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Comorbidities of Childhood Obesity

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1. Introduction

The epidemic of obesity is known to contribute annually to 2.6 million deaths worldwide. [1] Excessive adiposity is the primary etiology of major metabolic diseases and related mortality. These deaths are attributed mainly to the comorbidities associated with obesity, including hypertension (HTN), cardiovascular disease (CVD), and diabetes mellitus (DM). The global escalation of childhood obesity is a matter of grave concern. Recent data have demonstrated a nearly fourfold rise in the prevalence of childhood obesity, making the pediatric age group the fastest growing subpopulation of obese individuals in this country. [1] Corresponding data examining global obesity trends demonstrate similar patterns worldwide with rates of overweight—defined as having a body mass index (BMI) greater that 25 kg/m^2—occurring in 40% of men and 30% of women and rates of obesity (BMI≥30 kg/m^2) at approximately 25%. [2] This condition can have far-reaching consequences on the physical and mental health of the young obese patients with many of these chronic diseases surging in childhood rather than adulthood.

The normal BMI values used for defining overweight and obesity in adults cannot be extrapolated to the pediatric population as BMI is known to change with age and gender during childhood and adolescence. Center for Disease Control (CDC) BMI-for-age growth charts for girls and boys provide standard translation of a BMI number into a percentile with age and gender specific normograms. [3] Children with BMI equal to or exceeding the age-gender-specific 95th percentile are defined obese. Those with BMI equal to or exceeding the 85th but are below 95th percentiles are defined overweight. [4]

2. Risk factors

An inter-relationship of genetics and the environment is central to the regulation of energy balance, and thus body weight. Hence risk factors of the pandemic of obesity can be stratified on the basis of genetic and environmental sources.

Genetic influence of obesity is related to two primary processes: (1) susceptibility to overeating despite normal energy requirements, and (2) presence of a normal drive to eat despite low energy requirements. Appetite and the drive to eat may be impacted by several genetically programmed metabolic pathways, and this is demonstrated in the

specific but rare syndromes such as Prader–Willi and Bardet–Biedl. [5] Obesity caused by single-gene mutations has been well documented in mice and other rodents but is relatively rare and ill-defined in humans. [6] These include the agouti, leptin, and leptin receptor gene mutations. These mutations produce phenotypes of severe hyperphagia, obesity, DM, defective thermogenesis, and infertility. The polygenic mouse models of obesity more closely resemble the human obesity phenotypes than single gene models and have mutations that influence obesity, plasma cholesterol levels, body fat distribution, and propensity toward development of obesity on a high-fat diet. [4]

The impact of the environment on the regulation of energy balance, and thus body weight is paramount. The changes in the macronutrient content of the diet (i.e., carbohydrate, protein and fat), energy density, sugar-sweetened beverages, and portion size have been associated with the soaring trend of obesity over the last couple of decades. In addition, the global trend of increasing technology, automation, motorized transportation and sedentary occupations contributes to a lifestyle that requires minimal physical activity. While once essential for survival, regular physical activity is optional in our modern, low energy-demanding environment, thereby making its contribution to the escalation of the pandemic. Poor socioeconomic status with less consumption of more expensive fruits and vegetables and suboptimal cognitive stimulation at home mediate development of obesity in children. [7-9] The dietary habits of the parents significantly modify child food preferences and the degree of parental adiposity is a relatively direct measure of the child's dietary preferences. [10-12]

3. Pathophysiology

A breakdown in the complex interplay of the central nervous system, the gastrointestinal system and the adipose tissue of the body culminates in obesity. The central nervous system provides the feedback control system for integration of energy expenditure and for digestion, absorption, transport, and storage of nutrients and mobilization and use of fuels. Signals regarding alterations in fuel usage are tightly regulated and come primarily from adipocytes and from the gastrointestinal tract. This interaction of the different systems is responsible for the weight and fat balance of the human body.

Adipose tissue is now known to play a significant role in metabolic and immune function, possibly through the production of pro-inflammatory cytokines and other hormones secreted by adipocytes. [13-14] In the past decade, pro-inflammatory adipocytokines, including TNF-α, IL-6, and leptin, resistin, and many others, have received tremendous attention for their potential role in fuel metabolism, glucose homeostasis, insulin resistance, and perhaps atherosclerosis. [13-15] In contrast to the proinflammatory hormones, adiponectin, a 244-amino-acid peptide solely produced and secreted by adipose tissue, has been reported to improve insulin sensitivity and indeed could prevent diabetes mellitus and atherosclerosis. [16] Leptin, also produced by the adipocytes, circulates at levels proportionate to levels of body fat. It binds to receptors in the hypothalamus, activating signals to inhibit food intake and increase energy expenditure. In addition, leptin affects other hormones, both anorectic and orexigenic. [17-18]

Previous research has implicated gut hormones or incretins in appetite regulation, gastrointestinal motility, satiety, and changes in glucose, and in this regard may possibly

play a role in the occurrence of obesity. [19] In the foregut, ghrelin, produced in the stomach and duodenum, increases before meals and decreases after meals. [20] Ghrelin is elevated in the setting of obesity and increased after diet-induced weight loss, suggesting a role in the compensatory changes in appetite and energy expenditure that make maintenance of diet-induced weight loss difficult. [21] In the hind-gut, where the suppression of gastrointestinal motility is modulated by hormones, such as peptide YY (PYY), neurotensin, glucagon-like peptide −1 (GLP-1), and oxyntomodulin, perturbations in hormone release have been demonstrated with weight loss secondary to Roux-en-Y gastric bypass. Peptide YY is a hormone released after meals whose function is to reduce appetite. [22] Its postprandial levels have been found to remain markedly elevated after bariatric surgery. [23] Better understanding of the interactions of the gut hormones on appetite and fuel metabolism will hopefully provide important information on the development of future obesity management strategies.

4. Co-morbidities related to obesity

Obesity in children and adolescents appears to be identical to obesity in adults, in both pathophysiology and consequences of obesity-related co-morbidities. These can be categorized broadly into medical and psychosocial. The medical consequences can result in metabolic effects, involving the cardiovascular, endocrine, gastrointestinal and renal systems, and mechanical effects involving the pulmonary, skeletal and central nervous systems.

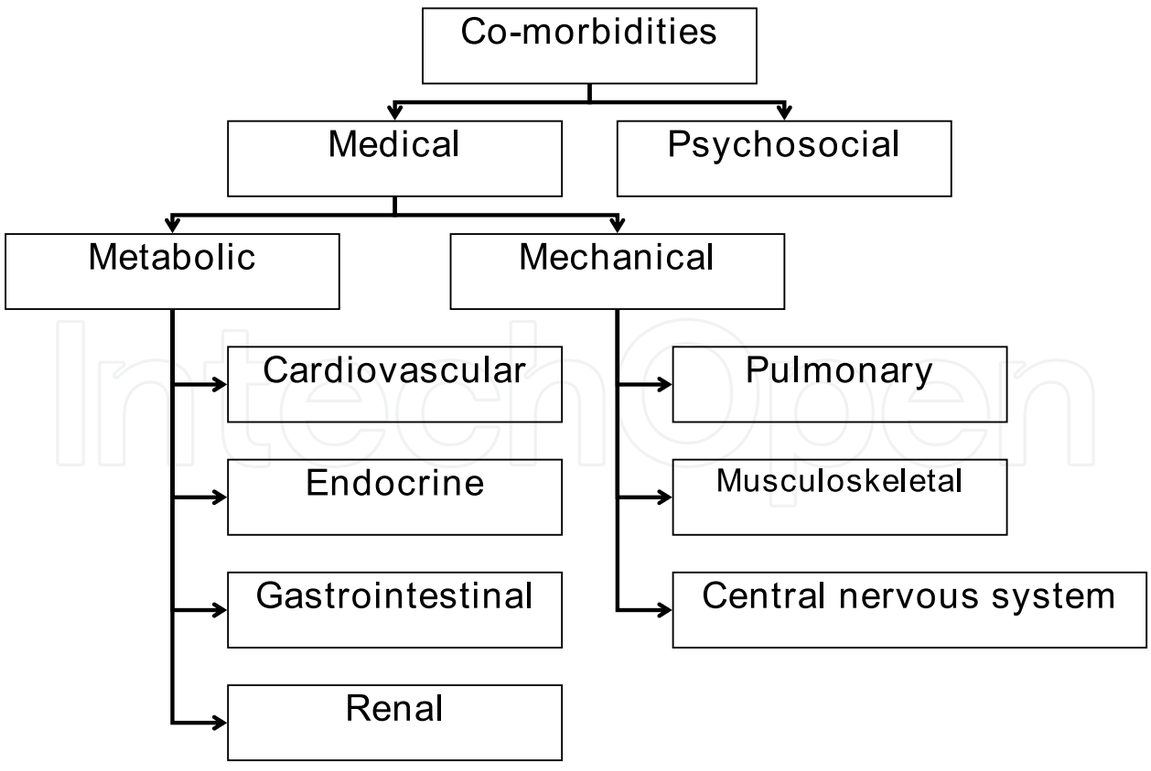

Fig. 1. Categories of co-morbidities

4.1 Metabolic consequences
4.1.1 Endocrine system

4.1.1.1 Insulin resistance

Obesity has a negative impact on multiple associated alterations in the glucose/insulin axis and on lipid metabolism. In particular, obese adults demonstrate reduced glucose disposal, primarily at the level of skeletal muscle (peripheral insulin resistance) [24] as well as impairment in insulin action on non-esterified fatty acid oxidation, [25] leading to insulin resistance and abnormal lipolysis. Yet it is unclear when these abnormalities occur in the setting of acute versus chronic obesity. Polonsky and coworkers [26] found that insulin secretory rates were significantly higher in the obese group when compared with the normal weight group. Furthermore, there was no difference in insulin clearance or hepatic insulin extraction between the groups. There was a diminished hepatic insulin extraction noted in a subset of the obese group that demonstrated a greater degree of hyperinsulinemia. To characterize this further, Monti and coworkers [27] examined obese children with normo-insulinemia to characterize early metabolic derangement and found peripheral insulin resistance in the obese children when compared with normal weight children but no significant differences in non-esterified fatty acids response to insulin infusion. Le Stunff and coworkers [28] found that the earliest abnormality in glucose metabolism in obese children (those with short duration of obesity) was an abnormal insulin response to a meal stimuli and that maximal glucose uptake decreased with age and obesity duration. Thus, it appears that one of the earliest negative effects of obesity is the development of insulin resistance.

4.1.1.2 Metabolic syndrome

The metabolic syndrome complex is comprised of hyperglycemia, HTN, dyslipidemia and obesity where truncal fat and insulin resistance are thought to be the primary problems. There is no consensus in the definition of this syndrome in children and its role in future cardiovascular events can only be extrapolated from corresponding adult studies. Goodman et al. [29] identified four groups of risk factors in adolescents and inferred that obesity had maximal influence on cumulative cardio-metabolic risk. Each of the components of this syndrome complex is found to aggravate with increasing obesity independent of age, sex and pubertal status. [30]

4.1.1.3 Type 2 diabetes mellitus

The prevalence of pediatric DM has increased significantly over the last decade with significant variability based on race and ethnicity. Obesity and DM have been tightly linked in both animal models and adult humans. Recently, data on increasing incidence and prevalence of DM in adolescents demonstrate that insulin resistance and increases in both total body fat and visceral fat play a role in DM development in adolescents, similar to that seen in adults. [31-32] Obesity is associated with increased TNF-α levels which lead to increased release of free fatty acids in adipocytes, blockade of the synthesis of adiponectin and activation of the insulin receptor. [33] Moreover, IL-6, released mainly by macrophages and adipocytes, influences glucose tolerance through antagonizing the secretion of adiponectin and by enhancing gluconeogenesis, glycogenolysis and inhibiting glycogenesis. [34] There are numerous other adipokines like resistin, adipsin and others which are believed to be the missing link between obesity and target tissue

resistance to insulin resulting in Type DM. [35-37] With early onset of obesity, the population is believed to be more susceptible to the disease and its inadvertent complications.

4.1.1.4 Gynecological disorders

4.1.1.4.1 Polycystic ovarian syndrome (PCOS)

Polycystic ovarian disease is one of the most common endocrine abnormalities and typically begins in adolescence. It is often accompanied by hyperandrogenism and hyperinsulinemia. Although the exact mechanism for this relationship is unclear, it is postulated that high circulating levels of insulin play a role in ovarian cyst development due to the anabolic effect of insulin at the IGF receptors on the ovaries. Up to 30% of women with polycystic ovarian disease are overweight/obese. Obesity can worsen the picture of polycystic ovary syndrome (PCOS) by increasing insulin resistance, diabetes, and metabolic syndrome, thereby commencing a vicious cycle. This cycle may culminate in infertility . The prevalence of impaired glucose tolerance in obese young women with PCOS has been estimated to be as high as 30-40%, with an additional 5-10% having frank DM. [38] Yet, there remains debate in the literature about the nature of the relationship between obesity and PCOS.

4.1.1.4.2 Menstrual abnormalities

Body weight and body fat are considered to be significant physiological triggers of menarche. [39] Hence, obese girls often present with menarche before the age of 10 years. [40] Obesity can also lead to oligomenorrhea or amenorrhea at the other end of the spectrum, all leading to an increased risk of complicated pregnancies.

4.1.2 Cardiovascular system

4.1.2.1 Hypertension

Multiple studies showed childhood obesity to be a major determinant of the cardiovascular risk factors in adulthood. [41-42] In addition to overall increased adiposity, truncal obesity is associated with increased atherothrombotic events and increased inflammatory markers. [43-44] Hypertension, especially systolic, in children and adolescents is closely associated with adiposity. [45-46] Intima media thickness (IMT), a noninvasive marker for early atherosclerotic changes, was found to be significantly increased in the obese children as compared with non-obese children of similar age, sex, and pubertal stage. [47-50] Reinehr et al. further demonstrated a significant association between these atherogenic changes and CVD risk factors, HTN, impaired glucose metabolism, and chronic inflammation. [51]

4.1.2.2 Left ventricular hypertrophy and coronary artery disease

The onset of left ventricular hypertrophy (LVH) was believed to date back to the adolescent years and developed into a formidable CVD risk factor by young adulthood in this sub-population. [52] Maggio et al. showed the onset of this relationship between obesity and LVH in the pre-pubertal age group and proposed the initiation of prevention and treatment of obesity to prevent end-stage organ damage. [53] A prospective follow-up over 57 years of the landmark Harvard Growth Study of 1922-1935 revealed that being overweight in adolescence was associated with a greater than two-fold increase in the relative risk of

coronary artery disease mortality, independent of adult weight.[54] Hence, these patients with an advanced vascular age may need intensive management, including pharmacotherapy for risk factor modification, with the final goal of halting the progression of atherosclerosis and altering the lifetime risk of excess morbidity and mortality.

4.1.3 Gastrointestinal system

4.1.3.1 Non-alcoholic steatohepatitis (NASH)

The incidence of hepatic steatosis is 38% in obese children. The underlying cause is unknown, but the condition is associated with DM, obesity, rapid weight loss, and hyperlipidemia—all of which are characterized by impaired fat metabolism. Non-alcoholic fatty liver disease (NAFLD) is the primary hepatic complication of obesity and insulin resistance, and may be considered the early hepatic manifestation of metabolic syndrome. [55] One study demonstrated that non-alcoholic fatty liver disease is associated with insulin resistance even in patients with normal glucose tolerance. In the pediatric population, results demonstrate increased adipose tissue lipolytic activity with resulting increased rates of fatty acid release into plasma throughout the day. This continual excess in fatty acid flux supports the hypothesis that adipose insulin resistance is implicated in the pathogenesis of steatosis and contributes to the metabolic complications associated with NASH. [56] The fats accumulate largely in adipose tissue and, inappropriately, in muscle and liver. The sequence of events leading to the ectopic accumulation of triglycerides which cause development of insulin resistance has been referred to as the "overflow hypothesis". [57] The severe cases of this disease are notorious to progress to hepatic fibrosis and cirrhosis.

4.1.3.2 Gallstones

The dyslipidemia induced by obesity is responsible for increased biliary excretion of cholesterol, thereby increasing the likelihood of gallstone formation. Unlike the majority of children, this subgroup of the population complains of gallstones without any underlying diseases like hemolytic disorders. Obesity is incriminated to cause 8% to 33% of gallstones in children, with insulin resistance and metabolic syndrome being other potential risk factors.[58-59]

4.1.4 Renal system

Obesity plays a major role in the development of chronic kidney disease (CKD). It predisposes the individual to diabetic nephropathy, hypertensive nephrosclerosis, focal and segmental glomerular sclerosis and urolithiasis. Even in the absence of other comorbidities, obesity has been found to cause structural changes such as glomerulomegaly and glomerular basement membrane (GBM) thickening resulting in obesity-related nephropathy. [60-61] The physiological modification in renal hemodynamics in the setting of obesity is comprised of hyperfiltration associated with hyperperfusion, which together play a role in renal injury. An increased glomerular filtration rate (GFR) was observed in overweight compared with lean subjects, being significantly positively related to BMI [62-63] and insulin resistance. [64] However, pathologic changes within the nephron can be seen before overt proteinuria and renal disease. A recent study conducted in our institution revealed that bariatric surgery induced weight loss is associated with an improvement in the overall long term renal function in the morbidly obese adult. [65] Such data are lacking for the pediatric population. Recent European studies concluded that renal impairment may not

be an early manifestation of adiposity in childhood but may contribute to the development of the disease in the long term. [66]

4.2 Mechanical consequences

4.2.1 Pulmonary system

4.2.1.1 Obstructive sleep apnea

Although there is limited data on obstructive sleep apnea (OSA) in children, the published estimate of prevalence is 7% in obese children. Obese children are six times more likely than lean, age-matched children to have OSA. This condition is known to cause daytime somnolence and neurocognitive deficits like concentration and memory lapses secondary to poor quality of sleep. [67-68] Sleep disturbance is linked to higher inflammatory biomarkers, such as CRP and IL-6. [69] Other hormone changes seen in OSA include a drop in leptin, an increase in ghrelin, increased insulin levels, and a decrease in insulin sensitivity. The etiology for these changes is unclear but felt to be related to the intermittent hypoxemia that may potentiate the inflammatory cascade which triggers systemic inflammation. [70-71]

4.2.1.2 Bronchial hyperactivity and exacerbation of asthma

Obesity is demonstrated to be significantly related to current asthma among children and adolescents with the association being stronger in non-atopic children than in atopic children. [72-73] The state of systemic inflammation, induced by adiposity, is hypothesized to result in this morbid condition. Overweight & obese children show a decreased response to inhaled steroids in the setting of asthma. [74] Childhood and adolescent adiposity is reported to be associated with significantly increased risk of asthma in the long term as well, thereby increasing the dependence on chronic medication. [75] Inability to exercise leads to the progression of obesity and the cycle continues.

4.2.2 Musculoskeletal system

Childhood obesity has been linked to increase frequency and severity of orthopedic problems in children. It appears that the orthopedic issues occur due to increased stress and strain on bone and cartilage that was not designed to carry excess weight. The more common orthopedic problems include bowing of the tibia and femurs that result in overgrowth of the medial aspect of the proximal tibial metaphysis or Blount syndrome and slipped capital femoral epiphysis due to increased weight on the growth plate of the hip. [76] Obesity during the growth spurt may increase the likelihood of fractures during falls as bone development does not adequately cope with excess weight. This weight/bone mass imbalance also places high levels of stress on growing bones and joints that may result in joint damage and may contribute to osteoarthritis in later years. [77] The occurrence of more severe fractures and bone disorders lead to the increased requirement of complex surgeries and joint replacements, especially in the setting of pediatric trauma, thus amplifying the physical and financial load of the disease in this population. [78]

4.2.3 Central nervous system

Corbett et al reported increased incidence of idiopathic intracranial hypertension at a relatively young age of less than 20 years in 90% of patients who had childhood obesity. [79] Moreover, about 30%-50% of children with pseudotumor cerebri are obese and probably this subgroup accounts for the majority of cases that are not associated with infection or

medication. [80] It is thought that the increased intra-abdominal pressure due to obesity causes rise in intra-thoracic pressure which is transmitted to the head as increased resistance to venous return from the brain. [81]

4.3 Psychosocial consequences

Childhood obesity represents a dynamic process, in which behavior, cognition and emotional regulation interact mutually with each other. The interconnection between obesity and psychological problems seems to be cyclical, in that clinically meaningful psychological distress might precipitate weight gain and obesity may lead to further psychosocial problems. [82] Depression in adulthood has been found to be related to obesity in adolescence. [83] Females appear to have a stronger association than males. These patients are found to have obsessive concern due to social stigma about body image, low esteem and poor self-perception of physical appearance. The expectation of rejection leads to further progression of depression. Overweight adolescents frequently reported reduced health-related quality of life in physical, emotional and social aspects. [84-86] These factors tend to have a negative influence on these individuals. A vicious cycle ensues and some of these obese adolescents may consequently have less education, lower incomes and higher poverty rates. [87-88]

5. Conclusion

Despite the lack of full understanding of the pathophysiology of obesity, it is clear that there are consistent findings of insulin resistance and inflammation seen in both obese adults and children. These metabolic abnormalities play a role in the development of obesity-related comorbidities that are manifested early in the disease process. Inflammation in the adipose tissue is the result of increased oxidative stress, possibly secondary to hypoxia. Hypoxia is precipitated by the overgrowth of adipose tissue during obesity. Adipose tissue is responsible for the production of a significant proportion of systemic interleukin-6 (IL-6) which may induce a degree of systemic inflammation in this population. Along with this, it is also believed to activate CD8+ T cells which promote the recruitment and activation of macrophages in the tissue. [89] The inflammatory markers secreted by the cells and oxygen free radicals resulting from oxidative stress increase vascular endothelial permeability and cause endothelial dysfunction. [90-91] These abnormalities lay the foundation for all the derangements associated with obesity. Unfortunately, there is very limited data on the progress of the various comorbidities from childhood and adolescence to their culmination in adulthood. A study reported that 43% of obese children persisted to be obese adults and another 29% were overweight as adults. [92] Early onset obesity is a risk factor for significant morbidity and mortality later in life, where the rates of DM, CAD, atherosclerosis, metabolic syndrome are increased. A heightened degree of suspicion is warranted when confronted with adult and pediatric obese patients to avoid underdiagnosing of the various diseases. Given the negative short- and long-term impact of obesity on children, careful attention should be paid to the unique health issues of this “at-risk” population with both prevention and aggressive early intervention strategies.

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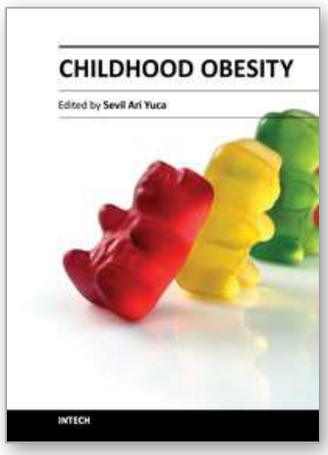

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This book aims to provide readers with a general as well as an advanced overview of the key trends in childhood obesity. Obesity is an illness that occurs due to a combination of genetic, environmental, psychosocial, metabolic and hormonal factors. The prevalence of obesity has shown a great rise both in adults and children in the last 30 years. It is known that one third of children who are obese in childhood and 80% of adolescents who are obese in their adolescent years continue to be obese later in life. Obesity is an important risk factor in serious illnesses such as heart disease, hyperlipidemia, hyperinsulinemia, hypertension and early atherosclerosis.

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