Childhood obesity and Craniofacial growth: recapitulating orthodontic implications

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ABSTRACT

Childhood obesity is a significant concern in many countries and is a condition of systemic inflammation to an impaired immunity. It is usually characterized by a low-grade inflammation depending mostly on the release of cytokines, adipokines and reactive oxygen. There is a vast difference of craniofacial morphology in obese and normal adolescents. The visceral adipose tissue (VAT) is the primary source of pro-inflammatory cytokines in obese individuals. This narrative review article focuses on the profile of immune response and illustrates the craniofacial morphological changes in obese adolescents. Furthermore, interventional studies which were aimed at preventing early occurrence of malocclusion in obese adolescents is elaborated.

Key words: Adolescents, childhood obesity, craniofacial morphology, immunity, malocclusion, visceral adipose tissue

INTRODUCTION

Childhood obesity, defined as excess of body fats which impairs the quality of life in an individual is a significant factor all over the world and most common in affluent countries. There has been dramatic increase in number of overweight (BMI >25 kg/m2) and obese (BMI >30 kg/m2) adults in recent years. There appears significant shift in the prevalence of childhood obesity which occurred between 1980 and 2004, doubling in just 25 years (from 15.0% in 1980 to 32.9% in 2004) globally. The number of children who were classified as extremely obese (BMI>40kg/m2) increased from 0.9% in 1960 to 5.1% in 2004 globally. Lot of current studies recently mention about the risks of type-2 diabetes mellitus, hypertension, hypercholesterolemia, dyslipidemia, hyperinsulinemia, respiratory disorders and increased risk of cancers in obese individuals. Genetic, epigenetic, environmental factors, health status, basal metabolism, physical exercise, race, hormonal balance, imbalanced diets and sedentary lifestyle contribute to obesity and overweight, irrespective of socio-economic status.

PREVALENCE

Overweight is defined as a BMI of 25-29 and obesity is BMI of 30 or greater. Recent surveys found that there is gradual upward trend in body weight which is equivalent to a 0.2kg rise in body weight/year at any age. Investigators have used Body Mass Index (BMI) to measure the overweight of an individual.

Race and ethnicity: The prevalence of obesity shows striking and significant disparities with regards to race and ethnicity in children. While childhood obesity is clearly a major public health issue in United States, the increased prevalence of obesity is not only limited to this country; indeed, obesity is now a global epidemic. The distribution of childhood obesity in 2–19 years old children with regards to race showed similar trends as seen in adults. The prevalence of obesity was lower among non-Hispanic white children compared to non-Hispanic African American children and Mexican American children. When gender and race were considered, higher rates of obesity were seen in Mexican American boys than in non-Hispanic white boys. Non-Hispanic African American girls had higher rates of

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obesity than non-Hispanic white girls.\textsuperscript{33} Various countries across the globe—North America, Central America, South America, Western Europe, the Middle East, Eastern Europe—report that minimum 40\% of their population are overweight or obese.\textsuperscript{24,25} While east Asian countries such as China, Japan, Vietnam, and India report decreased rates of obesity.\textsuperscript{25} Over the past 10 years, the World Health Organization (WHO) has recognized the increasing trend in overweight or obese children,\textsuperscript{24} and meticulous attention is now being given to the global implications associated with this increase.\textsuperscript{23} In various analysis of the leading causes of global mortality, childhood obesity and being overweight were among the top 10 etiologies for each.\textsuperscript{26-30}

**HORMONAL VARIATIONS AND OBESITY**

The mechanisms which control and regulate craniofacial growth and development are very complex and interactions between hormones, genes, nutrients and epigenetic factors will determine the final morphology of craniofacial bones.\textsuperscript{31,35} Usually GH deficiency exhibits decreased anterior and posterior facial heights and small sized cranial bases bones.\textsuperscript{36-40} Obese adolescents exhibit higher levels leptin, a hormone which secretes white adipose tissue for controlling appetite, rapid the process of skeletal growth by accelerating the production of gonadotrophin releasing hormone hence influencing the onset of malocclusions.\textsuperscript{51,42} So, some authors say that there is increased maxillary and mandibular sizes, prognathic jaws and smaller mandibular plane angles in obese children.\textsuperscript{42,43}

Human beings have the unique ability to deposit fats and then utilize during starvation. But, consumption of food in large quantities leads to increase of fat deposits. Obese adolescents consume more fats and have more irregularity of eating pattern than non-obese adolescents.\textsuperscript{44} Sleep pattern and duration also contributes inversely to BMI and the circumference of waist.\textsuperscript{44} Puberty is a critical period in females since there is a risk of obesity due to early menarche (<11 years).\textsuperscript{45} Evidence indicates that childhood obesity is associated with cardiovascular events in adult life and even increased levels of cholesterol.\textsuperscript{44} The major complications of childhood obesity include high levels of triacyl glycerides, low levels of lipoprotein cholesterol and defective glucose metabolism.\textsuperscript{44}

**ALTERATIONS OF INNATE AND ADAPTIVE IMMUNITY IN OBESITY**

Obesity is often associated with systemic inflammation and impaired immunity.\textsuperscript{44,45} It is reported that the visceral adipose tissue (VAT) is the most common source of pro-inflammatory cytokines through experimental as well as animal studies.\textsuperscript{45-52} Macrophages with an inflammatory phenotype account for 40-60\% of VAT immune cells in obesity and are called as ‘classically activated macrophages’ (M1).\textsuperscript{53-56} Large amounts of TNF-alpha, IL-6, IL-12, IL-1beta and MCP-1 (monocyte chemotactic protein-1) are secreted by M1.\textsuperscript{57} In non-obese groups, macrophages are termed as ‘alternatively activated macrophages (M2)’ and they secrete IL-10 and IL-1 receptor antagonist which exert anti-inflammatory activities.\textsuperscript{58} M1 macrophages seem to favor insulin resistance and their deactivation process helps against insulin resistance.\textsuperscript{59-61} Obese animals expressed increased amounts of adipose tissue-derived necrosis factor (TNF)-alpha.\textsuperscript{51} and proved association between C-reactive protein, interleukin(IL)-6 and developing risk of type-2 diabetes.\textsuperscript{52}

VAT contains increased numbers of T helper (Th) CD4+, T cytotoxic CD8+ and B cells. Th1 cells produce interferon (IFN)- gamma which in turn polarizes M1 macrophages and increase release of TNF-alpha.\textsuperscript{62-69} Increase in Th17 cells in obese humans, lead to great expression and release of IL-17 and Th17 dependent mechanism is considered as.70-72 important etiology associated to autoimmune disorders in obese individuals.\textsuperscript{73} T-regulatory (Treg) cells are reduced in obese mice and humans.\textsuperscript{66-67} Depletion of Treg cells lead to high insulin levels and decreased insulin receptor signaling.\textsuperscript{68} This particular data suggests that anti-inflammatory role exerted by Treg cells with the release of IL-10 suppress obesity induced inflammation.\textsuperscript{69}

**OBESITY INFLUENCING SKELETAL MATURATION**

Knowledge of skeletal development is important because early orthodontic treatment directed towards improving skeletal discrepancies completely depends on the nature and period of skeletal development. The most evaluated skeletal maturity indicators depend on either stage of bone development in hand-wrist radiographs or shape and size of cervical vertebrae as observed in lateral cephalogram.\textsuperscript{74-78} Literature suggest that leptin plays an important role in skeletal growth through the activation of various mediators like insulin-like growth factor 1 and sex hormones.\textsuperscript{79} Leptin might act directly on the skeletal growth centers and its receptors have been found in the cartilaginous growth centers that are significantly involved in skeletal maturation.\textsuperscript{79} Hence, an obese child would have a mechanism of central resistance to leptin and an increased leptin sensitivity at a peripheral level causing increased differentiation and proliferation of chondrocytes, which can lead to precocious skeletal maturation.\textsuperscript{79} Increasing the level of controversy, some authors mentioned that increased body weight could be a result of puberty, rather than a determining factor.\textsuperscript{80} Comparing skeletal maturity evaluated from hand-wrist and lateral cephalograms between the obese and normal-weight
Management strategies for childhood obesity

**Dietary plans**

**Targeted Initiatives**
- Childhood obesity health Target and access to nutrition and physical activities

**Increased Support**
- Guidance for weight management

**Broad Population Approaches**
- Health star rating promotion
- Marketing and advertising to children
- Information and resources to general public
- Play sport and physical activities
- Healthy food policies
- Health promoting schools
- Eating and activity guidelines

**Treatment plans**

**Obese child with snoring**
- Polysomnography
  - No OSA
  - With OSA
  - Poor Adherence

**Adenotonsillar Hypertrophy**
- No Hypertrophy
  - CPAP
  - Good Adherence

**Persistent snoring or symptoms**
- Polysomnography
- no OSA
- with OSA

**Symptoms monitoring and check weight gain**

1. Positional Therapy
2. Oral Appliance Therapy
3. Nasal, Nasopharyngeal narrowing, Oropharyngeal narrowing
4. Bariatric Surgery

Subjects yielded different results. Obese children had a higher mean cervical vertebral maturation score compared with the controls which is related to earlier skeletal maturation. It is a fact that discrepancy between the skeletal and chronologic ages because of systemic conditions or medications might jeopardize treatment results. It is time for orthodontic clinicians to consider body mass index standard deviations as part of their patient evaluation while considering growth modification with either orthopedic or functional appliance treatment plans.

**OBESITY AND DENTAL DEVELOPMENT**

Costacurta et al carried out a study using the method codified by Demerjian and reported that obese girls had more advanced dental age when compared to non-obese girls. These results were in concordance with that of Hilgers et al. who showed that dental development acceleration was
significantly higher for obese girls than boys. Briefly, the results highlighted out of these studies emphasized a correlation between accelerated dental maturity and increasing BMI percentile. In contrast, Eid et al. did not find a correlation between dental maturity and body mass index in Brazilian children, which could be attributed to genetic and/or dietary factors. Additionally, based on the results of a study increasing BMI percentile accelerates dental age and affects treatment duration such as in serial extraction or space maintenance. When permanent teeth erupt at an early stage in obese children, they may not have good oral hygiene habits leading to increased incidence of caries lesions.

**FACIAL SOFT TISSUE MORPHOLOGY IN OBESE PATIENTS**

Obese individuals have reported to show increased growth activity at dentofacial complex, but without any pronounce deviations in facial components and proportions when compared to the control group pertaining to a specific age. Even though obese children have a decreased level of GH, controversial literature exists saying increase as well decrease in craniofacial diameter. Specifically, facial prognathism is a characteristic feature of male and female obese individuals and is considered the effect of increased maxillary and mandibular lengths. Some reports found a combination of facial prognathism with smaller than average cranial base angle. It is also reported that obese females exhibited lesser inclination of maxilla, increased incisor inclination and larger alveolar prognathism than control group.

Considering the vertical plane relationships, there exists reports mentioning a greater posterior facial height with no alteration in anterior facial height in obese individuals creating a more upward and forward rotation pattern. It is reported that the growth changes in lower posterior face are responsible for increased posterior dimension in obese children and vital areas of growth are mainly the mandibular condyles and alveolar processes. The soft tissue profile of obese individuals appear to be straight and is attributed to large mandibular length and anterior position of pogonion. In contrast, cephalometric studies conducted on patients with GH deficiency, reported small anterior and posterior cranial base, decreased posterior facial height, and small posterior mandibular height. One study, which looked into the relationship between low BMI (less than 30) and craniofacial features in obstructive sleep apnoea patients reported short anterior cranial base, small and retrognathic mandible.

**OBESITY AND ITS RELATION TO RESPIRATION AND SLEEP**

Obesity is considered an important risk factor for the development and progression of obstructive sleep apnoea (OSA). Recent data showed that obese children have a 46% prevalence of OSA in comparison to normal weight children (33%). Furthermore, patients with mild OSA who increase 10% of their baseline weight are at a six-fold risk of OSA progression, and an equivalent weight loss can result in 20% improvement in severity of OSA. Obesity may worsen OSA because of fat deposition at certain sites surrounding the upper airway. This results in a decreased lumen and increased collapsibility of the upper airway and is considered a predisposing factor to apnea. However, the relationship between OSA and obesity is very complex. Factors such as decreased physical activity levels and increased appetite, particularly for refined carbohydrates contributes to weight gain in OSA patients. There exists genetic polymorphisms which might influence both sleep apnea and obesity. Patel et al. reported a correlation between AHI and anthropomorphic adiposity measures mentioning that obesity could explain 50% of the genetic variance in obstructive sleep apnea.

Hormones related to obesity, weight control, satiety, and energy expenditure may be altered in OSA. Leptin is a hormone secreted by adipose tissue and binds to the ventral medial nucleus of hypothalamus, called as the satiety center leading to signal the brain that the body has had enough to eat. Popko et al. mentioned that polymorphisms of the leptin receptor is involved in energy homeostasis and body weight regulation which are significantly correlated with OSA and obesity when compared with healthy controls. Hyperleptinemia is believed to be accompanied by desensitized cellular responses to leptin, therefore the effect of leptin is not achieved. Ghrelin, a hormone produced by cells lining the stomach, stimulates appetite and thus is considered a counter-regulator to leptin. Ghrelin is increased during reduced sleep and has been shown to stimulate appetite, and might lead to obesity and worsening of OSA. Thus, there exists a close correlation between obesity, sleep deprivation and OSA and share common pathophysiologic features of metabolic dysregulation. Weight loss may improve these conditions and hence might constitute a potential intervention for these patients. Type of Diet and molecular changes especially related to inflammation Obesity is often related to large amounts of production of reactive oxygen species (ROS) from sources like mitochondria and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which can increase the amount of body fat. Oxidative stress reduces the release of adiponectin with an increase in TNF-alpha and PAI-1 (plasminogen activator inhibitor) leading to a prothrombogenic status and insulin resistance. The overexpression of NOX-2 (the catalytic core of NADPH oxidase) and dependent oxidative stress suggests a condition
of endothelial dysfunction. Recent data reported that dietary anti-oxidants influence metabolic as well as inflammatory markers associated with low grade systemic inflammation. Low grade inflammation is determined by the ratio of IL-17 and IL-10. Normal weight children who followed dietary recommendations and emphasized practiced physical activity (PA) had a reduction in BMI and increase in IL-10 salivary levels while those who were unable to attend dietary recommendations and did not practice PA had increase in BMI and IL-7 salivary levels while IL-10 salivary levels were even low. Increased levels of IL-17 in these children with higher BMI are due to intake of junk food (hypercaloric food) and decreased PA and can be responsible for presence of low grade inflammation.

The Expert Committee of American Medical Association recently concluded that there is a vital evidence that eating away from home, specifically fast food, is a risk factor for childhood obesity. Some evidence suggests that a disproportionate number of fast food restaurants are situated near schools. Students with fast food restaurants within 0.5 miles of their home were more prone to be overweight or obese. Fast food meals for children were introduced in the late 1970s and have been very popular with adolescents. In terms of composition, fast food is high in total fat and TFAs, have high caloric density and offer less nutritional value and lead to obesity epidemic.

National School Lunch Program (NSLP) evaluation revealed that only 3% of the fast food meals met the NSLP criteria in terms of their percentage of energy from fat and carbohydrates. Children's meals are often offered with toys, which promotes brand recognition and frequent visits to the restaurant. Studies have found that children aged 3–6 years view, understand, and memorize advertising when cartoon characters are used. The fast food advertisements seemed to focus on building brand recognition and associations using logos and cartoon characters.

Increased consumption of soft drinks has been associated with metabolic syndrome and cardiovascular risk as the number of calories consumed in sodas and fruit juices has increased significantly over years. Along with this, the consumption of milk has been decreased by almost 38% contributing to the expansion of the obesity epidemic. Prospective studies have linked increased intake of sweetened beverages directly proportional with increased weight gain. Fructose typically comes from 3 sources: sucrose, high fructose corn syrup (HFCS), and fruits. The amount of fructose in fruits, which is relatively less compared to that in soft drinks, seems to entice individuals to consume other nutrients. In contrast, the HFCS added to soft drinks contains high concentrations of fructose and has no nutritional benefits. and is identified as a possible independent risk factor for the development of obesity.

MEASURING PARAMETERS FOR CHILDHOOD OBESITY AND A CRITICAL COMPARATIVE EVALUATION.

Obesity is the next important epidemiologic battle for physicians, public health experts, government officials and the public. Obesity has already surpassed smoking as the most pressing public health threat. Health initiatives should now be developed to effectively prevent obesity and diseases associated with it. Obesity is potentially more problematic since adequate nutrition is essential to survival; hence, abstinence from food is never an option. As changes to the healthcare systems in United States are discussed, plans should be offered that directly and aggressively target childhood obesity through health initiatives and prevention programs.

- Food Labeling: Labeling the nutritional content of food products has been proposed as a method to allow consumers to make informed choices about the types of foods they consume. The only problem with these labels is that they appear in small print and people do not read them. Again, the information provided as part of this is always difficult for consumers to comprehend. Little data exist to show that labeling food products has improved the habits of eating. Further, majority of consumers are unaware of the dietary content of restaurant foods. The Nutrition and Education Labeling Act of 1994 exempted restaurants from providing nutritional labeling of their products. Recently, New York City mandated that fast food companies provide nutritional labeling for their products. Overall, there may be a small role for nutritional labeling, but use of this technique along with other strategies or regulation of nutritional content can be expected to alter eating habits or prevent childhood obesity-related consequences.

- Eliminating Trans Fat in New York City, Denmark, and Beyond: The average daily per capita intake of TFAs in the United States has been shown to increase heart diseases risk and the most leading health organizations have introduced the complete removal of TFAs from foods. Because of the great efforts in New York City and Denmark, legislation to ban artificial TFAs from restaurants has been passed by 1 state legislature, 10 local city governments, and the country of Puerto Rico are considering almost similar legislation. To achieve this objective, consumers would need to read labels and become educated about the TFA content, and healthcare providers would need to provide counsel on TFA-free alternatives. The best option is to decrease the use of industrially produced TFAs and shift towards the use of...
safer fats in both packaged goods and restaurant food.\textsuperscript{113}

- Taxation of High Calorie Beverages: The current debate is how to decrease the consumption of high-calorie beverages in school systems of United States. Two ideas which have been proposed are to increase taxation on high calorie beverages and to restrict their availability in schools.\textsuperscript{114} The current level of taxation on high calorie beverages is insufficient to decrease consumption. Newly proposed legislative strategies have suggested increasing the tax on non-diet soda, fruit drinks and flavored milk.\textsuperscript{114}

**MANAGEMENT STRATEGIES**

- Diet plan for obese individuals: Prevention seems to be one of the accurate strategy to fight childhood obesity. Lots of reports mention that there are several factors which are to be given importance in the prevention of obesity.\textsuperscript{115} Breast feeding is very useful in decreasing the risk of childhood obesity. Dietary regulations like limited intake of sugar, sweetened beverages and meals with vegetables and fruits, avoiding junk foods and encouraging limited amounts of food is considered useful steps in reducing the incidence of obesity.

- Increasing activity and reducing sedentary plans: Increase in physical activities reducing sedentary life should be promoted to prevent childhood obesity. Walking, cycling, swimming and other play activities should be encouraged to prevent obesity in the initial phase itself. Home environment should be improved to encourage more physical activities for children.\textsuperscript{115}

- Pharmacological methods - Prebiotics and Probiotics: Prebiotics are non-digestible dietary fibers which stimulate the growth and activity of gut bacteria. There are many experimental studies which demonstrated the anti-obesogenic effects of prebiotics.\textsuperscript{115} In infants receiving formula rich in prebiotics (galacto-oligosaccharides, fructo-oligosaccharides), there was increase in bifido bacteria thus reporting the possibility of adipocyte growth influences through modulation of microbiota composition.\textsuperscript{116} With reference to childhood obesity, maternal supplementation in the first and third trimester with probiotics did not change prenatal and postnatal growth rates. But, breastfeeding of these mothers was rich in Staphylococcus and Lactobacillus which led to development of neonatal microbiota and decreased incidence of obesity in children.\textsuperscript{116} Synbiotics, which is a combination of pre-and probiotics modulate the microbiota and intestinal immunity.\textsuperscript{116} Studies even reveal that children treated with synbiotic (Protein), exhibited a decrease in weight as well as TNF-alpha and IL-6 with an increase in adiponectin.\textsuperscript{116}

Management strategies in childhood OSA with special emphasis on craniofacial morphology associated with obesity:

Sleep fragmentation is a vital consequence of OSA. Experimental sleep deprivation, as well as self-reported short sleep have been associated to metabolic dysregulation independent of childhood obesity and OSA, elaborating important interactions between these conditions and increasing the complexity of treatment.\textsuperscript{95} Currently, continuous positive airway pressure (CPAP) is the mainstay of treatment of OSA. Weight loss may be an effective therapy in overweight and obese patients, who may comprise 70% of subjects with OSA.\textsuperscript{97} Weight loss through bariatric surgery, has been shown to decrease the severity and symptoms of OSA.\textsuperscript{98} Weight loss may elicit important and significant changes in cholesterol, insulin resistance, leptin, inflammatory markers, and endothelial function.

Oral appliances are important management options for obese children with OSA.\textsuperscript{117} Oral devices can be broadly broken in to mandibular repositioning appliances ( devices that direct the movement of the lower jaw forward) and tongue retaining appliances (prevents the tongue from falling backward in sleep). The devices significantly increase the pharyngeal airway mechanically and have been proved to be efficacious in the treatment of mild to moderate OSA in obese individuals.\textsuperscript{118} A review of OSA treatments showed that the trial suffered significant methodological shortcomings like inappropriate randomisation and lack of an intention-to treat analysis.\textsuperscript{119} Other studies have concluded that in a subset of patients the use of an oral appliance would allow patients better to tolerate their CPAP therapy.\textsuperscript{120}

The presence of a maxillary transverse deficiency where the upper teeth are too narrow to occlude with the mandibular teeth is often found in children with OSA.\textsuperscript{121} This may be treated with rapid maxillary expansion (RME). The studies have all been small and randomized double blind trials may be needed for RME to gain wider acceptance but the treatment may be a reasonable approach for obese children with this specific orthodontic abnormality.\textsuperscript{125} It has been reported in a study that an anteriorly titrated mandibular position reduced Obstructive Sleep Apnea severity, enlarged the velopharynx, and decreased the curvature of the anterior velopharyngeal wall.\textsuperscript{123} Hence it was proposed that this change in the upper airway curvature associated with mandibular advancement may affect the severity of Obstructive Sleep Apnea through its effect on airflow dynamics.\textsuperscript{125} Maxillomandibular advancement through functional appliances is prescribed as a functional and curative treatment for OSA in obese children.\textsuperscript{124} It can
result in improvement in the quality of life and reduction in OSA health-related risks.\textsuperscript{124} Mandibular advancement appliances have been evaluated to be effective in the treatment of mild to moderate OSA.\textsuperscript{124} Treatment with removable functional appliances, like Twin Block appliance, has also been used to help growing pediatric OSA patients with a stimulation of mandibular growth.\textsuperscript{124}

CONCLUSIONS

Childhood obesity is so common in western countries and garners special attention currently due to increased orthodontic malocclusions and food related diseases in these subjects. A regular intake of junk foods can result in systemic inflammation in obese children. Interventional studies show the identification of gut microbiota associated in the development of obesity. Diets containing symbiotics are recommended to prevent noxious effects of obesity. Literature is replete which depicts marked differences in the craniofacial morphology between obese and normal children. Obese children have typical features of bimaxillary prognathism and larger facial dimensions.

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