Obesity And Type 2 Diabetes Mellitus In Adolescents - A Review

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Abstract: Obesity is highly prevalent in the modern world and it is associated with the development of a number of serious medical complications, like type 2 diabetes and cardiovascular diseases. Earlier, type 2 diabetes mellitus (T2DM) was regarded as a disease occurring in adults, while type 1 diabetes mellitus (T1DM) occurs in children and adolescents. This is true that T2DM is still more prevalent in adults, but there is increasing evidence that onset of type 2 diabetes in youth is frequently observed. Obesity increases the risk of T2DM by causing insulin resistance and directly or indirectly affecting the ability of the pancreas to secrete adequate amount of insulin. However, several risk factors have been identified as contributors to the development of type 2 diabetes in adolescents. These factors include ethnicity, genetic, unhealthy diet, inadequate sleep, physical inactivity and increased body fat and abdominal fat. There is no clear explanation of how these factors increase risk, but they appear to act in an additive fashion and create problems during the critical period of adolescent development. So efforts should be done to reduce the obesity will lower the risk of type 2 diabetes in children and adolescents.

Key Words: Obesity, Type 2 diabetes, Adolescent

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Introduction: Obesity is associated with significant health problems in adults have been well recognized but little attention has been paid to childhood and adolescent obesity. Obesity has been a rapidly developing medical and public health problems over the past few decades and excess body weight is the sixth most important risk factor contributing to the overall burden of disease worldwide[1]. Obese and overweight population has been increased more dramatically in economically developed countries and in urbanized populations.

Developing countries, like India, undergoing a rapid nutritional transition, from prevalence of underweight children to overweight children due to changes in quality of food, availability of high calorie food and sedentary life style[2]. As the prevalence of childhood obesity increases, its health implications are becoming more evident[3,4]. Childhood obesity frequently persists into adulthood. Many of the metabolic and cardiovascular complications of obesity are already present during childhood and are closely related to the presence of insulin resistance/hyperinsulinemia, the most common abnormality of obesity[5]. Over the past 20 years, Pediatric diabetologists and other health workers have recognized an emerging epidemic of type 2 diabetes among children and adolescents. This is due to increase prevalence of obesity[6].

A study indicates that the conversion into diabetes from prediabetic conditions is enhanced by low thresholds for the risk factors such as age, BMI and upper body adiposity. Indians have a genetic phenotype characterized by low BMI, but with high upper body adiposity, high body fat percentage and high level of insulin resistance[7]. With this low BMI, but with high body fat percentage, there is increased prevalence rate of metabolic perturbations and DM, which is one of the cardiovascular risk factors.

Risk Factors For Type 2 Diabetes Mellitus: The prevalence of overweight[8] and central adiposity[9] in childhood and adolescence has increased dramatically in recent years. Excess adiposity is considered a major risk factor for development of type 2 diabetes in youth[10,11]. Cross-sectional, longitudinal and experimental studies conducted in human populations across the world identified the various risk factors for youth type 2 diabetes mellitus. The important risk factors are listed below:

A. Non-Modifiable Risk Factors

1. Age
2. Ethnicity

3. Genetic Influence and family history

B. Modifiable Risk Factors

1. Unhealthy Life Style
- Unhealthy Diet
- Sleep Disorders/ Inadequate Sleep
- Physical Inactivity

2. Obesity
3. Hypertension

Influence of age on blood glucose level: Not long ago, type 2 diabetes mellitus (T2DM) was regarded as a disease of adulthood, with type 1 diabetes (T1DM) accounting for almost all cases seen in children and adolescents[12]. While it is true that T2DM is still more prevalent in adults, there is increasing evidence that onset in youth is frequently observed[13]. This relatively new phenomenon, strongly associated with the escalating prevalence of obesity, brings a serious new aspect to the diabetes epidemic.

Ethnic influence of blood glucose level: The highest incidence of T2DM in youth in the USA is evident in African-Americans, Native Americans, especially Pima Indians, and Hispanics[14,15,17]. Studies have shown that Black children and Hispanic youth are hyperinsulinemic and insulin-resistant compared with their white peers[18,19]. These racial differences could be attributable to genetic differences[20] or to environmental/cultural differences[18]. Moreover, differences in adiponectin levels, lower in Blacks, may be a biological marker which predisposes them to a greater risk of insulin resistance[21,22]. In the presence of such racial differences in risk of T2DM, it remains to be determined if the natural history and the progression to T2DM differ between different racial groups.

Genetic influence on blood glucose level: Although few susceptibility genes have been identified so far, a very recent finding points towards a gene locus that dramatically increases the risk of T2DM in Icelanders, Danes and a US cohort, specifically a variant of transcription factor 7-like 2 (TCF7L2) gene[23]. The genetic component of T2DM is evidenced by the strong heritability of the disease[24]. A strong family history of T2DM is present in most pediatric patients regardless of ethnic background[25]. The studies demonstrated that black African-American children with a family history of type 2 diabetes have 25% lower insulin-stimulated glucose disposal compared with black children without a family history of type 2 diabetes[26]. White children who do not have diabetes, but have a positive family history of the disease, have lower insulin sensitivity with inadequate β cell compensation in insulin secretion compared with youngsters without a family history of diabetes[27].

Unhealthy diet and blood glucose level: Adoption of a western lifestyle is strongly associated with type 2 diabetes. Obesity and lack of physical activity are known to be major determinants, but evidence also suggests that dietary factors play a role in the development of type 2 diabetes[28]. People eat meals mixing different foods, instead of isolated nutrients, giving several nutrients a chance to interact. These interactions between nutrients may potentially confound dietary studies. Several epidemiological studies conducted in relatively homogenous populations (predominantly white cohorts) have evaluated associations between dietary patterns and type 2 diabetes[29-33]. Generally, studies show that dietary patterns characterized by high whole grain, fruit/vegetable and low-fat dairy intake are inversely associated with type 2 diabetes risk. Analogously, dietary patterns characterized by high intake of red or processed meats, refined grains, fried foods and foods containing high amounts of added sugars are associated with greater type 2 diabetes risk. Study of Nettleton JA using participants from the Multi-Ethnic Study of Atherosclerosis (MESA) has evaluated that multiple food groups collectively influence type 2 diabetes risk beyond that of the individual food groups themselves[34].

Sleep duration and blood glucose level: The experimental study by Spiegel et al.[35] showed that restricted sleep in 11 healthy young men to 4 h per night for 6 nights and then allowed them to have a sleep recovery period of 6 nights. Despite the short duration of partial sleep deprivation, the subjects in that study

demonstrated impaired glucose tolerance, higher cortisol levels, increased sympathetic nervous system activity. Another study demonstrated that there was a reduction in leptin secretion in the sleep-deprived individuals versus the recovery state[36]. The Nurses Health Study in 2003[37] showed that Long and short sleep durations were associated with an increased risk of diabetes. Community based prospective study by Gottlieb DJ et al. showed metabolic effects of habitual sleep restriction. A sleep duration of 6 hours or less and long sleep duration of 9 hours or more, both are associated with increased prevalence of diabetes and impaired glucose tolerance[38]. A prospective cohort study of middle-aged and elderly men by Yaggi HK in 2006[39] observed that there is a significant U-shaped relationship between self-reported sleep duration and incidence of type 2 diabetes. Men reporting either short (≤5 or 6 h of sleep per night) or long (>8 h of sleep per night) sleep duration were at significantly increased risk of developing diabetes. These elevated risks remained after adjustment for age, hypertension, smoking status, self-rated health status, and education. Short and long sleep durations increase the risk of developing diabetes, independent of confounding factors. Thus sleep duration may represent a novel risk factor for diabetes.

These results suggest that habitually short sleep results in a reduction in insulin sensitivity, and therefore, could be a risk factor for the later development of diabetes. In contrast to that our study indicates that inadequate sleep duration at night (< 7 hrs) does not affect the blood glucose level of the Gujarati Indian adolescents[40]. The studies also indicate a possible association between sleep duration and risk of being overweight or obese in adolescents. Short sleep could lead to weight gain, but overweight or obesity could also lead to an inability to obtain sufficient amounts of sleep. Another study by us indicates that the sleep deprivation affects the body composition of the Gujarati adolescents and predisposes them to overweight and obesity[41]. So probable mechanism may be that the sleep deprivation leads to overweight and obesity and subsequently leads to diabetes. As another study by us in 2009 showed that body fat percentage affects the blood glucose level in adolescents[42].

Nurses health study observed that short self-reported sleep duration was significantly associated with the diagnosis of diabetes until BMI is controlled but, once BMI was added into the model, the association between diabetes diagnosis and short sleep was no longer significant. This finding could be due to two reasons. First, short sleep may lead to diabetes due to weight gain, as a high BMI may worsen sleep quality by creating a prediabetic state with increasing urination. Second, sleep restriction may directly lead to the development of diabetes through its effects on weight. Hypothesis behind this is that, if chronic self-imposed sleep restriction occurs that leads to reductions in leptin, so appetite and weight gain may be increased. This could thus represent a physiologic mechanism whereby sleep restriction may predispose to weight gain and subsequently contribute to the development of diabetes[37].

Physical activity and blood glucose level: Obesity and physical inactivity are well-known risk factors for the development of type 2 diabetes[43-45]. However Rana JS et al. found that obesity and physical inactivity independently contribute to the development of type 2 diabetes; however, the magnitude of risk contributed by obesity is much greater than that imparted by lack of physical activity[46]. Epidemiologic studies and clinical trials suggest a strong association between physical inactivity and incident type 2 diabetes[45,47,48].

The Da Qing Impaired glucose tolerance (IGT) and Diabetes Study[47] was the first randomized trial evaluating lifestyle interventions for the prevention of type 2 diabetes. In this study, 577 people with IGT from 33 clinics were randomized, by clinic, to diet only, exercise only, diet plus exercise, or control. After 6 years of follow-up, cumulative incidence of type 2 diabetes was 68% in control, 44% in diet only, 41% in exercise only, and 46% in diet plus

exercise groups. This study provides evidence that both diet and exercise can be effective diabetes prevention modalities, although their effects were not additive.

More evidence for the effectiveness of lifestyle interventions comes from two randomized controlled trials: the Finnish Diabetes Prevention Study[49.50] and the U.S. Diabetes Prevention Program (DPP)[51,52]. In the Finnish Diabetes Prevention Study[49,50], 522 overweight subjects, aged 40–65 years, with IGT were randomly assigned to a lifestyle intervention or control group. The goals were to reduce weight by at least 5%; perform moderate-intensity exercise at least 30 min/day; limit total and saturated fat intake to <30 and <10%, respectively, of energy consumed; and increase fiber intake to ≥15 g/1,000 kcal. Intervention group subjects had 1-h meetings with a dietitian seven times in the first year and every 3 months subsequently. Subjects in the intervention group were also offered an individualized exercise plan, thrice-weekly supervised facility-based aerobic and resistance exercise for 6–12 months free of charge. The cumulative incidence of type 2 diabetes was 11% in the intervention group and 23% in the control group.

Obesity and poor physical fitness constitute a health problem affecting an increasing number of children also. The Diabetes Prevention Program demonstrated a reduction in the incidence of diabetes in high-risk adults with lifestyle intervention. For children, the most successful programs are those that incorporate additional exercise or promoting healthy nutritional changes into the children's lifestyles, such as within the family or the school environment. Carrel AL showed that children who enrolled in fitness-oriented gym classes showed greater loss of body fat, increase in cardiovascular fitness, and improvement in fasting insulin levels than control subjects[53].

The study by Ferguson MA[54] on 79 obese, but otherwise healthy children to determine the effect of exercise training (ET) on components of the insulin resistance syndrome (IRS) in obese children found that Plasma triglycerides, fasting insulin and percentage body fat of the IRS are improved as a result of 4 months of ET in obese children. However, the benefits of ET are lost when obese children become less active. The cross sectional study on 421 black and white high school students[55] to observe how moderate and vigorous intensities of physical activity (PA) are associated with cardiovascular fitness (CVF) and percentage of body fat (%BF) showed that a higher index for CVF was associated with higher amounts of moderate and vigorous PA. Lower %BF was associated with higher amounts of vigorous PA but not with the amount of moderate PA. This suggests that adolescents who engaged in relatively large amounts of vigorous exercise were likely to be fit and lean and so there consequences like diabetes become also less.

Obesity and blood glucose level: Globalization has profound effects on health worldwide and we face huge public health challenge from both obesity and type 2 diabetes, from childhood to old age. Obesity has reached epidemic proportions globally. There is a strong association between obesity and type 2 diabetes mellitus, in both genders and all ethnic groups. Body composition especially the amount of adipose tissue has a significant effect on type 2 diabetes. The risk of diabetes increases with increasing BMI values in men and women. Data from the Nurses' Health Study showed an age-adjusted relative risk of 40 for diabetes in women with a BMI $\geqslant$31 kg/m^2, compared with women with a BMI <22 kg/m^{2,} [56]). A similar risk was shown for men in the Health Professionals Follow-up Study: a BMI of $\geqslant$35 kg/m^2 was associated with an age-adjusted relative risk for diabetes of 60.9, compared with a BMI of <23 kg/m^{2,} [43]. In addition, weight gain appears to precede the development of diabetes.

The importance of obesity as a risk factor for diabetes in the presence of other risk factors is underlined by a recent report from Israel. In a cohort of relatively young men in the Israel Defence Forces who were subjected to regular physical examinations, the combination of a

fasting plasma glucose in the high-normal range (91–99 mg/dl) and a BMI of >30 kg/m^2 was associated with a hazard ratio of 8.29 for developing diabetes, compared to those men with a BMI <25 kg/m^2 and a fasting plasma glucose <86 mg/dl[57]. Increases in abdominal fat mass, weight gain since young adulthood, and a sedentary lifestyle are additional obesity-related risk factors for diabetes[56,58].

The CAD and coronary risk factors hypercholesterolemia, hypertension, diabetes mellitus and sedentary life style were significantly associated with high and moderate body fat percent despite low body mass index[59]. Another studies suggested that insulin sensitivity has gender dependent changes during puberty. It is, thus, possible that these pubertal changes in insulin sensitivity relate to changes in body composition[60].

Obesity and blood glucose level in Adolescents: Overweight/obesity continues to increase in children and adolescents. Overweight children and adolescents are now being diagnosed with impaired glucose tolerance and type 2 diabetes, and they show early signs of the insulin resistance syndrome and cardiovascular risk. Several risk factors have been identified as contributors to the development of type 2 diabetes and cardiovascular risk in youth and one of these factors include increased body fat and abdominal fat. National Health and Nutrition Examination Study (NHANES) 1999–2000 data suggest that the prevalence of overweight was 15.5% among 12 to 19-year-olds, 15.3% among 6 to 11-year-olds, and 10.4% among 2 to 5-year-olds, compared with 10.5%, 11.3%, and 7.2%, respectively, in 1988-1994 (NHANES)[61]. Other studies show steady increases in overweight and obesity over the period 1986–1998, especially in Hispanic and African-American children[62]. By 1998, the prevalence of a BMI above the 85th percentile for age and gender had risen to 35% in Hispanic and African-American children and just over 20% in Caucasian children[62]. Although no national data are available, the prevalence of risk of overweight is also widespread in India. The overall prevalence of obesity and overweight was 11.1% and 14.2% respectively. The prevalence of obesity as well as overweight was higher in boys as compared to girls (12.4% vs 9.9%, 15.7% vs 12.9%). Prevalence of obesity decreased significantly with age, from 18.5% at 9 years to 7.6% at 14 years, rising at 15 years to 12.1%. Significantly more children from higher socio-economic status were obese and overweight than those from lower socio-economic status groups[63].

Of even greater concern is the fact that type 2 diabetes has now emerged as a critical health issue in overweight children, especially within minority overweight African-American, Hispanic American, and Native American adolescents[64]. Several clinical observations suggest a large increase in the incidence of type 2 diabetes in children and adolescents[11], with one study reporting a 10-fold increase between 1982 and 1994[14].

Many population-based studies conducted in high-risk pediatric populations estimated the prevalence of type 2 diabetes. The prevalence estimates of type 2 diabetes were 5% (CI 3.2–6.9) for Pima Indians aged 15–19 living in Arizona[16]. From 1966–1976 to 1987–1996, the prevalence increased fourfold for Pima Indian children aged 10 to 14 years and sixfold for children aged 15 to 19 years. The Third National Health and Nutrition Examination Survey (1988–1994) examined a representative sample of the U.S. population, which included adolescents aged 12–19 years who had serum glucose measured and estimated prevalence of diabetes. The estimated prevalence of diabetes per 100 adolescents ages 12–19 years was 0.41% , the prevalence of impaired fasting glucose was 1.76% and the prevalence of elevated HbA_{1c} was 0.39%[65].

The clearest factor contributing to increased risk of type 2 diabetes and cardiovascular disease in children and adolescents is increased body fat, and possibly specific depots of body fat. Some of the earliest evidence for this came from the Bogalusa Heart study that showed weak, but significant correlations (r = 0.3–0.4) in

children between central body fat (measured by skinfolds) and fasting insulin[66]. Later work[67] using more precise measures of body fat found higher correlations in 10-yr-old children between percentage body fat and fasting insulin (r = 0.78). Additional studies using other measures, in addition to fasting insulin, showed that insulin and the insulin-to-glucose ratio were significantly higher in obese versus control group boys during a oral glucose tolerance test[68]. The study by Gower BA in 1999 showed that visceral fat has unique metabolic effects on fasting insulin but not insulin sensitivity and that this effect was independent of other fat compartments and also has shown high inverse correlations between insulin sensitivity and body fat mass across the spectrum of lean and obese prepubertal boys and girls[20]. Another study was done by Goran MI to examine whether total body fat in general or visceral fat in particular was associated with greater metabolic risk in Caucasian and African-American children[69]. The influence of total body fat and visceral fat on insulin parameters was examined by comparing subgroups of children with high or low fat *vs.* high or low visceral fat and showed that body fat in general is the predominant factor influencing insulin sensitivity, but visceral fat may have additional effects on fasting insulin. Similar effects were shown in a later longitudinal study[70]. These data tend to support the hypothesis that in children, total body fat mass may influence insulin sensitivity, whereas visceral fat may influence fasting insulin.

Summary: Overweight/obesity continues to increase in children and adolescents. Overweight children and adolescents are now being diagnosed with impaired glucose tolerance and type 2 diabetes, and they show early signs of the insulin resistance syndrome and cardiovascular risk. Several risk factors have been identified as contributors to the development of type 2 diabetes and cardiovascular risk in youth. These factors include ethnicity (with greater risk in African-American, Hispanic, and Native American children), genetic, unhealthy diet, inadequate sleep, physical inactivity and increased body fat and abdominal fat. There is no clear explanation of how these factors increase risk, but they appear to act in an additive fashion. We hypothesize that the constellation of these risk factors may be especially problematic during the critical period of adolescent development, especially in individuals who may have compromised-cell function and an inability to compensate for severe insulin resistance.

Efforts to reduce childhood obesity could play an important role in preventing the spread of type 2 diabetes mellitus in the pediatric population. Government and communities should take care to cultivate environments where children are encouraged to make healthy lifestyle choices. Children should be educated on appropriate diet and exercise habits from preschool through high school. In-school intervention efforts may include 30 to 45 minutes of vigorous physical activity two or three times per week. Serious long-term approaches for primary prevention are needed to address this growing problem.

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