Review Article

Obesity and cardiovascular risk in children and adolescents

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ABSTRACT

The global prevalence of overweight and obesity in children and adolescents has increased substantially over the past several decades. These trends are also visible in developing economies like India. Childhood obesity impacts all the major organ systems of the body and is well known to result in significant morbidity and mortality. Obesity in childhood and adolescence is associated with established risk factors for cardiovascular diseases and accelerated atherosclerotic processes, including elevated blood pressure (BP), atherogenic dyslipidemia, atherosclerosis, metabolic syndrome, type II diabetes mellitus, cardiac structural and functional changes and obstructive sleep apnea. Probable mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of the renin–angiotensin–aldosterone system and altered vascular function. Adiposity promotes cardiovascular risk clustering during childhood and adolescence. Insulin resistance has a strong association with childhood obesity. A variety of proinflammatory mediators that are associated with cardiometabolic dysfunction are also known to be influenced by obesity levels. Obesity in early life promotes atherosclerotic disease in vascular structures such as the aorta and the coronary arteries. Childhood and adolescent adiposity has strong influences on the structure and function of the heart, predominantly of the left ventricle. Obesity compromises pulmonary function and increases the risk of sleep-disordered breathing and obstructive sleep apnea. Neglecting childhood and adolescent obesity will compromise the cardiovascular health of the pediatric population and is likely to result in a serious public health crisis in future.

Key words: Adolescents, cardiovascular risk, children, obesity, overweight

Introduction

Global trends of childhood obesity show huge shifts in recent times.[1] Surveys from 144 countries (in 2010) suggest that 43 million preschool children (35 million in developing countries) are overweight and obese and 92 million are at risk of overweight.[2] The worldwide prevalence of childhood overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010. This trend is likely to continue and the prevalence is expected to reach 9.1%, or 60 million, in 2020. The estimated prevalence of childhood overweight and obesity in Africa in 2010 was 8.5% and is expected to reach 12.7% in 2020. The prevalence is lower in Asia (4.9% in 2010) than in Africa, but the number of affected children (18 million) is higher in Asia.[2] Reports from various parts of India suggest significant heterogeneity in the distribution and growth of childhood obesity prevalence rates. A recent study conducted in south India among 24842 school children aged 5–16 years showed that the proportion of overweight children increased from 4.94% of the total students in 2003 to 6.57% in 2005, demonstrating the time trend of this rapidly growing epidemic.[3] There is significant heterogeneity in this time trend of obesity in India.[4] Socioeconomic trends in childhood obesity in India are also emerging. A study from northern India reported a childhood obesity prevalence of 5.59% in the higher socioeconomic strata, compared to 0.42% in the lower socioeconomic strata.[5] Nutritional transition among school-age children in India is remarkable, as demonstrated by a cohort of 12129 school children from south India.[6]

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Studies from north, south, east, west, and central parts of India have reported varying prevalence rates of overweight and obesity in children and adolescents, suggesting strong geographical, economic, and societal influences on the progression of this massive epidemic.[3,5,7-14]

Definition of Childhood Obesity and Overweight

For children and adolescents, overweight and obesity are defined using age- and sex-specific nomograms for body mass index (BMI). Children with BMI equal to or exceeding the age- and gender-specific 95th percentile are defined as obese. Those with BMI equal to or exceeding the 85th percentile – but below the 95th percentile – are defined as overweight. These children are at risk for obesity-related comorbidities.[15]

Obesity in Childhood and Future Cardiovascular Health

Large cohorts from various populations have demonstrated the important influence of childhood BMI on future cardiovascular health. In a recent extensive systematic review, Owen *et al.* reported that BMI in later childhood (i.e., age 7 to <18 years) was positively related to future coronary heart disease (CHD) risk [relative risk (RR): 1.09].[16] Bjorge *et al.* followed up 227000 adolescents in the Norwegian health surveys. In this cohort, the RR of death due to ischemic heart disease at the end of follow-up (mean follow-up: 34.9 years) was 2.9 for males and 3.7 for females in the highest BMI category (i.e., BMI >85th percentile) compared with the reference (i.e., BMI 25th–74th percentiles).[17]

Cardiovascular Risk Profile in Obese Children

Childhood obesity impacts all major organ systems of the body and is well known to result in significant morbidity and mortality.[18] Data accumulated over the past indicate that atherosclerotic cardiovascular disease (CVD) processes begin early in childhood and are influenced over the life course by genetic factors as well as other potentially modifiable risk factors such as environmental exposures, including obesity.[19] Cardiovascular risk becomes abnormal around the 85th percentile of body weight, above which lower high-density lipoprotein cholesterol (HDL-C) level, higher triglyceride level, and other risk factor changes are observed..[20] Obesity in childhood is the most consistent predictor of adult heart disease.[21] Prospective longitudinal studies have shown the impact of childhood BMI on the adolescent cardiovascular risk profile. The Avon longitudinal study of 5235 children reported that, in girls, a 1 standard deviation (SD) increase over mean BMI during 9–12 years was associated with cardiovascular risk factors at age 15–16 years in fully adjusted models, with odds ratio of 1.23 for high systolic blood pressure (BP) (≥130 mm Hg); 1.19 for high low-density lipoprotein cholesterol (LDL-C) (≥2.79 mmol/l); 1.43 for high triglycerides (≥1.7 mmol/l); 1.25 for low HDL-C (<1.03 mmol/l); and 1.45 for high levels of insulin (≥16.95 IU/l).[22] The corresponding values in boys were 1.24 for systolic BP, 1.30 for LDL-C, 1.96 for triglycerides; 1.39 for HDL-C, and 1.84 for high insulin levels.[22]

Hypertension

The relationship of childhood obesity with BP has been examined by many studies in the past. High BP (i.e., BP >95th percentile) was seen in 35.4% of overweight children in the European pediatric cohort.[23] Data from a recent study covering 25000 school children in the age-group of 5–16 years reported similar figures from India.[3] First instance hypertension was seen in 10.10% of normal-weight (nonoverweight, nonobese) children, 17.34% of overweight children, and 18.32% of obese children in this study. The corresponding figures for systolic (first instance) hypertension were 5.38%, 12.31%, and 14.66%, respectively and for diastolic hypertension (first instance) 6.45%, 8.86%, and 8.90%, respectively.[3] The rate of change in BMI appears to be more significant than the absolute level of BMI in influencing pediatric BP as evidenced by a recent cohort of 12129 children from India.[24] Probable mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system, and altered vascular function.[25] Sympathetic nervous system activity is increased in obesity, particularly sympathetic activity to the kidney and skeletal muscle.[26–28] The probable reasons for over activation of the sympathetic nervous system in obesity include hyperinsulinemia and/or insulin resistance; increase in leptin, adiponectin, or other adipokines; renin–angiotensin system overactivity; and lifestyle factors.[25] Hypertension is also causally related to sleep apnea, possibly due to sympathetic overflow as a consequence of intermittent hypoxia.[29] Obesity-related hypertension is associated with renal sodium retention and impaired pressure natriuresis.[30] Obese humans and subjects with the metabolic syndrome tend to be relatively salt sensitive.[31,32] Activation of the renin–angiotensin system may also contribute to obesity-related hypertension.[25] Several studies suggest that plasma renin activity and plasma angiotensin II concentrations are

elevated in obesity.[33,34] Vascular endothelial dysfunction is associated with a number of cardiovascular risk factors, including obesity, insulin resistance, and hypertension.[35,36] Increased sympathetic over activity is a probable mechanism by which leptin may increase arterial pressure.[25] Leptin activates the sympathetic nervous system both by centrally mediated effects on the hypothalamus and by local peripheral actions.[37] Circulating adiponectin levels are decreased in obesity-induced insulin resistance, and some studies suggest that adiponectin is protective against hypertension through an endothelial-dependent mechanism.[38,39] Whether hypertension is causally related to insulin resistance and/or hyperinsulinemia is a matter of debate. The probable reasons by which insulin resistance and/or hyperinsulinemia may increase BP include an antinatriuretic effect of insulin, increased sympathetic nervous system activity, augmented responses to endogenous vasoconstrictors, altered vascular membrane cation transport, impaired endothelium-dependent vasodilatation, and stimulation of vascular smooth muscle growth by insulin.[25] The putative role of insulin resistance in childhood obesity assumes significance in view of the fact that Indian children exhibit higher BPs in comparison to their Western (US) counterparts.[40]

Metabolic Syndrome and Clustering of Cardiovascular Risk Factors

The metabolic syndrome is a clustering of traits, including hyperinsulinemia, obesity, hypertension, and hyperlipidemia.[41] De Ferranti *et al.* defined pediatric metabolic syndrome using five diagnostic components.[42] This syndrome is believed to be triggered by genetic factors acting in combination with environmental factors.[43] The primary cause of the syndrome appears to be obesity, which leads to excess insulin production that in turn is associated with an increase in BP and dyslipidemia.[43] The effects of increased insulin resistance are multiple and include increased hepatic synthesis of very-low-density lipoprotein, resistance to the action of insulin on lipoprotein lipase in peripheral tissues, enhanced cholesterol synthesis, increased HDL degradation, increased sympathetic activity, proliferation of vascular smooth muscle cells, and increased formation and decreased reduction of plaque.[43] One cross-sectional survey done on 1083 school-going Indian children (12–17 years) reported an overall prevalence of 4.2% (3.2% in boys, 5.5% in girls).[44] The criteria for metabolic syndrome were met by 36.6% of the overweight adolescents, 11.5% of at-risk-for-overweight adolescents, and 1.9% of the remaining normal-weight (nonoverweight, not-at-risk-of-overweight) adolescents. All five metabolic syndrome components, i.e., abdominal obesity (1.0%, 18.6%, and 41.6%, respectively, for normal, at-risk, and overweight groups), hyperglycemia (3.6%, 4.6%, 28.3%), hypertriglyceridemia (18.8%, 27.9%, 40.0%), low HDL-C (24.4%, 39.5%, 61.7%), and elevated BP (5.5%, 25.5%, 31.6%) demonstrated a trend for increase in prevalence as BMI increased.[44] These findings reiterate the dominant role of adiposity in cardiovascular risk clustering during childhood and adolescence.

Insulin Resistance and Type 2 Diabetes Mellitus

Insulin resistance, a well-known cardiovascular risk factor in adult life, has a strong association with childhood obesity. In a recent study on 208 obese children and adolescents, the rate of insulin resistance was 37% in boys and 27.8% in girls in the prepubertal period, while in the pubertal period the rates were 61.7% and 66.7%, respectively.[45] In another study of 710 obese children, Invitti *et al.* reported an overall prevalence of glucose intolerance of 4.5%.[46] Obesity and the associated insulin resistance have significant influence on glucose metabolism, with hypersecretion of insulin and chronic hyperinsulinemia in obese adults as well as obese children, both without diabetes.[47,48] This scenario frequently leads to the development of type 2 diabetes.[49] In a retrospective analysis of 1301 obese children, Jin *et al.* reported the prevalence of type 2 diabetes as 2.2% and that of prediabetes as 19.6%. It is interesting to note that 52.2% of the prediabetic children had dyslipidemia and 20.8% had hypertension; this only reiterates the fact that there is clustering of cardiovascular risk factors in the setting of obesity.[50]

Inflammation and Oxidative Stress

A variety of proinflammatory mediators that are associated with cardiometabolic dysfunction are known to be influenced by obesity. In a recent study of 354 obese children and their matched controls, obese children had significantly higher levels of high-sensitivity C-reactive protein (hsCRP), interleukin interleukin-6 (IL-6), myeloid-related protein (MRP) 8/14, P-selectin, intercellular adhesion molecule-1 (ICAM-1), interleukin-20 (IL-20), retinol-binding protein-4 (RBP-4), macrophage inhibitory factor (MIF), and tumor necrosis factor-α (TNF-α) compared to nonobese children.[51] Studies in adults and children have demonstrated a correlation between obesity and oxidative stress.[52–55] Atabek *et al.* have shown a higher level of peroxy radicals (a marker of oxidative stress) in obese children compared with nonobese children.[54]

In another study, Ostrow *et al.* demonstrated higher urine 8-isoprostane and hydrogen peroxide levels (markers

of oxidative stress) in the obese group as compared to their nonobese counterparts.[55] This study also reported a high correlation between mean 24-hour systolic BP and 8-isoprostane. Inflammatory processes and oxidative stress are known to worsen cardiovascular health. The above findings suggest that oxidative stress plays a major role in promoting an adverse cardiovascular health profile among obese children.

Atherogenic Dyslipidemia and Atherosclerosis

Obesity has a strong association with atherogenic dyslipidemia. In a large series of 26000 overweight children, concentrations of one or more of the lipids were abnormal in 32%: total cholesterol in 14.1%, LDL-C in 15.8%, HDL-C in 11.1%, and triglycerides in 14.3% of those in whom data were available.[23] In a series of 943 school-going adolescents, Musso *et al.* reported significant differences in the levels of triglycerides (73 mg/dl *vs* 90 mg/dl; $P< 0.001$) and HDL-C (52 mg/dl *vs* 47 mg/dl; $P< 0.001$) between nonoverweight and overweight groups.[56]

Atherosclerosis is a process that is known to start as early as the first years of life.[57] In a series of 204 autopsies done on young individuals aged 2–39 years, Berenson *et al.* reported that BMI, systolic and diastolic BP, and serum concentrations of total cholesterol, triglycerides, LDL-C, and HDL-C were strongly associated with the extent of lesions in the aorta and the coronary arteries.[57] Subjects with 0, 1, 2, and 3 or 4 risk factors had, respectively, 19.1%, 30.3%, 37.9%, and 35.0% of the intimal surface covered with fatty streaks in the aorta. The corresponding figures for the coronary arteries were 1.3%, 2.5%, 7.9%, and 11.0%, respectively, for fatty streaks and 0.6%, 0.7%, 2.4%, and 7.2%, respectively, for collagenous fibrous plaques.[57] Surrogate markers of atherosclerotic disease like aortic intima media thickness (aIMT) and carotid intima media thickness (cIMT) are indirect evidence of the progression of atherosclerotic disease. Both aIMT and cIMT are documented to be associated with cardiovascular risk factors.[58] In a series of 228 adolescents (ages 11–17) aIMT was positively correlated with triglycerides, systolic BP, diastolic BP, BMI, and waist/hip ratio, after adjusting for age, gender, and height. In the same population, cIMT was positively correlated with systolic BP, pulse pressure, heart rate, BMI, and waist/hip ratio.[58] These findings (from autopsy as well as from surrogate markers) and their correlations expose the putative effect of obesity in early life on vascular structures like the aorta and the coronary arteries, which are the principal targets of atherosclerotic disease.

Cardiac Structural and Functional Changes

The chambers of the heart are known to respond to the hemodynamic changes that are associated with obesity, both in adults and children. There is evidence confirming that left ventricular (LV) mass is increased in normotensive obese adults, and that it is closely associated with BMI and insulin resistance.[59,60] In an echocardiographic series of 467 youth, Li *et al.* reported that adiposity (as represented by BMI) in childhood, adiposity and systolic BP in adulthood, and the cumulative burden of adiposity and systolic BP from childhood to adulthood were significant predictors of left ventricular mass (LVM) index in young adults.[61] In another series of 460 adolescents, Chinali *et al.* reported that both overweight and obese subjects had greater LV diameter and mass than normal-weight subjects.[62] LV hypertrophy was more prevalent in the obese (33.5%) and overweight (12.4%), as compared with normal-weight participants (3.5%), largely compensating for the increased cardiac workload. However, obese subjects had four-fold higher probability of having an LV mass exceeding values compensatory for their cardiac workload, a feature associated with lower ejection fraction, lower myocardial contractility, and greater force needed to be developed by the left atrium to complete LV filling.[62] One study performed in adolescents reported an association between visceral fat and LV relative wall thickness.[63] Another study, involving a series of 131 children (obese and nonobese), reported that obese children show increased LVM indexed for height (LVMi) and preserved LV function.[64] Central adiposity was reported to be the major determinant of LVM in this series. All these studies underline the fact that childhood and adolescent adiposity has strong influences on the structure and function of the heart, especially the left ventricle.

Sleep-Disordered Breathing and Obstructive Sleep Apnea

Obesity is known to compromise pulmonary function among adults.[65] In a study of 400 children and adolescents, Redline *et al.* reported that obesity (i.e., BMI >28 kg/m^2) was associated with a 4.7-times higher likelihood of sleep-disordered breathing (SDB), defined as an apnea–hypopnea index (AHI) >10.[66] The risk of having moderate obstructive sleep apnea syndrome (OSAS) increased 12% with each unit of BMI above the mean.[66] In OSAS among children, the pathophysiologic changes of cardiovascular importance includes altered sympathovagal balance, increased oxidative stress, production of inflammatory cytokines, vascular remodeling, and endothelial cell dysfunction.[67]

BP dysregulation has been reported in children with OSAS (as compared to controls) during wakefulness and sleep, but, hypertension is rare.[68-70] Children with OSAS have echocardiographic evidence of LV hypertrophy, right ventricular (RV) hypertrophy, and decreased LV function.[71,72] In a series of 101 children aged 6–13 years Chan *et al.* reported that children with moderate to severe OSAS had greater RV systolic volume index (RVSVI), lower RV ejection fraction (RVEF), and higher RV myocardial performance index (RVMPI) than the reference group.[73] They also had more significant LV diastolic dysfunction and remodeling, with larger interventricular septal thickness index (IVSI) and relative wall thickness, than those with lower AHI values.[73] The increase in systolic BP, morning BP surge, and BP variability has been associated with increase in LV wall thickness.[68,74] Children with OSAS have elevated serum levels of tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interferon-γ (INF-γ), interleukin (IL)-6, and IL-8, suggesting a role for this sleep disorder in the augmentation of chronic inflammatory processes.[75-77] As noted earlier, chronic inflammation leads to an adverse cardiovascular risk profile later in adulthood.

Conclusions

Current evidence relating childhood obesity to worsening of cardiovascular health, both immediate and long term, is convincing. The contribution of this pathological state in early life to future cardiovascular morbidity and mortality is one of grave concern. A holistic, multipronged, approach in the early phase of life is needed to contain this epidemic. Neglecting this threat will compromise the future cardiovascular health of our population and result in a serious public health crisis.

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