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Review Article

Biochemistry Section

Endothelial Dysfunction in Obese Children

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ABSTRACT

The magnitude of lifetime risk of cardiovascular disease (CVD) has radically increased along with the high prevalence of obesity in children. The risk factors emerge quite early in the clinical course of obesity, which might have important consequences for the development of atherosclerosis later in life. Endothelial dysfunction represents a key early step in the development of atherosclerosis and is also involved in plaque progression and the occurrence of atherosclerotic complications. Endothelial changes are known to commence in childhood and are present in severely obese children. In endothelial dysfunction, there is a reduction in the bio-availability of vasodilators whereas endothelial derived contracting factors are increased; aside from that there is a state of 'Endothelial activation' that favors all stages of atherogenesis. Insulin resistance and the presence of a proinflammatory state are two likely mechanisms that link obesity to endothelial dysfunction. Endothelial dysfunction is a reversible disorder, pharmacological and non pharmacological interventions can reverse the changes. Weight loss leads to an attenuation of the pro-inflammatory state and the physical exercise increases the synthesis and release of nitric oxide, which leads to augmented flow-mediated dilation and improvement in endothelial function. These changes are consistent with a decreased risk of atherosclerotic progression and reduced risk of cardiovascular disease in obese children.

Obesity is associated with both endothelial dysfunction and increased risk of CVD. Measurement of endothelial dysfunction in children can predict the onset of atherosclerosis. Non pharmacological and pharmacological interventions targeting obesity can improve clinical cardiovascular outcomes in obese children.

Keywords: Atherosclerosis, Cardiovascular disease (CVD), Endothelial dysfunction, Endothelial activation, Insulin resistance, Nitric oxide, Obesity

INTRODUCTION

The increasing prevalence of medically significant childhood obesity raises great concern. Childhood obesity has more than doubled in children and tripled in adolescents in the past 30 years [1]. In 2010, more than one third of children and adolescents were overweight or obese [1].

Although body mass index (BMI) >25 indicates overweight and >30 defines obesity in adults, the diagnosis of overweight in children relies on age-adjusted percentiles [2]. The World Health Organization and U.S. Centers for Disease Control and Prevention, each have definitions of overweight and obesity in children and adolescents [Table/Fig-1]. At different ages, these criteria give somewhat different estimates of overweight and obesity prevalence [3-6]. The increased incidence of childhood obesity cannot be blamed on either environment or genetics alone. Several factors contribute to the obesity epidemic. The sustained excess of energy-dense foods, an increasingly sedentary lifestyle—attributed in part to urbanization, which limits the opportunities for physical activity, are the major causes of energy imbalance leading to childhood obesity.

The metabolic programming can occur as a result of in utero environmental exposures [7]. Small-for-gestational age babies have an increased incidence of adverse health outcomes later in life associated with insulin resistance, including type 2 diabetes, obesity, and cardiovascular disease. Some instances of severe, early-onset, morbid obesity may result from defects in genes encoding adipose-derived hormones such as leptin, neuropeptides such as proopiomelanocortin, cocaine- and amphetamine-regulated transcript (CART), and melanocortin-4, or the receptors for these ligands [8].

Organization	Definition of Childhood Obesity
World Health Organization	**WHO Child Growth Standards (birth to age 5) [3]** • Obese: Body mass index (BMI) > 3 standard deviations above the WHO growth standard median • Overweight: BMI > 2 standard deviations above the WHO growth standard median • Underweight: BMI < 2 standard deviations below the WHO growth standard median **WHO Reference 2007 (ages 5 to 19) [4]** • Obese: Body mass index (BMI) > 2 standard deviations above the WHO growth standard median • Overweight: BMI > 1 standard deviation above the WHO growth standard median • Underweight: BMI < 2 standard deviations below the WHO growth standard median
U.S. Centers for Disease Control and Prevention	**CDC Growth Charts [5]** In children ages 2 to 19, BMI is assessed by age- and sex-specific percentiles: • Obese: BMI ? 95th percentile • Overweight: BMI ? 85th and < 95th percentile • Normal weight: BMI ? 5th and < 85th percentile • Underweight: BMI < 5th percentile In children from birth to age 2, the CDC uses a modified version of the WHO criteria [6]

[Table/Fig-1]: Childhood obesity definition [3-6]

S.No.	Organ System	Implications
1)	Cardiovascular	a) Hypertension
		b) Dyslipidemia
		c) Endothelial dysfunction
		d) Ischemic heart disease
		e) Left ventricular hypertrophy
		f) Increased Carotid artery stiffness
		g) Increased carotid artery intima media thickness
2)	Endocrinal	a) Impaired glucose tolerance
		b) Insulin resistance
		c) Diabetes mellitus
		d) Metabolic syndrome
		e) Early puberty
		f) Early menarche
3)	Respiratory	a) Sleep apneas
		b) Obesity hypoventilation syndrome
		c) Bronchial asthma
4)	Gastrointestinal	a) Non alcoholic fatty liver disease
		b) Cholelithiasis
5)	Skin	a) Furunculosis
		b) Intertrigo
6)	Psychosocial	a) Poor self esteem
		b) Distorted peer relationships
		c) Anxiety
		d) Depression

[Table/Fig-2]: The clustering of obesity induced cardiovascular risk factors in childhood can explain the increased risk of adult coronary heart disease [10]

IMPLICATIONS OF CHILDHOOD OBESITY

Obesity is associated with an increase in mortality, with a 50–100% increased risk of death mostly due to cardiovascular causes. Although the data in childhood are less exhaustive, about 60% of overweight 5 to10-year-old children are reported to have at least one associated cardiovascular risk factor, and 25% have two or more [9]. The important implications of childhood obesity [10] have been highlighted in [Table/Fig-2]. It has been recognized that the risk factors emerge quite early in the clinical course of obesity, which might have important consequences for development of atherosclerosis later in life.

Increase in body mass index (BMI), an indicator of general obesity, is often an independent risk factor for the development of elevated blood pressure, clustering of various cardiovascular risk factors in metabolic syndrome, abnormal vascular wall thickness, endothelial dysfunction and left ventricular hypertrophy [11]. Baker et al., reported the association between BMI in childhood (7 to 13 years of age) and coronary heart disease in adulthood (25 years or older) in a huge cohort of men and women in whom childhood BMI data were available [12]. The results of various studies have indicated that a deleterious alteration of endothelial physiology, also referred to as endothelial dysfunction, represents a key early step in the development of atherosclerosis and is also involved in plaque progression and the occurrence of atherosclerotic complications [13]. Endothelial changes are known to commence in childhood [14,15] and are present in severely obese children [15]. Diabetes mellitus, hypercholesterolemia, and arterial hypertension have all been shown to promote atherosclerosis by their cumulative effects on the vascular endothelium.

FUNCTION OF ENDOTHELIUM

Endothelium is no more considered an inert lining of the blood vessels; it is actually a highly specialized, metabolically

S.No.	Function	Examples of biomolecules
1	Vasodilators	Nitric oxide
		Bradykinin
		Prostacyclins
		Endothelium-derived hyperpolarizing factor
		Histamine
		Substance P
		Serotonin
2	Vasoconstrictors	Angiotensin II (AII)
		Thrombin
		Serotonin
		Prostaglandin H2
		Arachidonic acid
		Endothelin (ET-1)
		Thromboxane A2
3	Growth Promoters	Platelet derived growth factor (PDGF)
		Basic fibroblast growth factor (PGF)
		Insulin-like growth factor – I (IGF-I)
		Endothelin (ET1)
		Angiotensin
4	Growth Inhibitors	Nitric oxide
		Transforming growth factor I (TGFB)
		Prostacyclins
		Bradykinin
		Heparin sulfate
5	Adhesion molecules	Endothelial leukocyte adhesion molecule; (ICAM)
		Intercellular adhesion molecule
		Vascular cell adhesion molecule (VCAM)
6	Thrombolytic factors	Tissue-type plasminogen activator
		Thrombomodulin
		Plasminogen activator inhibitor-1 (PAI-I)

[Table/Fig-3]: The vascular homeostasis is maintained by endothelium derived biomolecules [16]

active interface between blood and the underlying tissues. The endothelium plays a vital role in vascular homeostasis, vascular tone regulation, vascular smooth cell proliferation, trans endothelial leukocyte migration, thrombosis and thrombolytic balance. In response to various mechanical and chemical stimuli, endothelial cells synthesize and release a large number of vasoactive substances, growth modulators and other factors that mediate these functions [16]. [Table/Fig-3] depicts the details of the biomolecules release by endothelium to maintain the vascular homeostasis [16].

ROLE OF NITRIC OXIDE

The most critical of the substances released by endothelium is nitric oxide (NO). Like other vasodilators, NO exerts its effect on the vascular smooth muscle by activating soluble guanylate cyclase to produce cyclic Guanosine monophosphate (cGMP), which is the intracellular second messenger of NO [17]. Shear stress and/or acetylcholine stimulate the release of NO from endothelial cells [18]. There is a well-established relationship between reactive oxygen species (ROS) and NO. NO has a direct effect on oxidative stress by scavenging ROS, and NO inactivation is enhanced in the presence of excess ROS [19].

NO not only regulates vascular tone, it also has a key "antiatherogenic" role with the regulation of vascular permeability, the inhibition of platelet adhesion/aggregation, leukocyte/wall interaction, and smooth muscle proliferation [20]. These biologic actions of NO make it an important component in the endogenous defense against vascular injury, inflammation, and thrombosis, which are all key events in the progression of atherosclerosis [21].

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction can be defined as, "the partial or complete loss of balance between vasoconstrictors and vasodilators, growth promoting and growth inhibiting factors, proatherogenic and anti-atherogenic factors" [22]. In endothelial dysfunction, there is reduction in the bio-availability of vasodilators, in particular, nitric oxide (NO), whereas endothelial derived contracting factors are increased [23]. Endothelial dysfunction, aside from denoting impaired endothelium dependent vasodilatation, also comprises a specific state of 'Endothelial activation' which is characterized by a pro-inflammatory, proliferative and procoagulatory milieu that favors all stages of atherogenesis [19]. It is thought that disruption of the functional integrity of the vascular endothelium plays an integral role in all stages of atherogenesis ranging from lesion initiation to plaque rupture.

Obesity is associated with both endothelial dysfunction and increased risk of CVD in adults; therefore it is hypothesized that a similar relationship can be found between these variables in children. It is suggested that programming effects and the classical cardiovascular risk factors such as obesity, impair the endothelial function from as early as the first decade of life [20]. Thus, measurement of endothelial dysfunction in children can predict the onset of atherosclerosis without the need to follow to an age when clinical manifestations of CVD become apparent.

MECHANISM OF OBESITY INDUCED ENDOTHELIAL DYSFUNCTION

While the causes of endothelial dysfunction in obesity remain unclear and incompletely explored, insulin resistance and the presence of a proinflammatory state are two likely mechanisms linking obesity to endothelial dysfunction. Abnormalities in LDL characteristics, increased activity of the renin–angiotensin system and elevated concentrations of non esterified fatty

acids (NEFA) have all been implicated. However, the most compelling evidences are for insulin resistance, an effect of inflammation and/or elevated leptin concentration on the endothelium [24].

Several factors including visceral adiposity, physical inactivity and genetic factors contribute to the development of insulin resistance. Insulin resistance is associated with endothelial dysfunction and insulin sensitivity is inversely proportional to the development of atherosclerosis [25]. Petrie et al., showed a close positive relationship between insulin sensitivity and basal endothelial NO production [26]. Winkler et al., showed that increased levels of TNF-α may be one of the linking factors in the insulin resistance and endothelial dysfunction relationship [27].

As obesity is associated with features of acute-phase activation and low-grade inflammation, elevated levels of inflammatory markers such as fibrinogen, C-reactive protein and IL-6 might also affect vascular dysfunction. Furthermore, adipose tissue produces cytokine-like molecules such as leptin and TNF-α, collectively termed adipokines that could affect vascular function by their local and distant actions [28].

Various studies have shown that overweight children have higher CRP levels than normal weight children [29,30]. Fichtlscherer et al., showed that elevated CRP levels indicative of a systemic inflammatory response reflected blunted systemic endothelial function and normalization of CRP levels over time were associated with a significant improvement in endothelium-mediated blood flow responses [31].

IL-6 is a proinflammatory, endocrine cytokine that stimulates the production of acute-phase proteins, including CRP [29]. Within adipose tissue, both adipocytes and macrophages secrete IL-6, with roughly 30 percent of total production being initiated in the adipose tissue [32]. Production of IL-6 by adipose tissue increases with increasing adiposity, and circulating IL-6 concentrations are highly correlated with both percent body fat [33] and insulin resistance [34].

TNF-α, a proinflammatory cytokine has been shown to induce an impairment of endothelium-dependent vasodilatation in a variety of vascular beds by increasing oxidative stress and decreasing the release of NO [35]. TNF-α has a major role in adipose tissue and there is evidence of a three-fold increase in TNF-α mRNA protein and circulating levels in obese individuals [36]. Within adipose tissue, macrophages account for nearly all TNF-α production [32] and increased TNF- α expression has also been linked to the development of insulin resistance [27].

In an obese state, plasma concentrations of adiponectin are decreased [37]. Adiponectin plays an important role in the regulation of insulin action, and has been shown to be negatively correlated with insulin resistance [38]. In addition to its effect on glucose metabolism, adiponectin appears to modulate endothelial function. Adiponectin has been shown to stimulate production of NO and suppress adhesion molecule expression in vascular endothelial cells. In clinical studies in adults, hypoadiponectinemia has been found to be directly correlated with endothelial function of the peripheral arteries [39-41].

Leptin concentrations rise exponentially with increasing percentage body fat, and obese individuals have markedly increased leptin production, probably as a consequence of resistance to its actions. However, the widespread distribution of functioning leptin receptors on vascular cells and other cell populations and on atherosclerotic lesions suggests that leptin also plays an important role in vascular physiology [28].

Taken together, the status of endothelial function represents an integrated index of both the overall cardiovascular risk factor burden and the sum of all vasculoprotective factors in any given individual [42]. The presence of endothelial dysfunction can be regarded as a clinical syndrome that per se is associated with and predicts an increased rate of adverse cardiovascular events [43].

ASSESSMENT OF ENDOTHELIAL DYSFUNCTION

A common approach to the evaluation of endothelial function is the assessment of blood flow and vascular reactivity since the first description of endothelial dysfunction in atherosclerotic epicardial coronary arteries in 1986 by Ludmer et al., [44]. The consequences of an abnormal vasodilator response (i.e. impaired vasodilatation and even paradoxical vasoconstriction of coronary arteries upon the administration of acetylcholine) have thereafter been extensively studied. Epicardial and microvascular coronary endothelial dysfunction predicts CV events in patients with and without coronary artery disease [45]. Measurement of flow-mediated dilation (FMD) at the level of a large conduit artery, usually the brachial artery, has since then become the most applied technique [46]. Typically, ischemia is induced in the forearm or hand using a tourniquet inflated to above systolic pressure. Release of the tourniquet causes reactive hyperemia, an increase in blood flow through the brachial artery, and hence a release of NO. The resulting vasodilation is measured by continuous high-resolution ultrasound and the maximum vasodilation is expressed as a percentage of the baseline brachial arterial diameter [47]. Peripheral arterial tonometry was developed as a novel technique to overcome the disadvantages of user dependence of FMD. Invasive assessment of coronary endothelial function by quantitative coronary angiography and coronary Doppler flow measurements, along with graded intracoronary infusions of endothelium dependent vasodilators such as acetylcholine were considered the 'Gold standard' for endothelial function testing [47] but the invasive characters prohibit their use in healthy individuals and children.

Another approach is to measure levels of the members of endothelial activation, such as soluble vascular cell adhesion molecule (VCAM), soluble intracellular adhesion molecules (ICAM), Endothelin-I (ET-I) and other markers of coagulation and fibrinolysis such as PAI-I, Tissue plasminogen activator

or Von-Willebrand factors (VWP) and markers of low grade inflammation such as C-reactive proteins, IL-I, IL-6, and TNF-alpha [36].

The identification and quantification of circulating endothelial cells (CECs) has evolved as a novel marker of endothelial function. CECs appear to be a different population of cells to endothelial progenitor cells [48]. As a technique, it correlates with other markers of endothelial function such as flow-mediated dilation, the measurement of von Willebrand factor, and tissue plasminogen activator. Quantification of CECs is difficult due to low numbers, variable morphology, and a lack of standardization in current techniques used.

MANAGEMENT OF ENDOTHELIAL DYSFUNCTION IN OBESE CHILDREN

Endothelial dysfunction is a reversible disorder, pharmacological and non pharmacological interventions can reverse the changes.

Non pharmacological Interventions

a) Weight management- Weight loss leads to an improvement of CV risk factors associated with endothelial dysfunction in childhood obesity [49]. Weight loss leads to a reduction in the plasma levels of various adipocytokines, to an attenuation of the pro-inflammatory state, and to improvement in endothelial function [50].

b) Physical exercise- The increase in blood flow and shear stress that accompanies regular aerobic exercise elicits an adaptive response that alters the intrinsic responsiveness of the endothelium by increasing mRNA expression of eNOS. This in turn increases the synthesis and release of NO which leads to augmented flow-mediated dilation and ultimately improves endothelial function [51].

On top of increasing NO synthesis, exercise decreases production of ROS by reducing Nicotinamide Adenine Dinucleotide Phosphate (NAD (P) H) oxidase activity [52] and by enhancement of antioxidant capacity [53]. Other contributing mechanisms might include improvements in insulin sensitivity, proinflammatory cytokines, and/or lipoprotein profiles [54].

Watts et al., [55] reported that FMD was impaired in obese children, and the exercise was successful in improving the impairment. As little as eight weeks of exercise training consisting of three 1-hour sessions of circuit training each week led to a significant improvement in endothelial function, even without weight loss in a randomized cross-over study [55,56]. Two other studies, one involving endurance training and another applying aerobic interval training, confirmed the effect of exercise alone on endothelial function [56,57]

c) Dietary Interventions- It is not obesity itself that causes endothelial dysfunction but rather the hypercaloric high-fat diet that precedes the weight gain [2]. In obese adults (BMI 35±5), a low-calorie diet can significantly enhance flow-mediated brachial artery vasodilation by 60% and reduce body weight by 11% [58].

The pathological vasoreactivity in obesity is a complex multifactorial phenomenon. Increased serum levels of vasoconstrictive prostaglandins, proinflammatory cytokines, and adiponectin and changes in lipoproteins (elevated serum LDL and chylomicron remnants, lowered HDL) have all been implicated in its pathogenesis [2].

Although the mechanisms by which diet alone improves endothelial function remain far from being fully understood, evidence is accumulating that a combined reduction of LDL and other atherogenic lipoproteins, reduced rate of hyperglycemia, and lower oxidative stress are involved [59].

A combination of diet and exercise leads to a better improvement of endothelial function as contrast to diet alone [60]. Although results from several randomized controlled trials with dietary components are quite promising, effects need to be confirmed in larger population-based studies.

Pharmacological Interventions

Orlistat, a reversible blocker of lipase, is the only drug available to help weight loss. A meta-analysis of available data in children stated that the drug caused 5kg weight loss and 5cm reduction in waist circumference after at least six months of therapy compared with placebo, but failed to improve dyslipidemia and insulin levels [61]. Rimonabant and sibutramine, the other two drugs due the increased risk of psychiatric adverse events [62] and increased CV risk [63], respectively, have been withdrawn from the international market. Metformin significantly improves both endothelial function and insulin resistance in adults with metabolic syndrome [64] but the results are less satisfactory in children [65].

Given that increased oxidative stress plays a pivotal role in the pathogenesis of endothelial dysfunction, administration of antioxidants would be expected to be a reasonable strategy to treat this disorder. Supplementation with antioxidants such as Glutathione, N-acetyl cysteine, and vitamin C has been shown to reverse endothelial dysfunction in coronary and peripheral arteries [66]. LDL reduction by either diet or statin therapy has been related to improved endothelial function in previous intervention studies [59,67]. Although statin therapy has been effectively used to normalize endothelial dysfunction in children with familial hypercholesterolemia,[68] the consensus is that pharmacological interventions should not be the first choice to treat alimentary-induced hyperlipidemia and endothelial dysfunction in obesity [2].

The treatment of obesity remains difficult. Certain effective drug therapies have been withdrawn from the market because of dangerous cardiovascular effects, [69]. Nonpharmacological interventions such as low- calorie diet and physical exercise therefore represent the mainstays of obesity prevention and treatment.

CONCLUSION

Endothelial dysfunction is significantly associated with obesity in otherwise healthy, non-hypertensive and pre-pubertal children. Prevention of obesity or early management of

obesity can abate or reverse almost all of the cardiovascular consequences of obesity. Further studies are needed to identify surrogate markers of endothelial dysfunction to best assess, predict, and treat the children who are vulnerable to developing CVD.

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ABBREVIATIONS

BMI (Body mass index; CVD (cardiovascular disease) ; CV(cardiovascular); NO(nitric oxide); ROS (reactive oxygen species); NEFA(non esterified fatty acids) ; LDL(low density lipoprotein); CRP(c- reactive protein); IL-6 (interleukin-6); TNF-α(tumor necrosis factor-alpha); mRNA(messenger RNA); VCAM (vascular cell adhesion molecules); VWP (Von-Willebrand factors); PAI (plasminogen activator inhibitor).

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