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Review Article

Biochemical Parameters as Cardiovascular Risk Factors in Obese Children and Adults

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Abstract

Childhood obesity is a global health problem with short- and long-term health consequences. There is increasing prevalence of obesity among children and there is increased risk for coronary heart disease. A number of clinical and biochemical parameter becomes abnormal in children and adults with obesity. Preventative measures involving family and community-based intervention as well as clinical measures from early childhood should assist in decreasing the prevalence rates. This review focus on current knowledge on the prevalence of overweight and obesity in children and adults, and the biochemical parameters that are abnormal.

INTRODUCTION

Obesity in children and adults is a serious public health problem in developed as well as in developing countries with immense health and economic implications. Worldwide estimates done in 2010 indicated that approximately 1.5 billion adults, 20 years and older are overweight. Of these about 300 million women and more than 200 million men are obese [1]. According to the World Health Organization (WHO), approximately 43 million children under the age of 5 years are overweight. In low and middle-income countries, especially in urban dwellings the prevalence of overweight and obesity are increasing [1].

Obesity is a risk factor for coronary artery disease and is increasing in prevalence among youths as well as adults. In childhood, obesity has become a major concern globally, and excessive adiposity is a cause of metabolic and cardiovascular diseases, and related mortality [2,3].

A detailed literature search was conducted from 1990 to 2017 using Pub Med and subsequent reference searches of retrieved articles. The selection of studies included in this review is based on rigor of scientific design, hypothesis testing, adequate sample size, quality of the data and statistical analysis. This review will focus on current knowledge on the prevalence of overweight and obesity in children and adults, lipid and lipoprotein profile in obese subjects including non-HDL-cholesterol, and atherosclerosis. This review will also present information on abnormal levels of biochemical parameters such as C-reactive protein, homocysteine and isoprostanes in overweight and obese children and adults.

PREVALENCE OF OVERWEIGHT AND OBESITY IN CHILDREN AND ADULTS

Body mass index (BMI) is internationally accepted for use in defining both overweight and obesity and is found to be an appropriate measure of adiposity in adults [4]. In adult populations, overweight and obesity are defined as BMI values of 25 kg/m^2 and 30 kg/m^2 respectively [5]. Conversely, in children and adolescents BMI and waist circumference constantly changes with normal growth and maturation and so there is a challenge in determining the adiposity status [6]. However, several expert committees have recommended BMI as the most suitable measure of adiposity status in children and adolescents [7,8].

Obesity in paediatrics is generally defined as the 95th percentile or greater of BMI for age. Children who are considered overweight are those with BMI between the 85th and 94th percentiles [9]. Obesity in childhood is also defined as weight being greater than 120%, and those who are severely overweight greater than 140% to 150%, of ideal weight for height [10].

Obesity is a major risk factor for developing type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemias, musculoskeletal diseases, and certain types of cancer. In a systematic review which compared estimates of the prevalence of overweight and obesity in 137,593 children and adolescents (10-16 years) from 34 countries (participating in the 2001-2002 Health Behaviour in School-Aged Children Study) across North America and Europe using the international obesity classification system, childhood obesity was present in 77% of the countries examined. Child obesity was high in countries in Great Britain, North America and South-Western European countries such as Spain, Italy and Greece. Further, at least 10% of youths were overweight and in 20% of the countries at least 3% were obese [11] (Table 1).

A number of prospective studies have been carried out looking at the prevalence of overweight and obesity in both children and adults in a number of countries. In the past thirty

Table 1: Prevalence of overweight and obesity in children and adults.

Population	Number of subjects	Prevalence of overweight/ obesity	References
National Health and Nutrition Survey: children and adults aged ≥7 years	9,244	11% of children and 30% of adults are overweight	14
Health Behaviour in School-Aged Children Study) across North America and Europe: children and adolescents (10-16 years) from 34 countries	137,593	At least 10% of youths were overweight and in 20% of the countries at least 3% were obese	11
National Health and Nutrition Examination Survey in 1999-2000: children (from birth through 19 years of age)	4,722	The prevalence of overweight was 10.4% among 2 to 5year-olds, 15.3% among 6 to11yearolds and 15.5% among 12 to19yearolds	12
Transversal and prospective study in Brazil: Children (6 to 9 years; 10 to 12 years; 13 to 15 years and 16 to 19 years)	437	28.8% were overweight, 36.2% had a high adiposity index	16
Cross-sectional study: pre-pubertal students (6 to 11 years old)	677	Prevalence of overweight and obesity were 13.3% and 12.0% respectively	92
Avon Longitudinal Study of Parents and Children (mean age 9.9 years)	7,589	Overweight -18.8% girls and 13.0% boys; obese - 5.0% girls and 5.3% boys	69
Chinese adolescents (15.0 to 17.9 years)	NCEP ATP III	Overweight (18.3%) and obesity (38.1%)	47

years the prevalence of overweight and obesity among children and adolescents in the United States of America has doubled and tripled, respectively [12,13]. In the National Health and Nutrition Examination Survey (NHANES) in 1999-2000 of 4,722 children (from birth through 19 years of age), the prevalence of overweight was 10.4% among 2 to 5year-olds, 15.3% among 6 to 11year-olds and 15.5% among 12 to 19-year-olds compared with 7.2%, 11.3% and 10.5%, respectively, in 1988-1994 (NHANES III) [12].

In China, 11.0% of children and 30.0% of adults are overweight and the rates of diabetes mellitus, hypertension, dyslipidemia and inflammation are increasing, and increased with age [14]. In Mexico the prevalence of overweight and obesity is 30.9% in adolescents, 26.2% in school children and 16.7% in preschool children. For adults, the prevalence of overweight and obesity is 39.7% and 29.9%, respectively [15].

In a transversal and prospective study in Brazil of 437 children (6 to 9 years old; 10 to 12 years old; 13 to 15 years old and 16 to 19 years old), 28.8% were overweight, 36.2% had a high adiposity index, and 41.0% had deranged lipid profile [16]. A number of studies conducted in Turkey between 2000 and 2010 reported prevalence rates for overweight and obesity of 10.3%-17.6% and 1.9%-7.8% respectively, in children aged 6-16 years old [17]. Further, childhood obesity is associated with increased morbidity and mortality due to cardiovascular disease in adulthood, which is independent of adult weight as shown in the Harvard Growth Study. The relative risk for mortality among overweight male adolescent subject was 1.8 from all causes and 2.3 for mortality from coronary heart disease [18]. In an observational study of 2.3 million Israeli adolescents from 1967–2010, there was a strong association between overweight and obesity, and increased cardiovascular mortality in adulthood [19].

HYPERTENSION AND OBESITY

Hypertension in children and adolescents is defined as systolic and/or diastolic blood pressure values at or above the 90th percentile on repeated measurement [20]. Many studies involving a variety of ethnic and racial groups have reported an association between obesity and primary hypertension in children and adolescents, with most reporting elevated blood pressures and/or higher prevalence of primary hypertension in obese children compared with their lean counterparts [21-22]

In a school-based hypertension and obesity screening study of 2,460 students conducted in eight urban public schools, there was a three times greater prevalence of hypertension in obese compared with non-obese students [21,22]. Rosner et al., (2000) reported a comprehensive study where data was pooled from eight large epidemiologic studies conducted in the United States of America involving 47,196 Black and Caucasian children. The study examined the effects of gender, age and body size on ethnic differences in blood pressure levels and found that

irrespective of these factors, the risk of increased blood pressure was significantly higher for children in the upper decile of BMI compared with their counterparts in the lower decile and the former had an odds ratio of 2.5 - 3.7 for systolic hypertension. In this same study, a linear elevation in the prevalence of diastolic hypertension in both Black and Caucasian children of all age and gender combinations as BMI increased [22-24].

Nawrot and colleagues reported that in 120 girls and 80 boys in Belgium (mean age of 17.4 years), systolic and diastolic blood pressures were significantly higher in boys than in girls. In addition, systolic blood pressure increases by 1.2 mmHg per 1 kg/m^2 increase in BMI in girls and 0.8 mmHg per 1 kg/m^2 increase in BMI in boys. Based on these findings the authors suggest that health education and prevention of hypertension and obesity is critical during adolescence [25]. Likewise, in The Bogalusa Heart Study which consisted of seven cross-sectional studies of 9167, 5- to 17-year-olds, overweight school children were 2.4 and 4.5 times likely to have elevated diastolic blood pressure and systolic blood pressure, respectively [26].

LIPID AND LIPOPROTEIN PROFILE IN OBESE SUBJECTS

Dyslipidemia is present if one or more of these lipid, lipoprotein, or apolipoprotein levels are abnormal. A lipoprotein profile is usually measured after an overnight fast. Such a profile includes total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and non-high density lipoprotein-cholesterol (non-HDL-C). Low density lipoprotein-cholesterol is calculated from the Friedewald equation: LDL-C = TC − (HDL-C + TG/5). Triglyceride in the fasting state divided by 5 is used to estimate very-low-density lipoprotein-cholesterol (VLDL-cholesterol). If the triglyceride concentration is more than 400 mg/dL, the Friedewald equation formula should not be used, and a direct LDL-cholesterol should be determined [27]. Total cholesterol, HDL-cholesterol and non-HDL-cholesterol can be determined in the non-fasting state [28].

Research investigators from the Project Heart Beat Study a community-based longitudinal study in Texas, and from a national population sample survey, the Third NHANES reported that lipid and lipoprotein concentrations changed in different ways for males and females during development [29]. There are studies such as The Lipid Research Clinics Program Prevalence Study that have shown that the concentration of serum lipids and lipoproteins increases during early childhood and reaches concentrations similar to those seen in young adults [30,31].

In the NHANES study of 2,661 participants during the period 1999 - 2004, approximately 10.0% of the subjects had elevated total cholesterol, 7.0 had decreased HDL-cholesterol, 9.7% had elevated triglycerides, and 7.6% had elevated LDL-cholesterol [32]. Similarly, in a study of 16,585 children in 170 schools in India, mean total cholesterol, LDL-cholesterol and triglyceride concentrations were significantly higher in obese children compared with their matched lean counterparts, and BMI correlated with lipid profile [33]. However, there was no association between lipid profile and BMI or external body measurements (skin-fold thickness, waist circumference, waist-to-hip ratio) in 47 obese female adolescents (aged 10 to 15 years) [34].

In a study involving 159 lean and obese Portuguese children and adolescents, obese subjects (n=73) had higher total cholesterol, LDL-cholesterol, total cholesterol/HDL-cholesterol, and apolipoprotein B than their non-obese counterparts. There was also significant association between central adiposity, triglycerides and HDL-cholesterol concentrations in obese children and adolescents [35]. Similarly, in a study of 285 children and adolescents (mean age of 14.3 years), obese adolescents have significantly elevated triglyceride concentrations and LDL-cholesterol, and significantly decreased HDL-cholesterol concentrations than their age matched, non-obese controls [36].

Among children the levels of lipoproteins vary by race/ethnicity and gender and are associated with age, obesity, and other characteristics. In examining advanced lipoprotein testing, in The Bogalusa Heart Study plasma levels of VLDL-cholesterol and LDL subclasses were determined in 918 boys and girls (10 to 17 years old) by nuclear magnetic resonance (NMR) spectroscopy. It was found that boys had a smaller (0.1 nm) mean LDL particle size and a larger (0.9 nm) mean VLDL size compared with girls. The authors suggested that the determination of VLDL and LDL subclasses presents critical information of the role of different risk factors in the development of coronary heart disease [37]. In the same study involving 367 Black and 549 Caucasian children, the association between waist circumference and large VLDL was 6-fold stronger among Caucasian children compared with Black children. This could give more information on the risk of obesity-related ischemic heart disease [38].

It has been shown that measurement of apolipoprotein B is better than LDL-cholesterol as a predictor of coronary artery disease and as an index of residual risk of the same disease [39,40]. Apolipoprotein B indicates the amount of atherogenic apolipoprotein B-containing lipoproteins that is atherogenic and is a better predictor of the number of size and number of LDL particles. Methods used to measure apolipoprotein B include density gradient ultracentrifugation, gradient gel electrophoresis and nuclear magnetic resonance spectroscopy [41,42].

The role of obesity and insulin resistance in relation to paediatric dyslipidemia deserves considerable attention. In The Bogalusa Heart Study of a cross-sectional survey of 4,136 young Black and Caucasian children, adolescents and young adults aged 5 to 30 years investigated whether insulin is a significant contributor to adverse lipid profiles. It was observed that fasting insulin concentrations were significantly positively associated with serum VLDL-cholesterol and triglyceride concentrations, and negatively correlated with HDL-cholesterol concentration in all age groups. Furthermore, there was a strong correlation of insulin level with lipoprotein fractions in obese than in non-obese Caucasian males [43].

In addition to pharmacological intervention, dyslipidemia in children, adolescents and adults may be improved by increased physical activity. Studies have reported increased HDL-cholesterol, decreased triglyceride and LDL-cholesterol concentrations as a result of physical activity [44,45]. A systematic literature review of 850 articles by Strong and colleagues showed that there is

supportive data from epidemiologic studies of the positive effect of physical activity as a specific intervention for obese children and adolescents [43]. Physical activity has been negatively associated with cardio-metabolic risk. The Iwata population-based follow-up study of 914 Japanese school children (451 boys and 463 girls; aged 10 years who were followed up until 14 years of age) examined the effect of recovery from obesity on cardiovascular risk factors. Of the 12% who were obese at 10 years of age, 40% were no longer obese at 14 years of age. Boys had the greatest decrease in non-HDL-cholesterol compared with girls, who also had significantly lower concentrations [46].

NON-HDL-CHOLESTEROL AND OBESITY

Non-HDL-cholesterol is a measure of the amount of cholesterol carried by the atherogenic B containing lipoproteins such as very VLDL, intermediate-density lipoprotein (IDL), LDL, lipoprotein (a) and chylomicron remnants [47]. Non-high density lipoprotein-cholesterol is calculated from a standard lipid panel by subtracting the concentration of HDL-cholesterol from the total cholesterol [48,49]. A cross-sectional chart review on 928 public hospital patients was performed in the United States found that 53% of all patients had metabolic syndrome. Among those with metabolic syndrome, 74% had non-HDL-cholesterol of greater than 130 mg/dL with this parameter being significantly elevated compared with total cholesterol or LDL-cholesterol [50].

In a recent cross-sectional study of 4,104 adolescents (51% male; mean age of 14.6 ± 0.5 years old), obesity in adolescents was associated with statistically significantly lower levels of HDL-cholesterol and higher non-HDL-cholesterol [51]. Similarly, in the Slovak Lipid Community Study, a cross-sectional study of 788 Roma and Caucasian children (aged 7-17), general obesity (as measured by BMI), waist circumference and per capita income were significantly positively correlated with non-HDL-cholesterol. Further, by using cut-off points for non-HDL-cholesterol (acceptable < 3.30, borderline 3.31-3.81 and high > 3.82 mmol/L), the prevalence of dyslipidemia was determined as 4.2% in Caucasian and 5.4% in Roma children [52]. Likewise, in the Floripa study of 1,009 children and adolescents in Brazil, there were also significant correlations among high non HDL-cholesterol and skin colour, economic class and abdominal obesity as indicated by high waist circumference [53]. In addition, analysis of data from the cross-sectional Scottish Health Survey conducted in 1998, showed that obesity among patients was significantly associated with higher odds ratio for C-reactive protein (CRP), elevated total cholesterol, non-HDL-cholesterol and lower HDL-cholesterol. These obese patients also had greater predicted risk for coronary heart disease [54].

There are a number of studies that involve subjects with and without cardiovascular disease that has found that non-HDL-cholesterol concentrations relate to the severity of atherosclerosis and subsequent cardiovascular mortality and morbidity [47,55,56]. In the multi-centre Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study of 3,000 individuals aged 15-34 years of age who died and were autopsied in central forensic laboratories, raised lesions of the coronary arteries which indicates advanced lesions of atherosclerosis which subsequently cause coronary heart disease were positively correlated with non-HDL-cholesterol concentration, hypertension, and obesity in men [57,58].

Non-HDL-cholesterol has been found to be significantly associated with apolipoprotein B and therefore indication of the cholesterol gives in atherogenic particles [59,60]. In a prospective cohort study of 15,632 healthy women (interquartile range, 48-59 years old) in the United States of America who were followed up over a 10-year period for the occurrence of future cardiovascular events, the hazard ratio for non-HDL-cholesterol was 1.62, 1.75 for apolipoprotein A-I, 2.50 for apolipoprotein B-100 and 2.51 for non-HDL-cholesterol. The authors suggest that non-HDL-cholesterol is better than apolipoprotein fractions in the prediction of future cardiovascular events [61]. Likewise in 53 obese men the non-HDL-cholesterol concentration was significantly inversely correlated with the fractional catabolic rate of LDL-apoB-100 and positively correlated with the secretion rate of VLDL-apoB-100. This suggests that in overweight and obese men plasma concentrations of non-HDL-cholesterol are partly dependent on catabolism of apoB-100 containing lipoproteins [62].

LINK BETWEEN DERANGED LIPID AND LIPOPROTEIN PROFILE IN CHILDREN AND ADULTS

There have been various studies that have consistently indicated that overweight and obese children and adolescents have a more unfavourable lipid and lipoprotein profile than their leaner counterparts [35,63,64]. As shown in The Bogalusa Heart Study lipoprotein concentrations vary with age and gender [65]. At-risk lipoprotein concentrations during the growing years are also of particular concern because they tend to track into adulthood [66]. The Bogalusa Heart Study reported tracking serum lipids and lipoproteins from childhood to into young adulthood. It was found that deranged levels of LDL-cholesterol in childhood persist over time and may progress to adult dyslipidemias [66]. In an earlier publication of the same study, the prevalence of clinically recognized dyslipidemia increased 3.1- to 8.3-fold in the overweight adolescents (aged 13 to 17 years) and those who remained overweight in adulthood had a 3, 2.4 and 8 times greater prevalence of elevated triglycerides, elevated LDL-cholesterol, and decreased HDL-cholesterol concentrations, respectively compared with those who remained non-obese [67].

In the Cardiovascular Risk in Young Finns Study which tracked serum lipid levels, blood pressure, and BMI in 2,204 subjects from childhood (ages 3 - 18 years) to adulthood (ages 30 to 45 years) for 27-year follow, serum lipids, blood pressure and BMI in childhood were strongly associated with values measured in adulthood [68]. Similarly, in the Avon Longitudinal Study of Parents and Children of 7,589 with mean age 9.9 years, 18.8% of girls and 13.0% of boys were overweight, and 5% of girls and 5.3% of boys were obese. It was also found that each increase of 1 kg/m^2 BMI was associated with 1.4 mmHg higher systolic blood pressure, 0.03 mmol/L lower HDL-cholesterol and 0.05 mmol/L higher non-HDL-cholesterol [69]. Further, research has shown that obesity in childhood can be tracked into obesity in adulthood and cause further elevation of carotid intima medial thickness (CIMT**)** [70,71].

OBESITY AND ITS ASSOCIATION WITH ATHEROSCLEROSIS

Accelerated coronary atherosclerosis is associated with an obese state in adolescent and young adult men. Established risk factors of atherosclerotic disease such as dyslipidemia, hypertension, glucose intolerance and insulin resistance are intensified by the obese state. Deranged lipid profile in the obese subject include elevated total cholesterol, elevated fasting (and postprandial) triglyceride concentrations, elevated apolipoprotein B and small dense lipoprotein particles, decreased HDL-cholesterol, and alterations of serum and tissue lipoprotein lipase (LPL)-activity [72,73]. Elevated lipids and lipoproteins can modify the function of the vascular endothelial and impair some of its hyperlipidemia can alter vascular endothelial function and impair some of its anti-thrombotic regulatory and pro-fibrinolytic properties, resulting in the initiation of atherosclerosis [74,75].

Obesity in childhood is associated with an increased mortality due to cardiovascular diseases in adulthood, independent of adult weight. The atherosclerosis process starts at an early age and is linked to obesity. A number of population studies have shown that abnormal lipoprotein concentrations in children and adolescents have been associated with preclinical atherosclerosis [76-78]. Further, various prospective cohort studies published in the last decade have reported that adverse levels of lipoprotein in childhood and adolescence may induce changes in arteries that contribute to adult atherosclerosis [79,80].

Obesity and familial dyslipidemia in children are associated with accelerated atherosclerosis by pathological examination. Prospective epidemiological studies such as The Muscatine Study [79], the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study [81] and the Cardiovascular Risk in Young Finns Study [82,83], showed that cardiovascular disease risk factors such as elevated triglycerides and LDL-cholesterol, and obesity predicted clinical manifestations of atherosclerosis in young adults, as evident from increased CIMT, and increased odds of coronary artery calcium. Carotid artery intima-media thickness, a marker of atherosclerosis and heart disease in adults, and pediatric epidemiologic studies have reported that elevated BMI, elevated total cholesterol and BMI, in children and adolescents are correlated with elevated CIMT [71,84]. In an earlier study involving 1,079 men and 364 women (15 - 34 years of age) who died of external causes and autopsied in forensic laboratories, the extent of fatty streaks and raised lesions in right coronary artery and aorta was negatively correlated with HDL-cholesterol and positively correlated with VLDL and LDL-cholesterol [85].

In the 55-year follow up of the Harvard Growth Study of 1922-1935 which included 508 lean and overweight adolescents (age 13 - 18 years old), overweight adolescent subjects had a 2.3-fold risk for mortality from coronary heart disease, independent of adult weight [86]. Similarly, in a British study involving a 57-year follow-up of a cohort of 1,165 males and 1,234 females (aged 2 - 14.75 years old when first examined), all-cause (hazard ratio 1.5) and ischemic heart disease (hazard ratio 2.0) mortality was elevated in those with BMI greater than 75th percentile in childhood [87].

Pathology studies such as the Bogalusa Heart Study showed that cardiovascular risk factors such as increased BMI, elevated systolic and diastolic blood pressures, elevated serum concentrations of total cholesterol, triglycerides, LDL-cholesterol and decreased HDL-cholesterol are associated with increased risk of fatty streaks and fibrous plaques in the aorta and coronary arteries of 204 young subjects (2 to 39 years of age) who had died from various causes including trauma [76]. Further, in a recent study by Juonala and colleagues of 6,328 subjects, those individuals with consistently high adiposity status from childhood to adulthood, had a relative risk of 2.7 for hypertension, 1.8 for increased LDL- cholesterol concentrations, 2.1 for decreased HDL-cholesterol concentrations, 3.0 for increased triglyceride concentrations, and 1.7 for carotid-artery atherosclerosis as indicated by increased CIMIT [88].

OTHER BIOCHEMICAL PARAMETERS IN OBESE SUBJECTS

Atherosclerosis begins in childhood and progresses from fatty streaks to raised lesions in arteries in adolescence and young adults. Elevated serum homocysteine concentration is a new risk factor for atherosclerosis and other vascular diseases. Elevated homocysteine concentration was significantly higher in 48 children with atherosclerosis risk factors compared with 25 healthy children [89]. However, C-reactive protein levels were not associated with increased CIMIT in a group of 104 obese subjects [90].

Increased levels of serum homocysteine have been reported as an independent risk factor of cardiovascular disease in adults [91]. In a cross-sectional study of 677 pre-pubertal children (6 to 11 years old) of which 13.3% and 12.0% were overweight and obesity respectively, those with a waist circumference above the 90th percentile was found to be 2.4 times more likely to have elevated homocysteine concentrations [92]. Similarly, in 65 hypertensive patients and the same number of normotensive patients, elevated homocysteine was observed in the former and there was significantly increased homocysteine in overweight and obese hypertensive patients. Among the hypertensives, homocysteine was significantly positively correlated with obesity and arterial blood pressure levels [93]. Further, obese patients (40 children and adolescents) had significantly higher total homocysteine levels than non-obese controls. The authors suggested that elevated levels of leptin and apolipoprotein B may contribute to the impairment of total homocysteine metabolism [94]. In a later study, elevated plasma total homocysteine was found in 41 obese school children with hypertension and dyslipidemia. Plasma homocysteine correlated significantly with BMI ($r = 0.56$) and increased ICA intima-media thickness in obese girls [95].

However, a number of studies have found no correlation between plasma homocysteine levels and risk factors of cardiovascular disease including obesity. In a study of 524 school children (aged 6-15 years), there was no significant difference in homocysteine levels between the overweight and obese group compared with those in the normal group [96]. There was also there was no association between plasma homocysteine and BMI, diastolic or systolic pressures in 28 obese children and

adolescents (13 girls, 15 boys; BMI >95 per thousand for age and gender) [97]; and no significant difference between total homocysteine in 86 overweight and 153 lean controls [98].

Elevated homocysteine and metabolic syndrome are associated with increased cardiovascular risk [99]. In a study of 66 morbidly obese patients (47 females and 19 males; aged 41 ± 12 years old) and 66 normal weight subjects (43 females and 23 males; aged 45 ± 11 years old), statistically higher homocysteine levels were observed in the obese patients than controls. However, there was no difference in homocysteine levels in obese patients with metabolic syndrome compared with those without [100]. In an earlier reported case-control study in a Mediterranean population of 61 metabolic syndrome patients (41 men, 20 women, mean age 51 ± 11 years old) and in 98 controls without metabolic syndrome (59 men, 39 females, mean age 50 ± 10 years old), there was also no difference in homocysteine levels between the two groups of patients [101].

Obesity has been associated with elevated levels of CRP, a marker of inflammation and predictor of cardiovascular risk. Data from 51 cross-sectional studies that used BMI, waist circumference and waist-to-hip ratio as measure of obesity, showed that obesity is associated with increased levels of CRP and the association is stronger in females, and North Americans and Europeans [102]. In The Third NHANES (from 1988 to 1994) of young adults aged 17 to 39 years, overweight and obese subjects were more likely to have increased levels of CRP than their lean counterparts [103].

High sensitivity C-reactive protein (hs-CRP) is a marker of systemic inflammation and a predictor of cardiovascular disease, type 2 diabetes mellitus, and there is evidence that it is associated with the metabolic syndrome and as well as the its separate components [104,105]. There are a number of studies that have reported that increased plasma high-sensitivity CRP levels are associated with adverse cardiovascular disease outcomes, obesity and metabolic syndrome [105,106]. In a study conducted in The Netherlands of a population of 1,165 subjects with central obesity but without any previous diagnosis of cardiovascular disease, diabetes mellitus, dyslipidemia or hypertension (aged 20-70 years), median high-sensitivity CRP concentrations were statistically significantly in subjects with central obesity and metabolic syndrome compared with those without metabolic syndrome [104]. Similarly, in a cross-sectional study of 9,517 Indian subjects with 4,066 having metabolic syndrome (using the NECP ATP III criteria) median levels of high-sensitivity CRP was higher in those persons with metabolic syndrome, with higher levels in females than males [107]. In a latter study of200 Iranian middle aged females with BMI ≥25 kg/m^2, serum high-sensitivity CRP was found to be associated with triglycerides total cholesterol, BMI, waist circumference and body fat mass [108].

Interleukin 6 (IL-6), pro-inflammatory cytokine is expressed in human adipose tissue, which produces approximately 25% of the systemic interleukin 6 *in vivo* [109]. Interleukin 6 has inflammatory properties which include the stimulation of the production of acute phase in the liver and its release may induce low-grade systemic inflammation in obese persons [110]. In a study of a cohort of 677 young and middle-aged overweight/obese and age-matched normal weight individuals, interleukin 6 levels were significantly elevated in the overweight/obese group. Significantly higher levels of interleukin 6 were observed in obese subjects compared with their overweight counterparts, and also in subjects with metabolic syndrome [111]. Similarly, elevated levels of serum interleukin 6 and CRP were observed in 40 obese (mean age 35.8 years) [112]. Other studies have reported a significantly positive correlation between serum interleukin 6 levels and BMI, waist circumference and visceral fat layer in 108 overweight or obese postmenopausal females [113]; and interleukin 6 was significantly associated with BMI, waist-hip ratio circumference and waist circumference in 100 Korean obese subjects [114]. However, in a study of 10 obese and 13 normal weight males, there was no significant difference in interleukin 6 concentrations in both groups [115].

Isoprostanes (IsoPs) of which several isoforms have been identified is one of the most accurate *in vivo* biomarker of systemic oxidative injury [116]. It is formed of in a non-enzymatic manner involving free radical-mediated lipid peroxidation of arachidonic acid [117,118]. Increased levels of F2-IsoPs have been found patients with cardiovascular disease as well as those with atherosclerotic plaques [119,120]. Studies have reported that adults with elevated levels of proatherogenic LDL-cholesterol have approximately 2-fold higher levels of IsoPs compared with aged matched controls [121,122].

Isoprostanes are a marker of oxidant stress and atherosclerotic risk, and a number of studies have reported elevated levels in obese children and adults and those with metabolic syndrome. In a cross-sectional study of 233 subjects (mean age 42.56 years; BMI 25.78 kg/m^2), plasma F2-IsoPs was significantly associated with CRP and systolic blood pressure, and increased with BMI [123]. Similarly, in a case-controlled study of 30 individuals with metabolic syndrome and matched controls, plasma and urinary and F(2)-IsoPs were significantly elevated in participants with metabolic syndrome [124]. There was a 32% F2-IsoP elevation in a group of 133 peri-pubertal children (55 obese and 15 overweight) which suggest excessive peroxidation of lipid and future risk of cardiovascular events [125].

A reduction in cardiovascular risk factors is associated with a decrease in IsoP formation in humans [126]. In a 6-month, randomized, double-blind, placebo-controlled trial involving 80 overweight subjects (60 females and 20 males, BMI >27 kg/m^2), plasma 8-isoprostane concentrations significantly decreased due to vitamin E supplementation during the period [127].

CONCLUSION

apid changes are occurring in economic, nutritional, social and lifestyle aspect in both developed and developing countries. Based on the studies discussed in this review, it is clear that obesity is a public health problem of increasing importance as there are increasing trends of overweight and obesity among children and adults in many populations. Rising prevalence of childhood obesity will result in an increase in incidence and an earlier onset of coronary artery disease, negative impact on the social, psychosocial, and physical well-being of children and adolescents in the coming decades as well as on the cost of health care, national economies and life expectancy.

There is evidence that obesity in childhood is associated with

noticeably morbidities, which not only have immediate impact on the physical health of the obese children, but also significantly elevate the risk of morbidities in adulthood. One of the major morbidity and mortality factors in obese adults with hypertension and dyslipidemia is macroangiopathy and CIMT is a non-invasive marker of early atherosclerotic changes. As highlighted in this review, increased CIMT has been reported in obese children and adults and is related to both dyslipidemia and hyperglycaemia, and there is usually a strong association between CIMT and the parameters of metabolic syndrome. A reduction in morbidity and mortality among obese subjects due to the reversibility of the early atherosclerotic changes could be achieved if there is effective therapy of cardiovascular risk factors.

In order to combat the rising trends of childhood and adult obesity there is the need for the effective implementation of comprehensive, multi-level and multi-sectoral policies that are well coordinated with well-defined goals of changing eating patterns and encouraging physical activity among children and adults so as to reduce the prevalence of overweight and obesity, and the prevention of chronic diseases. Population-based strategies should be community-based and include treatment modalities including psychological counselling, behavioural modification, and pharmacological therapies which should be ongoing, supportive and multi-disciplinary. Future studies are needed to determine whether treatment intervention of dyslipidemia early in life is beneficial and prevents cardiovascular disease in adulthood.

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