20 years in countries around the world[8–10]. In 2010 in the United States, 17 percent of children and adolescents were obese – including those with severe obesity[11], with the prevalence of obesity having tripled since 1980[3]. Particularly worrisome is the 10.4% prevalence of obesity among the 2 to 5 year olds in the US[12], with other parts of the world catching up[13, 14]. The World Health Organization (WHO) defines obesity (in adults: BMI >30 kg/m^2) as a disease for which excessive calorie intake, in conjunction with lack of physical exercise, have been identified as major predisposing and aggravating factors[15, 16]. Obesity also serves as soil for the development of other diseases[15], particularly insulin resistance (pre-diabetes), type 2 diabetes mellitus, arterial hypertension, dyslipidemia/hypertriglyceridemia, and fatty liver disease/non-alcoholic steatohepatitis (NASH)[15, 17, 18]. At the same time, obesity also worsens these conditions once they have developed [15]. In addition, mutations in certain genes such as the leptin receptor are associated with early-onset childhood obesity and excessive body mass indices[19–21]. High birth weights or diabetes of the mother (pregnancy-associated diabetes) have been proposed as potential factors affecting postnatal health, and lack of breastfeeding has been suggested to contribute to a higher risk for obesity during adolescence[22]. A number of other factors have been associated with a higher risk to develop obesity, which include the disease susceptibility of certain ethnic groups, poverty and/or low socioeconomic status, which are often associated with a low health concerns/self-concern[3, 7]. By contrast, some Asian countries such as Japan which have a very low overall prevalence of obesity[23]. This may be in part due to composition of Asian diets, while excess access to inexpensive, high calorie food has been identified as a major factor contributing to the rising number of obese children in countries such as the USA and in European countries[24]. Not surprisingly, childhood obesity has also been steadily growing in China where over the past decades people have in part adopted Western dietary patterns[24]. Increased health risk is not limited to obesity, but already apparent with overweight. Indeed, long-term studies following the health of overweight children for more than 40 years found significantly increased risks for a number of diseases [25] (Figure 1).

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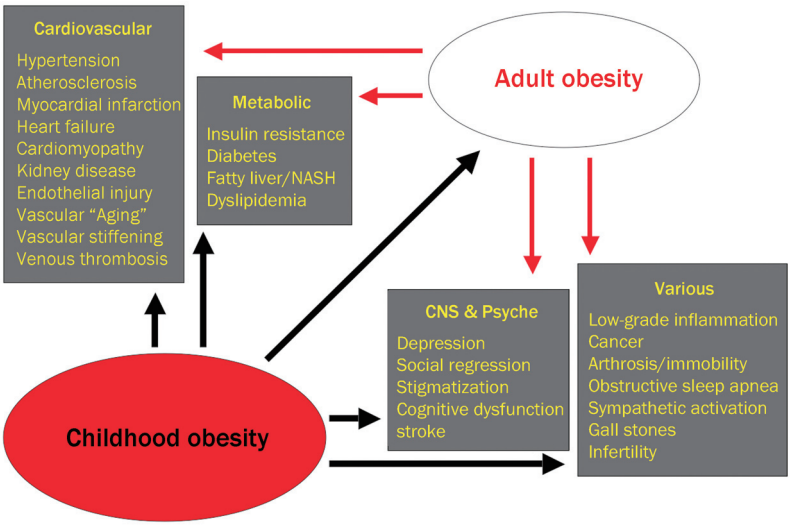

Figure 1. Aggravating effect of childhood obesity on the life-time risk for other disease conditions, including a greater risk for adult obesity, which itself continues to worsen disease development.

Atherosclerosis begins in childhood

Obese children are at a higher risk for accelerated development of vascular disease[26], which is aggravated by the worsening of risk factors secondary to obesity. Atherosclerosis, a systemic chronic inflammatory disease of the large arteries, is the main cause of cardiovascular and cerebrovascular events[27]. The disease accounts for the majority of deaths due to myocardial infarction and stroke in Western as well as in Eastern and developing countries[27]. First vascular abnormalities, inflammatory changes and plaque development can be observed in children already in the first year of life[28]; consistent with these observations, the disease process begins in utero, during which the precursor of the atherosclerotic plaque — the "fatty streak" — is already present[29, 30]. The development of fatty streaks, which represent inflammatory accumulations of macrophages in the subintimal space — is aggravated by maternal hypercholesterolemia and thus sets the basis for vascular disease later in life[30]. The cause of cardiovascular and cerebrovascular events most often is due to rupture of "soft" atherosclerotic plaques filled with a lipid core underlying a thinned fibrous cap[27], pathological findings some of which are already present in young adults[26, 31]. Plaque development is accelerated in the presence of risk factors such as arterial hypertension, dyslipidemia, diabetes, male sex, and obesity, which are equally important for children and adults[26, 31]. Interestingly, girls and young women appear to be largely protected from the aggravating effect of obesity on plaque progression[26]. Among all cardiovascular risk factors, obesity is of particular importance since it aggravates several other risk factors such as arterial hypertension, insulin resistance/diabetes, or dyslipidemia.

Childhood obesity causes changes consistent with "Premature" vascular aging

Inflammation also plays a role for insulin resistance and metabolic changes associated with obesity[32] and abnormal inflammatory activation has been reported to occur in obese children[33]. In both children and adults, obesity causes generalized injury to the vasculature. This process also involves inflammatory activation, both locally in the vascular wall[32] as well as in adipose tissue[34]. Inflammation also underlies insulin resistance (pre-diabetes) and type 2 diabetes[34], conditions originally believed to be restricted to elderly individuals, but now increasingly found in obese juveniles[35, 36]. Similarly, an important aspect of obesity-associated vascular injury obtained from preclinical and clinical studies, is that many of the vascular changes found in obesity are highly similar to those seen with aging[37], which not only represents a physiological process but in itself represents a strong and independent risk factor for future cardiovascular events[37]. As with aging[37], experimental or human obesity shows an attenuation of endothelium-dependent vasodilation[38, 39], a decrease in NO bioactivity[38, 39] in conjunction with NO synthase uncoupling[37], an increase in prostanoid-mediated endothelium-dependent contractions[40–42], telomere shortening[43–46], increased vascular stiffness[47], and increased arterial intima-media thickness[26, 48]. Obesity also increases tissue levels of endothelin-1[38, 49, 50], a strong vasoconstrictor peptide and atherogenic growth factor and proinflammatory stimulus[51]. Picard and Guarente recently reported interactions between life-span regulating genes and adipose tissue functions[52]. Thus, obesity can be considered a process which is compatible with accelerated aging which may — at least in part — explain the accelerated atherosclerosis development in children and young adults with obesity[26].

Potential role for post-natal dietary vascular programming

A few years ago results from two clinical studies were reported that childhood obesity is associated with a several fold increased risk for cardiovascular events in adult life, even if body weight had meanwhile normalized[9, 53, 54]. These very intriguing observations, which are in part supported by an earlier study[55], not only emphasize the importance of childhood obesity prevention but also suggest that still unknown mechanisms exist that must be set-off by the "childhood obesity

environment" and, once activated, remain irreversibly active until later in life irrespective of changes in body weight. Thus, possible local "post-natal dietary programming" mechanisms may contribute to the underlying disease-promoting process in the arterial wall. Alternatively, acceletated progression of atherosclerosis in youth due to obesity may simply lead to established, irreversible atherosclerotic lesions that no longer can be affected by weight normalization. Indeed, advanced coronary artery disease present in their late teenage years and death from myocardial infarction has been described in young men exposed to extremely high stress conditions[56, 57].

Continued need for disease prevention

Aside from highly complex disease processes, simple factors such as overnutrition and lack of knowledge about obesity prevention, respectively, are likely to be at least equally important. This can be exemplified by a case report from Germany where parents fed their infant almost exclusively with sugared water[58]. This infant developed severe obesity and at 2 years of age, was diagnosed with early cerebrovascular disease[58] similar to increased vascular stiffening found in obese juveniles[59], conditions normally found only at much later stages in life. Not surprisingly, reducing body weight in obese juveniles is associated with markedly improved cognitive function[60], and recent data suggest that even cerebral and cerebellar development is negatively affected by childhood obesity[61]. Thus, awareness and education of parents[12], educators, and pediatric medical staff should remain one of the key goals in order to achieve prevention of childhood obesity which, subsequently, should also result in a reduction of diseases associated with it. One of the questions is how we can monitor vascular health. The function of the vasculature, particularly endothelium-dependent vasomotion, reflects quite well the overall health status of the arterial system[62]. Human obesity, characterized by accumulation of ectopic (particularly visceral) fat[63], is associated with abnormal endothelium-dependent vasomotion and enhanced contractility to endothelin-1[64, 65]. Accordingly, a reduction in energy intake[66] or reduction in body weight[67] improves vascular function in obese patients. In human resistance arteries obesity is associated with vascular hypertrophy as indicated by an increased media-to-lumen ratio[68], and a recent important study demonstrated that functional vascular abnormalities observed in obese individuals can be largely normalized by lowering body weight by reducing intra-abdominal fat mass in adults[67]. Thus, any reduction of obesity — in children as well as adults — is likely to translate into improved overall health and survival[4, 15, 69]. Indeed, preserved endothelium-dependent vasoreactivity is associated with greater survival in patients with cardiovascular disease[62]. Possibly, reducing subcutaneous fat may also have some beneficial effect on the pro-inflammatory risk profile[70, 71].

Physical activity as therapeutic

The question remains of how to achieve a sustained reduction of childhood obesity, both at the individual level as well as for overall prevalence[72]. One of the central components of obesity prevention and therapy or – if absent a promotor of obesity — is physical exercise[4, 73–75]. Physical inactivity is a key cause contributing to and worsening childhood obesity[76], and has now even become a concern in developing countries[77]. Exercise not only has a number of beneficial effects on several risk factors associated with obesity (reduction of sympathetic activation and blood pressure, improved lipid profile, improved insulin sensitivity[4, 73–75]), but also improves consumption of excess energy stores of fat and thus helps to reduce adipose tissue mass[78]. There is recent evidence that regular exercise may even infer with cellular processes associated with vascular aging[79]. A most recent study indicates that vascular elasticity as a function of age is also increased in obese children compared with their lean counterparts[80], indicative of accelerated vascular growth and maturation and thus compatible with early aging. It is important, both for therapy and prevention of childhood obesity, that sufficient and regular exercise becomes and remains a part of children's everyday life in conjunction with normal calorie intake. It has been recently shown that weight loss in children reduces inflammatory activation[81], one of the key factors for vascular disease progression[82]. Caloric restriction prolongs life in a number of species, including rodents and primates[83, 84]. It can only be speculated that in humans "global caloric restriction" in those countries with excess access to food would have similar effects on life expectancy and overall well-being[5]. Indeed some countries have taken political measures such as issuing special taxes on fat as the dietary componant with highest energy value[85, 86]. The prevention of childhood obesity is a chance that must be taken early in life by parents, health professionals, educators, and politicians[69]. Fortunately, health agencies have already begun to implement this need into their information policies provided to parents[12] with whom children spend the most time. If we succeed with this task of promoting, achieving, and maintaining health among children — including a regular "regimen" of physical exercise[16, 87, 88] —, this will ultimately reduce the number of tomorrow's patients and enable healthy aging at a low cardiovascular risk[89].

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