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Role of obesity in inflammatory changes in atherosclerosis: A review

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Abstract
The prevalence of obesity has nearly doubled between 1980 and 2008, about 35% of world's adult population is overweight with BMI> 25 kg/m^2. The similar trend of increase in prevalence is seen in children; in 2013, 42 million children under age of 5 years were overweight or obese. Overweight and obesity are linked to more deaths than underweight (this includes all high income and middle income countries). With increase in adiposity due to weight gain, a low grade inflammation follows, which influences the insulin sensitivity, glucose metabolism and atherosclerosis leading to various disorders. In addition to obesity physical inactivity is also associated with increased level of inflammatory markers in lean, overweight and obese individuals. However the literature is inconsistent about the association between physical inactivity and inflammation is independent risk factor for increase in inflammatory markers. The purpose of this review is to find the relation between adiposity and low grade systemic inflammation and its impact of various disorders like endothelial dysfunction, atherosclerosis, insulin resistance which leads to various disorders and potential health implications. Here dearth of literature is presented to understand the interaction between obesity, physical inactivity on inflammatory markers, especially in children as their anthropometrics changes with age. This review highlights the need for further research for better understanding of the complexity of obesity, inflammation and health implications.

Keywords: IL-6, IL-8, TNF-α, CRP, Met S, FFA, HDL, LDL, MAPK, PAF, BMI, W/H, IL-1, SMC, ECM, MMP

Introduction
The prevalence of obesity in the pre-pubertal age group or pre-school children is increasing worldwide irrespective of ethnicity and region [1],where in 2008 35% adults above the age 20 years are found to be obese with BMI>25 kg/m [2]. While about 13% of world's adult population is obese (11% of men and 15% of women).In 2013 42 million children under age of 5 years were overweight or obese.

As in adults this growing trend of obesity in children is mainly due to less physical activity and high calorie diet intake [1, 2]. Obesity in childhood frequently is continued to adulthood and is the major contributor of adult obesity and leads to various disorders like endothelial dysfunction, cardiovascular diseases like coronary artery disease, atherosclerosis, metabolic complications like insulin resistance and diabetes, and long term vascular complications [2., 10].

In human body intra-abdominal fat is always considered clinically more relevant risk factor for development of various metabolic complications[16]. However the association between body fat distribution and risk of development of various associated diseases is not very clear [16]. From last decade various studies has shown that adipose tissue itself releases certain cytokines like interleukin-6(IL-6), interleukin-8(IL-8), tumor necrosis factor-alpha(TNF-α), plasminogen activator inhibitor-1(PAI-1), leptin and adiponectin all of which may contribute significantly in development of increased adiposity and health complications [4].

The prevalence of above diseases and Metabolic Syndrome increases in direct proportion with severity of obesity and reaches up to 50% in severely obese youngsters [9].

Certain pleotrophic cytokines like IL-6, IL-8, C-Reactive Proteins, Tumor Necrosis Factor-α, plasminogen activator inhibitor-I (PAI-1) appears to be sequel of both endothelial dysfunction and related diseases like Metabolic Syndromes [10].

Endothelial dysfunction can be defined as both, partial or complete loss of balance between vasoconstrictor and vasodilator activity, pro-atherogenic and anti-atherogenic factors, pro-coagulant and anti coagulant factors, growth promoting and inhibiting factors. It plays an early pivotal role in atherogenesis, and precedes the clinically detectable atherosclerotic plaque formation and cardiovascular diseases. It also plays important role in micro-vascular complication in Diabetes Mellitus [11].

Inflammation is one of the pathways precluding endothelial dysfunction and atherogenesis, inflammatory marker like IL-6, IL-8, CRP, TNF-α are having direct effect on above pathway and have been shown to damage the innermost intimal layer of endothelium stimulating atherosclerotic lesions that causes hypertension and thrombosis [11]. Inflammatory markers have impact on metabolic control by negatively influencing insulin sensitivity, glucose uptake and transport. TNF-α, IL-6 and CRP are the predictors for type-2 diabetes, metabolic diseases and cardiovascular diseases. Also two prospective studies of large natural cohorts with healthy female individuals have shown that inflammatory markers are predictors of type-2 diabetes. IL-6 is potent stimulus for production of CRP in liver, which have some direct deleterious effect in vascular wall. CRP and TNF-α is considered as an excellent marker of low grade inflammation

in the vascular wall, which is a well recognized mechanism in development of atherosclerosis and cascades of events [11, 12].
Compared with lean and non obese individuals, obese showed increased levels of inflammatory markers separately in few studies only and thus positively correlated with Body Mass Index (BMI), body fat, waist circumference, Hs-CRP, IL-6. Whereas in some studies IL-6 was found to be positively correlated with CRP and TNF-α [11].
Most studies examining obesity and inflammatory markers in children used BMI and waist hip circumference which was strongly related to elevated CRP, TNF-α and IL-6 levels, with its association found in as young as three years of age in children. Centripetal obesity has been more strongly associated with adult cardiovascular disease and diabetes risk even in subjects who are simply overweight by BMI, the mechanism underlying this association is unknown and may relate to the fact that intra-abdominal adipocytes are more lipolytically active than those from other depots [12, 13].
HsCRP, IL-6, IL-1, TNF-α are acute-phase reactant proteins, produced exclusively by the liver in response to inflammatory cytokines [14, 15]. Also published evidences associates it with the development of cardiovascular events considering it therefore as an important determinant of atherosclerotic changes [14].
For assessment of obesity BMI is considered most often due to its simplicity and understanding. BMI for the midpoint of all heights and frames among both men and women of all age groups and ethnicity ranges between 19-26 kg/m [16, 17]; at similar BMI women predisposes more for body fat than men[16]. Further depending upon on the data of substantial morbidity, a BMI of 30 is considered as a threshold for obesity in both males and females all over the world in adults but no clear cut off point is devised for children [16]. WHO says BMI equal or greater than 25 is overweight and BMI greater or equivalent to 30 is obese. BMI is considered as crude not an accurate method to determine obesity as it may not correspond to same degree of fatness in different individual. Morbidity as it tends to rise even though at slower rate when BMI is more than >25, suggesting that cutoff of obesity should be lowered accordingly, whereas other specific measurement like DEXA scan is associated with high cost and radiation exposure making it less assessable [18].
Except BMI there are other approaches to quantify obesity like anthropometric measurements, waist circumference, body density assessment by DEXA scan, skin fold thickness and waist hip circumference ratio [19]. This distinction of obesity is made by the waist-hip circumference ratio, indicating a ratio of >0.9 in females and >1.0 in males being abnormal and predisposing [16, 19].

Obesity, atherogenic dyslipidemia and MetS

High serum cholesterol has been acknowledged as being a major risk factor for coronary heart disease (CHD). As much of the serum cholesterol is transported by LDL, most people with high serum cholesterol also have elevated LDL. The National Cholesterol Education Program (NCEP) specifically targeted LDL cholesterol as the chief goal of cholesterol-lowering therapy [20, 23].
Statin (HMG CoA reductase inhibitors) therapy has produced marked reductions in new coronary events; these reductions almost definitely were connected to decreases in LDL levels [24, 25]. Strong evidence also indicates that high LDL concentrations initiate atherogenesis and promote atherosclerosis [26]. A strong link between increased abdominal (visceral) fat and hyperinsulinemia, insulin resistance, elevated plasma free fatty acid (FFA) levels, hypertension, predisposition to thrombosis, hypertriglyceridemia, small dense LDL particles, and reduced HDL has been established [27, 28]. Elevated LDL cholesterol is not a feature of the dyslipidemia seen with abdominal obesity. Other features of the dyslipidemia of abdominal adiposity include elevated very low density lipoproteins (VLDL), and reduced HDL, which are the large buoyant anti atherogenic subspecies of total HDL. In some individuals, apo B levels may be elevated, reflecting an increase in the number of small, dense lipoprotein particles (VLDL and LDL) [27].

Obesity and Inflammation

C-reactive protein

C-reactive protein is a well-known unspecific marker of inflammation and tissue damage. It is a part of a molecular family called acute phase reactants made by the liver cells. Inflammation and tissue injury is followed by the acute phase response, a group of physiological processes that occur soon after the onset of trauma, infection, inflammatory processes and other non-physiological states. The acute phase response comprises several factors like fever and increased vascular permeability. It also includes a change in the concentration of acute phase reactants in the serum.
C-reactive protein is a well-known marker of inflammation and tissue damage, although its function has not yet been fully established. Its rapid response shows that it is a part of the innate immune system. It is one of many known acute phase reactants produced by the hepatocytes. Acute phase reactants are proteins whose serum concentrations increase or decrease at least 25% during inflammatory states. Changes in the levels of these proteins are influenced by inflammatory molecules called cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha). During inflammatory processes cytokines are mainly produced by immune cells like monocytes and macrophages, but can also be produced by other cells, such as fat cells. Despite being called acute phase reactants they not only accompany acute inflammatory conditions, but also chronic inflammatory states (metabolic syndrome) [29]. The signs of acute inflammation are missing in obesity and the acute-phase response is only minor. It seems that the purpose of low-grade inflammation is to restore homeostasis in times of metabolic stress, and not to fight infection or clear necrotic cells as is the case with acute inflammation. This appears to be the basis for low-grade inflammation as seen in obesity [30]. CRP is synthesized by hepatocytes in response to inflammatory processes. It is up-regulated by cytokines, IL-6 being the chief stimulator of CRP production [32]. In healthy individuals the levels of CRP are seldom above 5 mg/L, with medians values ranging from 0.9 mg/L – 2.05 mg/L in different studies[33]. High plasma concentrations are seen 6-12 hours after the initiation of a disease process, and it may increase several hundred-fold. It has a half-life of 15-25 hours, so its concentration falls fast as the healing progresses. C-reactive protein is commonly used

to differentiate between bacterial and viral infection [34]. Higher values are seen in diseases characterized by cell necrosis, and values above 40 mg/L may suggest bacterial infection. It is a stable molecule and can easily be measured in laboratory. It increases in relation with IL-6 and TNF-α and upregulated in obese [35, 36].

Early development and progression of atheroclerotic lesion

Maturing Monocytes become tissue macrophages and express scavenger receptor such as SR-A, CD-36 and importantly LDL receptor (LOX-1) [39]. LOX-1 is particularly important as it allows phagocytosis of modified LDL and providing that blood lipid levels remain high, the macrophages gorge themselves and become lipid laden "foam cells" [40, 41]. The fatty acid streaks develop as more monocytes arrive and mature in the pro-inflammatory cytokine network.

Angiotensin-II produced by the activated endothelium is a vasoconstrictor that opposes nitrous oxide (NO action). NO normally regulates Angiotensin-II production, although this feedback is disturbed during endothelial dysfunction. This molecule may be important in initial development of pro-inflammatory local cytokine network through its action on smooth muscle cells(SMCs) which also produces IL-6 and hence initiate the systemic acute phase response (APR), through hepatocyte activation as IL-6 is primary APR secreted by hepatocytes [42].

IL-6 also acts in Autocrine manner to further activate the local SMCs [43], which then proliferates [44, 45]. SMCs control the maintenance of extra-cellular matrix (ECM) through collagen production[46]. Which is normally offset by matrix turn over and is mediated by matrix mettaloproteinases (MMPs) [47]. The MMPs are the family of Zinc atom containing endopeptidases, consisting of collagenases, gelatinases and stomylesins. Degradatative turnover of ECM is controlled both by collagen production and tissue inhibition of MMPs both of which are produced by SMCs [48]. Disturbance of matrix hemostasis is a major cause of vascular pathology. In this way the plaque becomes more lipid laden and cellular, but in the early stages formation matrix deposition by proliferating SMCs provide mechanical support for increasing complex structure of lesion, which is also contributing to luminal occlusion.

Inflammatory risk markers

As the aforementioned role of inflammation in atherogenesis would suggest, a great deal of work has been done looking for the inflammatory markers that are risk factors for CVD [49]. The most extensively examined markers are fibrinogen, C-Reactive proteins (CRP), white cell count (WCC) and IL-6. All of these markers are APR associated, and hence the circulating levels reflect the current inflammatory state of the individual. WCC and CRP being the routine clinical measure of inflammation, they have been epidemiologically studied to examine the hypothesis "Elevated baseline inflammation predicts risk in CVD". Meta Analysis of prospective studies in general healthy population has shown that WCC[50], CRP[51] and fibrinogen [52] are the risk predictors of CVD. CRP level measurement have been suggested to add established risk factor for individual risk prediction for cardiovascular prevention in USA [53].

The conference that debated this decision in USA assessed several potential inflammatory markers like IL-6, IL-8, TNF-α, MMP-9 and fibrinogen to be added to Framingham Risk Assessment. The criteria for marker consideration include:

1. The ability to standardize the assay and to control the variability of the measurement.
2. Independence from established risk factors.
3. Association with CVD clinical end points in observational studies and clinical trials.
4. Presence of population norms to guide interpretation of results.
5. Ability to improve the overall prediction beyond that of traditional risk factors.
6. Generalization of result to various population groups.
7. Acceptable cast of assay [54].

Therefore from the above studies it was predicted that CRP was the best marker for predicting the CVD. However other markers like IL-6, fibrinogen was also recommended which has to be further assayed for its individual potential.

IL-6 and CVD risk

The literature therefore appears to confirm that both CRP and Fibrinogen are the markers of CVD risk. Since both of these inflammatory markers are proteins of APR, it stands the reason that stimulation of APR may also be the risk factor, though at very last due to indirect association with APR. In this regard the pro-inflammatory cytokine IL-6 has been extensively examined.

IL-6 is a 26 kDa cytokine mainly produced by the endothelial cells, macrophages, adipocytes and lymphocytes [54, 55]. As mentioned previously IL-6 is implicated as pivotal APR inducing cytokine. In addition to its role in APR it is thought to stimulate hemostasis and influence T and B cell differentiation[56]. It stimulates the endothelial cells to produce chemokines in complex with soluble IL-6 receptors SIL-6R [57] and plays a role in transition between acute and chronic inflammatory response and activation of endothelial SMCs [58].

Activation of endothelium begins the process of localized inflammation, allowing leukocyte extravasations through selectins and integrins production. The selectins weakly binds Lewi X-Antigen on surface of leukocyte allowing "rolling" along the surface of endothelial barriers. This expression is not uniform and is patchy in appearance and subsequent Fatty Streaks develop [59].

This probably reflects the areas of low shear stress and flow turbulence, hence disturbing the integrity of endothelium sufficiently for lipids to migrate through the intima. The same hemodynamic stress may cause the rupture of more complex plaques and intensify the complication of atherosclerosis.

Maturing monocyte underlying the tunica intima expresses cytokines like TNF-α which also helps to initiate and perpetuates the immune response and endothelial activation. Chemokines such as IL-8 and monocyte chemoattractant protein (MCP-1) allows recruitment of monocyte to areas of concentrated inflammation [60]. As explained the maturing monocyte becomes macrophages and expresses scavenger receptor such as SR-A, CD-36 and LDL receptors and allows

the phagocytosis of LDL and make them "lipid laden" "foam cells" causing atherosclerosis and development of risk for CVD.

In chronically hyperlipidemic condition like obesity due to the low grade systemic inflammation and recruitment of Macrophages which is stimulated by the APR proteins like IL-6, CRP, TNF-α the vasculature is exposed to LDL cholesterol, which penetrates the endothelial cell layer around the areas of lower shear stress and moves into the intima, and under oxidizing condition forms oxidized LDL (ox LDL) [61]. This modified lipoproteins can bind to the endothelium and causes increase in the superoxide production, at the expense of lowering vascular concentration of NO, resulting in endothelial activation [62] and vasoconstriction and further endothelial dysfunction.

TNF-α role in inflammation

TNF-α is now recognized as being the pluripotent cytokine and the mechanism of many of its biological activities are still not clearly understood. Burns *et al* reported regression of tumor in humans following some bacterial infections [63]. It was demonstrated that these effects were caused by an inducible serum factor mediator, concomitantly named Tumor Necrotizing Factor[64] which was later renamed as Tumor Necrosis Factor (TNF) [65].TNF-α seems to be capable of inducing diverse at times contra-indicatory physiological effects depending upon the experimental settings. It is known that TNF-α can cause apoptosis, septic shock, inflammation and cachexia systemically [66].Yet in contrast it can induce growth through mitosis, it immunologically protects the host and may also induce obesity by metabolic mechanisms [67].

The TNF-α and TNF-β genes are single copy genes located on the short arm of human chromosome 6 near the MHC Region. TNF-α is produced by the neutrophils, activated T Cells and B cells, NK cells, macrophages, astrocytes, SMCs, endothelial cells, Adipose tissue and some transformed cells. Whereas,TNF-β is restricted to the production by lymphocytes [68].

Human TNF-α is a polypeptide of 157 amino acids [68] and the biologically active form of TNF-α has homotrimeric structure that is hallmark of TNF superfamily [69]. TNF-α unlike the TNF-β has no signal peptide sequence containing hydrophilic and hydrophobic domains. It is hence expressed in membrane bound forms initially [70] and is biologically active in this form, physiologically acting in the lytic manner [71]. It is currently thought that it is membrane bound and proteolytically cleaved by TNF-α converting enzyme proteases (TACE).

Most inflammatory settings result in early upregulation of TNF-α production which help establish an innate immune response. In the acute stages of inflammation TNF-α is known largely to regulate itself in autocrine fashion [72], although it also induce the specific negative regulatory elements to maintain tight control of its production [73]. TNF-α also initiates the production of many cytokines like IL-8, IL-6, IL-1 [74].

There is strong evidence for role of TNF-α in the development of atherosclerosis. Circulating TNF-α is present in the vasculature at baseline in all individuals, although it does increase with age [75] and the blood vessels themselves produces increased level of TNF-α in response to stimulation as seen in mice model [76]. TNF-α is also detected in many human atheromas [77]. It is produced in human atherosclerotic lesion primarily by the macrophages/foam cells activated T cells, smooth muscle cells (SMCs), endothelial cells [78, 79, 80]. TNF-α has the potential to promote the cellular infiltration to the plaques by endothelial activation [81] and may induce endothelial dysfunction [82]. It also promote the production of other cytokines [83] and promote the angiogenesis [84]. This is the main pro-atherogenic effect of TNF-α.

IL-8 and its role in inflammatory changes and atherosclerosis

IL-8 is a chemokine produced by macrophages and other cell types such as epithelial cells, airway smooth muscle cells, endothelial cell, macrophages, hepatocytes [85]. Endothelial cells store IL-8 in their storage vesicles, the Weibel-Palade bodies [86, 87]. In humans, the interleukin-8 protein is encoded by the IL8 gene[88]. IL-8 is a member of CXC chemokine family.

It is known as neutrophil chemotactic factor and has two primary functions, causing chemotaxis in the target cells primarily neutrophil and also ganulocytes, this causes migration towards the site of inflammation and leads to phagocytosis of the antigen. Other role of IL-8 is angiogenesis, intracellular calcium exocytosis, immune response and endothelial activation and allowing the recruitment of mature monocytes at the site of inflammation [89]. Further these monocytes underlying the tunica intima expresses cytokines such as TNF-α and IL-8 which help and initiate immune response and endothelial activation. Chemokines such as IL-8 and monocyte chemoattractant protein (MMP-1) allows recruitment of monocyte to area of concentrated inflammation [89].

Activation of endothelium begins the process of localized inflammation allowing leukocyte extravasation through selectins and integrins production and rapid externalization of Weibel-Palade bodies and result in P-selectins and E-selectin expression on the endothelial surface [90]. These selectins weakly binds to the Lewi-X Antigen on the surface of leukocyte allowing the rolling along the surface of endothelial barriers. Endothelial expression of Integrins such as VCAM-1 (Vasular cellular adhesion molecule) allows arresting of MAC-1 (CD-18/CD-116) and expressing monocyte which then extravasate into tunica intima underlying the endothelium[25] and recruitment of lipid laden foam cells at the area of inflammation leading to formation of atherosclerotic plaque. In the above process presence of excess of LDL and inflammation is pre-requisite as seen in obesity [91].

The expression of VCAM-1 is not uniform and is patchy in appearance and subsequently fatty streaks and plaque forms which is not uniform all over the endothelial surface as it is expected and form patch plaques in the area of bifurcation of arteries [92]. This also reflects the area of low shear stress and flow turbulence, hence disturbing the integrity of vascular endothelium sufficiently for lipid to migrate through the intima. Accordingly same hemodynamic stress may ultimately cause the rupture of more complex plaques and development of acute vascular complication in cardiovascular disorders.

Physical activity and inflammatory marker levels

Physical activity was found to be inversely related to CRP, IL-6 and TNF-α levels and remained even after the adjusting BMI, waist hip circumference ratio or body fat [93, 94, 101]. In adults moderate to vigorous physical activity was inversely related to CRP. In few studies it was also correlated with sitting time in women, with higher sitting time had higher level of inflammatory markers CRP and IL-6 [102]. It was therefore found to that lack of physical activity influences inflammatory marker with role of adiposity.It was found that obese unfit children had the highest level of IL-6 in all the groups. The obese fit children had similar comparable levels of IL-6 to fit and lean children [93].Various adult based studies have shown that increase in physical activity decreases the inflammatory marker for individuals with and without cardiovascular disorders [103, 105] and obesity [106, 108]. However the exercise studies involving children do not always shows the decrease in inflammatory marker also with uncertain uniformity [113, 115]. The variations may be attributable to change in anthropometric measurements with age and change in life style. So it can be said from these studies that the overall change in body composition rather than decrease in obesity is more important for decrease in inflammation [116]. The reason for inconclusiveness of the literature was due to lack of association between physical activity and inflammation independent of body fat mass

Conclusion

Obesity with its high prevalence worldwide is considered to be a complex epidemic with its causal role in metabolic, cardiovascular, endothelial and vascular complications. Low grade systemic inflammation that occurs with obesity is likely to have influence on insulin resistance, glucose metabolism and atherosclerosis. Due to increase incidence of obesity in children continuing obesity in adulthood, early identification of these markers and inclusion as diagnostic tool can help in early diagnosis and rehabilitation. One such intervention is increase in physical activity due to its relationship with decrease in inflammation. This review is a platform to highlight the role of obesity and sedentary life style in chronic low grade systemic inflammation leading to various disorders and draw insight into further research required to identify interaction between obesity, physical activities and systemic inflammation.

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