Review Article

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Obesity-related inflammation & cardiovascular disease: Efficacy of a yoga-based lifestyle intervention

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Obesity is a global health burden and its prevalence is increasing substantially due to changing lifestyle. Chronic adiposity is associated with metabolic imbalance leading to dyslipidaemia, diabetes, hypertension and cardiovascular diseases (CVD). Adipose tissue acts as an endocrine organ releasing several adipocytokines, and is associated with increased levels of tissue and circulating inflammatory biomolecules causing vascular inflammation and atherogenesis. Further, inflammation is also associated independently with obesity as well as CVD. Keeping this in view, it is possible that a reduction in weight may lead to a decrease in inflammation, resulting in CVD risk reduction, and better management of patients with CVD. Lifestyle intervention has been endorsed by several health authorities in prevention and management of chronic diseases. A yoga-based lifestyle intervention appears to be a promising option in reducing the risk for CVD as well as management of patients with CVD as it is simple to follow and cost-effective with high compliance. The efficacy of such lifestyle intervention programmes is multifaceted, and is achieved via reduction in weight, obesity-related inflammation and stress, thereby culminating into risk reduction towards several chronic diseases including CVD. In this review, the association between obesity-related inflammation and CVD, and the role of yoga-based lifestyle intervention in prevention and management of CVD are discussed.

Key words Cardiovascular disease - inflammation - obesity - yoga-based lifestyle intervention

Introduction

Obesity is defined as an excess accumulation of fat due to positive energy balance, resulting from energy intake that exceeds the energy expenditure[1], leading to adipocyte hypertrophy and hyperplasia, stress and inflammation within the adipose tissue. A recent study reported that the prevalence of adult overweight and obesity increased by 27.5 per cent with and number of overweight and obese individuals increasing from 857 million to 21 billion from 1980 to 2013[2]. Obesity is an independent predictor for risk of various metabolic diseases and also a predictor of disease progression and mortality[3]. Excessive fat alone can contribute to several metabolic and cardiovascular diseases (CVD)[4]. Various studies conducted in Indian population have shown an association of obesity, dyslipidaemia, vascular inflammation, and metabolic syndrome[5,6]. Further, Asians, particularly South Asians have a higher prevalence of CVD, which can be attributed to an increased adipocyte size[7], increased visceral adipose tissue[8], higher levels of leptin[9] and inflammatory

mediators[10]. Keeping this in view, the body mass index (BMI) cut-off values for Asians were revised, and set at a lower level for obesity as compared to that for Western population (Table I). Studies done in different parts of India suggest that cumulative prevalence of obesity ranges from 10 to 50 per cent in adults (18-64 yr), however, there was a large variability in prevalence owing to different methods and cut-off points for defining obesity[15]. A study by Ray *et al*[16] showed a high estimated prevalence of obesity in India, about 29.9 per cent even in young, physically active military subjects. This can be attributed to the improved socio-economic conditions, changing dietary habits and globalization of food market.

Therefore, it has been proposed that a modest weight-reduction will reduce the risk towards such chronic diseases including CVD[17]. For this risk reduction, a weight-loss of about 10-20 per cent of the initial body weight is recommended, which may be achieved through lifestyle interventions[14] which have shown efficacy in weight-loss, resulting in CVD risk reduction[15]. Yoga is one such intervention that emphasizes on lifestyle modification and increased physical activity, and has been found to be efficacious in weight-loss and improvement of lipid profile in patients with coronary artery disease, diabetes and hypertension[20-22].

Obesity: a state of inflammation

Obesity is a state of low grade inflammation[23], which may later culminate in a chronic disorder if remains untreated many number of inflammatory mediators have been shown to be released by adipose tissue, which acts as an endocrine organ with autocrine regulation[24]. Leptin and adiponectin are primary adipocytokines which are synthesized in the adipose tissue itself[25]. Apart from leptin and adiponectin there are multiple adipocytokines which are upregulated in obesity such as interleukin-6 (IL-6), IL-1β, IL-10, tumour necrosis factor-α (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), plasminogen activator inhibitor- 1 (PAI-1), angiotensinogen-1, endothelin-1 (ET-1), visfatin, resistin, retinol binding protein-4 (RBP-4) and serum amyloid A (SAA)[26-29].

Inflammation can be both obesity- as well as disease-related. Obesity-related inflammation is a low grade inflammation associated with adipocytokines released from adipose tissue. In disease-related inflammation there is moderate to severe grade inflammation, and cytokines are site-specific[30]. Obesity related inflammation predisposes to a chronic inflammatory state which can culminate into various metabolic dysregulations, *e.g.* increased insulin resistance and endothelial dysfunction precipitating diabetes and CVD, respectively. In both obesity- as well as disease-related inflammation, cytokines are both contributors and sequelae[31]. The specific role of these adipocytokines in relation to pathophyisology of CVD is discussed here.

Adipokines: Leptin is a polypeptide hormone synthesized primarily in white adipose tissue and secreted in circulation. Classically, leptin is known for hypothalamic control of body weight and thermogenesis but in the last decade, its role in regulation of energy intake and energy expenditure has been well established[32]. Increased levels of leptin are known to be associated with elevated blood pressure and increased inflammation[33]. Adiponectin, another adipocytokine is exclusively expressed in adipose tissue, and the levels are negatively correlated with visceral fat[34]. Adiponectin levels tend to be lower in obesity along with increased levels of plasma interleukins[35]. Also, adiponectin is preventive not only against obesity but also against various metabolic disorders[36].

Endothelin (ET-1): ET-1 is the most potent vasoconstrictor peptide released by the endothelium, which plays a key role in the regulation of vascular tone and the aetiology of atherosclerosis. Endothelial function is shown to be impaired in overweight/obese women with elevated levels of ET-1[35]. Hyperinsulinaemia[37] and oxidative stress[38] stimulate

Table I. Body mass index cut-off values (in kg/m^2) for different populations

Population	References	Overweight	Obese
Global	World Health Organization (WHO)[11]	≥ 25	≥ 30
South Asians/Asians/Indians	International Association for the Study of Obesity (IASO), the International Obesity Task Force (IOTF) and the WHO proposed BMI cut-points[12-14]	23.0 to 24.9	≥25.0

ET-1 production, increasing its pathophysiological potential in obesity. Weil *et al* have demonstrated that overweight and obesity are associated with enhanced ET-1 levels in adiposity[39].

Cytokines: Two important cytokines implicated in obesity and its metabolic consequences are IL-6 and TNF-α. It has been shown that levels of IL-6 are increased in overweight men, though circulating levels of IL-6 are shown to be associated with visceral obesity, while TNF-α levels with overall obesity[40]. Serum IL-6 concentration was shown to be positively correlated with the level of obesity as assessed by BMI and adipocyte size[30], and total body fat percentage[41]. These findings suggested a possible role of adipose tissue in regulation of serum levels of IL-6[42], especially in individuals with central (visceral) obesity. Both IL-6 and TNF-α are known to impair adipocyte differentiation and promote inflammation[43]. Local production of TNF-α and IL-6 may ensue from epicardial adipose tissue[44], which is indicative of cardiac and visceral obesity and related to intima media thickness and increase in vascular stiffness[45]. IL-6 possesses both pro-inflammatory and anti-inflammatory effects and impacts both B-cell immunoglobulin production and T-cell cytotoxic activity. IL-6 also affects platelet production and reactivity, endothelial function, and induces synthesis of acute phase proteins in liver by increasing the levels of nuclear factor kappa beta (NFκβ) in a concentration-dependent manner[46]. TNF-α induces at least five different types of signals that include activation of NF-κB, apoptosis pathways, extracellular signal regulated kinase (ERK), p38 mitogen-activated protein kinase (p38MAPK), and c-Jun N-terminal kinase (JNK), playing a pivotal role in regulation of vascular functions. TNF-α along with neopterin, a biomolecule produced in monocyte/macrophages, increases expression of inducible nitric oxide synthase (iNOS), resulting in the production of cytotoxic radicals[47]. Neopterin has been found to be associated with cell-mediated immunity, and higher levels of neopterin have been reported in obesity[48].

In summary, obesity is a state of ongoing low to moderate grade inflammation, which is largely related to visceral adipose tissue wherein adipose tissue acts as a depot for several inflammatory cytokines such as IL-6 and TNF-α.

Inflammation and cardiovascular diseases

Accumulating data suggest that inflammation contributes to the causation and progression of CVD[49,50]. Further, inflammatory mediators may trigger rupture of the atherosclerotic plaque which may result in coronary thrombosis, and ischaemia[51]. The key triggers that have recently gained recognition include IL-6[52], fibrinogen[53], and C-reactive protein[54] all of which are now identified as independent predictors of coronary heart disease[55], and may serve as prospective novel biomarkers[56]. A practical framework for assessing the value of a novel risk marker and proposed standards with respect to critical appraisal of risk assessment methods that might be used clinically has been published by American Heart Association[57]. It has been shown that within the fatty streaks and atheromatous lesions, there is an overexpression of IL-6, which further strengthens its role in progression of atherosclerosis. Besides adipose tissue, IL-6 is locally produced in vascular endothelial and smooth muscle cells, and IL-6 gene is overtly expressed in human atherosclerotic lesions[58]. IL-6 stimulates monocytes and contributes towards deposition of fibrinogen in vessel wall and decreases lipoprotein lipase activity, which increases macrophage uptake of lipids. Additionally, circulating IL-6 stimulates the hypothalamic–pituitary–adrenal (HPA) axis, which is associated with central obesity, hypertension and insulin resistance[59]. In another study it has been demonstrated that plasma IL-6 levels ≥5 ng/ml are associated with a higher mortality than levels less than 5 ng/ml, suggesting that circulating IL-6 is a strong independent predictor of mortality in unstable coronary artery disease (CAD)[60]. TNF-α also plays an important role in endothelial dysfunction, and is implicated in heart failure[61]. It also causes vascular dysregulation, monocyte adhesion to endothelial cells, vascular oxidative stress, apoptosis, and atherogenic response, thereby resulting in thrombosis and coagulation through multiple signaling pathways[62].

Increased levels of leptin are shown to be associated with CVD, myocardial infarction and stroke[63]. This association can be explained by a positive correlation of leptin with CRP[64] and soluble IL-6 receptor (sIL-6R)[65], which supports its role in pathophysiology of atherosclerosis. Leptin is also known to stimulate vascular remodelling by enhancing profibrotic cytokines and proatherogenic lipoprotein lipase production, platelet aggregation, PAI-1 expression, thereby development of atherosclerosis[66]. Adiponectin, an important regulator of endothelial nitric oxide synthase, is also a key determinant of endothelial function and angiogenesis[67], and is known to oppose ET-1[68]. It has been suggested that hypoadiponaectinaemia is an independent risk factor

for hypertension[69], and promotes aortic stiffness[70]. Prospective relationship of adiponectin to vascular disease in a case-control series selected from the Strong Heart Study, the largest cardiovascular study of American Indians, suggested a relation between low plasma adiponectin and insulin resistance in causation of CAD[71]. Kaplan-Meir survival analysis showed a step-wise decrease in event free survival across quartiles of adiponectin baseline concentration, which indicated that the lower level of adiponectin was associated with an adverse outcome in CAD[72]. Such protective effects of adiponectin may be due to several factors such as antiapoptotic and angiogenic actions on the vasculature, blocking inflammation and foam cell formation from macrophages[73], and inhibiting oxidative stress[66]. Additionally, adiponectin also plays a protective role against cardiac ischaemic injury, hypertrophy, cardiomyopathy, and systolic dysfunction[74].

Endothelins are primarily produced in the endothelium with a key role in vascular homeostasis, and are implicated in vascular diseases in various organs[75]. In an initial study it was observed that plasma levels of ET-1 were significantly higher in patients with symptomatic atherosclerosis as compared to control subjects, thereby suggesting that ET-1 could be a marker of arterial vascular disease[76]. Results from another study demonstrated that the plasma ET-1 levels were raised in patients with CAD, and possibly acted as a marker of risk of rapid stenosis progression[77]. A recent study has shown that plasma endothelin-1 level is a predictor of 10-year mortality in a general population[78]. It has been shown that adiponectin opposes endothelin-1 (ET-1)[68] while leptin upregulates ET-1[79,80]. An enhanced vascular activity of ET-1 was observed in the obese hypertensive and overweight subjects but not in lean hypertensive subjects[81]. Since the levels of ET-1 are increased in overweight and obese subjects and inhibit adiponectin secretion[82], it is likely to cause endothelial vasodilator dysfunction and hence may play a role in the increased prevalence of hypertension with increased adiposity[39].

Overall, a rise in plasma levels of these mediators induces release of various adhesion molecules, fibrinogen and PAI-1 causing hypercoagulability of blood. Apart from this, adipose tissue also releases esterified fatty acids, which in turn increase the concentration of LDL- cholesterol. Increased LDL cholesterol gets oxidized and engulfed by macrophages, which may lead to increased release of cytokines. Inflammatory cytokine signaling leads to smooth muscle proliferation and migration to sub-endothelial layer leading to initiation of atherosclerotic process[83].

Obesity, inflammation and cardiovascular diseases

Obesity is among the most important causes of cardiovascular pathologies associated with endothelial dysfunction, such as arterial hypertension and atherosclerosis. Further, obesity is inadvertently associated with elevated plasma triglyceride levels, which is independently associated with an increased risk of CVD[84]. Adipokines directly impact triglyceride metabolism and adipocyte hypertrophy, which may lead to many changes in adipocyte function and production of anti- and pro-inflammatory cytokines (Table II). The inflammatory cytokines (adipokines) are secreted by adipose tissue, which is also located epicardially in addition to visceral location contributing to unfavourable cardio-metabolic complications[85]. Leptin and TNF-α are shown to diminish endothelial-dependent vasodilation when administered exogenously at pathophysiologically relevant concentrations[86]. On the other hand, adiponectin is associated with endothelial improvement and vascular protection[87] and improves endothelial function through endothelial NO synthase (eNOS)-dependent pathways[88]. Therefore, lower level of adiponectin expression by epicardial adipose tissue in obesity sets the stage for coronary inflammation and endothelial dysfunction. An overview of adipocytokines in relation to CVD is presented in Fig. 1. Besides these adipocytokines, elevated CRP levels in obesity and its decrease associated with weight loss are indicative of link between CRP and obesity-associated risks for CVD[89,90].

The production and release of inflammatory mediators linked to nutritional overload leads to organellar stress in obesity, with maximum stress to the endoplasmic reticulum. Endoplasmic reticulum stress is accompanied by accumulation of unfolded and misfolded proteins, which evoke unfolded protein response (UPR). UPR is associated with phosphorylation of various transcription factors and kinases, which in turn cause activation of nuclear factor-kappa beta (NF-κβ)[91]. Activation of NF-κβ leads to increased production of various cytokines including IL-6 and decrease in adiponectin[92]. Reactive oxygen species, endoplasmic reticulum stress, and ceramides are increased by adiposity, and all have also been shown to activate both JNK and NF-κβ[93,94]. Further, oxidative stress is an important link between obesity, inflammation, diabetes mellitus, and CVD[95]

Table II. Inflammatory biomarkers relevant to cardiovascular diseases (CVD)

Family of biomarkers	Markers	Functional aspects with respect to CVD
Acute phase proteins	Alpha-1 antichymotrypsin	Increase inflammation
	Alpha-1 antitrypsin	
	Ceruloplasmin	
	Ferritin	
	C-reactive protein (CRP)	
	Serum amyloid A	
Adipocytokines	Adiponectin	Decreased in obesity and CVD, reduces insulin resistance, oxidative stress and inflammation
	Apelin	Increases inflammation
	Interleukin (IL)-6, IL-1β, IL-10	Increase inflammation
	Leptin	Increased expression in obesity and CVD, increases inflammation
	Lipocalin-2	Increased expression in stress and inflammation
	Monocyte chemoattractant protein-1 (MCP-1)	Increased expression in obesity and CVD, increases inflammation
	Pigment epithelium-derived factor	Potent neuronal differentiating activity, anti-oxidative and anti-inflammatory properties in vascular wall cells, leukocytes and platelet
	Plasminogen activator inhibitor-1 (PAI-1)	Increased expression in obesity and CVD, increases thrombosis
	Retinol binding protein-4 (RBP-4)	Increase insulin resistance
	Resistin	Increased in coronary artery diseases, increase insulin resistance
	Tumour necrosis factor-α (TNF-α)	Increased in obesity and CAD, increase inflammation
	Vaspin	Newly emerging, role is not well-defined
	Visfatin	Increased expression in obesity and CVD, increases inflammation
Proteins	Endothelin-1	Mitogenic and atherogenic, vasoconstrictor
	Vascular cellular adhesion molecule-1 (VCAM-1)	Increase insulin resistance and inflammation

as it has been associated independently with all of these. A model of obesity, inflammation and vascular endothelial changes is presented in Fig. 2.

These findings are important as non-traditional CVD risk factors have been identified by the American Heart Association[96], and these factors may be responsible for a lowered age of CVD onset, which implicates that younger population is at an increased risk. Such premature onset of metabolic syndrome, and a subsequent risk to cardiovascular morbidity and mortality need to be addressed adequately[98]. Keeping these factors in view, it is important to control obesity using appropriate interventions aiming at weight loss and healthy lifestyle.

Risk factors as biomarkers: The clinical utility of these biomarkers is based on practicability, reproducibility, cost, and how well these can predict the risk *vis-à-vis* established biomarkers or in combination with them[50]. Most explored of these biomarkers in relation to CVD that have shown promising results include IL-6 and high-sensitivity CRP (hs-CRP). Of these two, CRP is a strong contender as the levels remain stable over years, and the test has high reliability, reproducibility and is cost-effective[99-101]. The IL-6 is the major

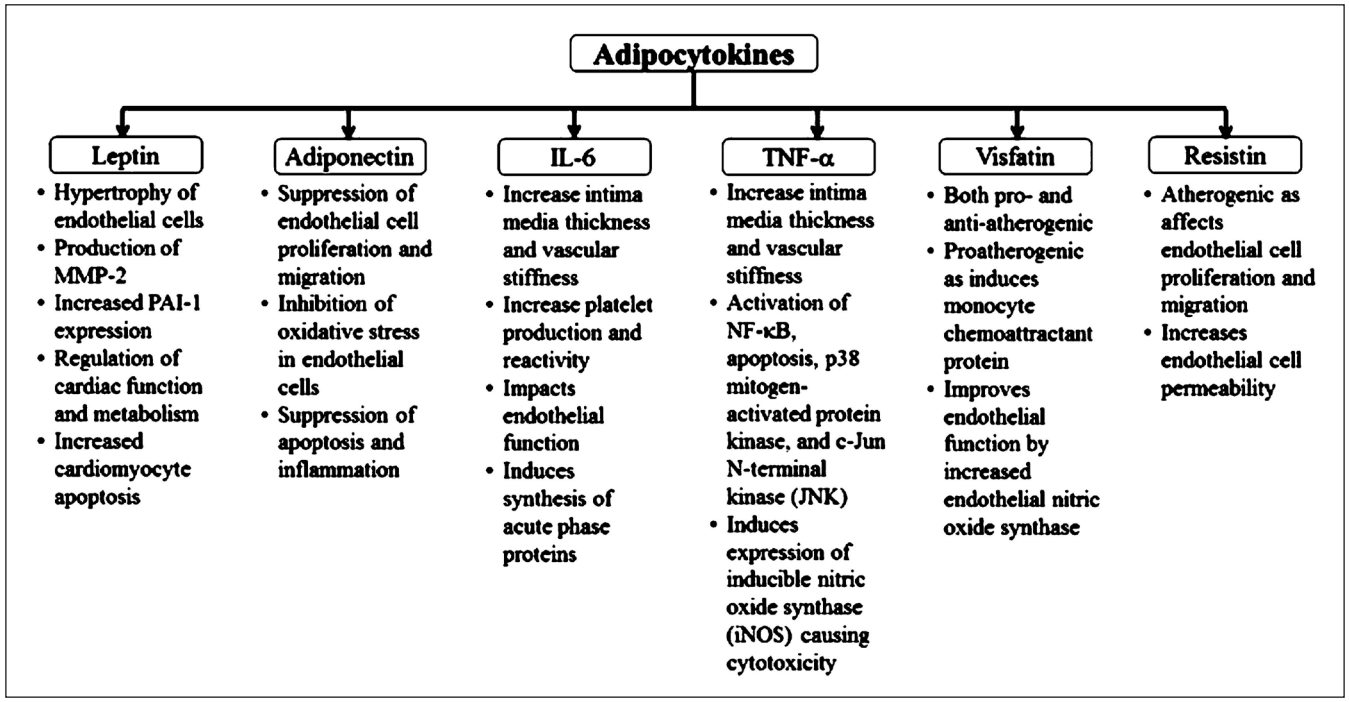

Fig. 1. Overview of adipocytokines in relation to cardiovascular diseases. IL-6, interleukin-6; MMP, matrix metalloproteinases; NKκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAI, plasminogen activator inhibitor-1; TNF-α, tumour necrosis factor-alpha.

initiator of acute phase response by hepatocytes and a primary determinant of hepatic CRP production[102]. The predictive value of IL-6 for cardiovascular ischaemic events was evaluated in a prospective cohort study and it was observed that IL-6 was associated with increased risk of future myocardial infarction in healthy middle-aged men[52].

Yoga-based lifestyle intervention in obesity: Effects on inflammation and cardiovascular diseases

Despite significant progress in therapeutic modalities in CVD, an efficacious treatment remains a challenge. The treatment modalities for weight loss in the management of patients with CVD and those at an increased risk are focused on dietary interventions, increased physical activity, and pharmacotherapy[103,104]. Newer studies have shown that lifestyle intervention is a promising option in patients with CVD as well as those at an increased risk of CVD[105,106]. It has been stressed that weight loss is the key contributor towards correction of dyslipidaemia[107], especially by reduction in visceral fat[108]. An important finding is that blood pressure can be reduced by lifestyle/behaviour modification; and though reduction may seem to be trivial, even small reduction in systolic BP (for example, 3-5 mm Hg) may produce clinically meaningful reductions[109]. Therefore, lifestyle modifications aiming at weight reduction by physical activity, dietary changes, breathing exercises and stress relaxation have a specific role in the management as well as prevention of chronic diseases[110].

Yoga as a lifestyle intervention: Yoga combines a healthy lifestyle with mental peace[111], and a modification in lifestyle and calming practices are shown to improve clinical profile of patients with various pathologies[22,112]. Regular practice of *pranayama* and meditation in healthy volunteers led to an improved cardiovascular metabolic status[113,114], and lipid peroxidation even by a short term yoga based lifestyle intervention[115]. In a randomized controlled trial in patients with coronary atherosclerosis, a regression was observed in disease activity following a comprehensive lifestyle intervention[116]. In the study conducted by the same group, it has been shown that intensive lifestyle intervention may lead to regression of coronary atherosclerosis after one year and more regression of coronary atherosclerosis occurred after 5 years than after one year in the experimental group[117]. In a study conducted in India, the possible role of yoga-based lifestyle on retardation of coronary atherosclerosis disease was evaluated. At the end of one year, the yoga group showed significant reduction in number of angina episodes per week, an improved exercise capacity and

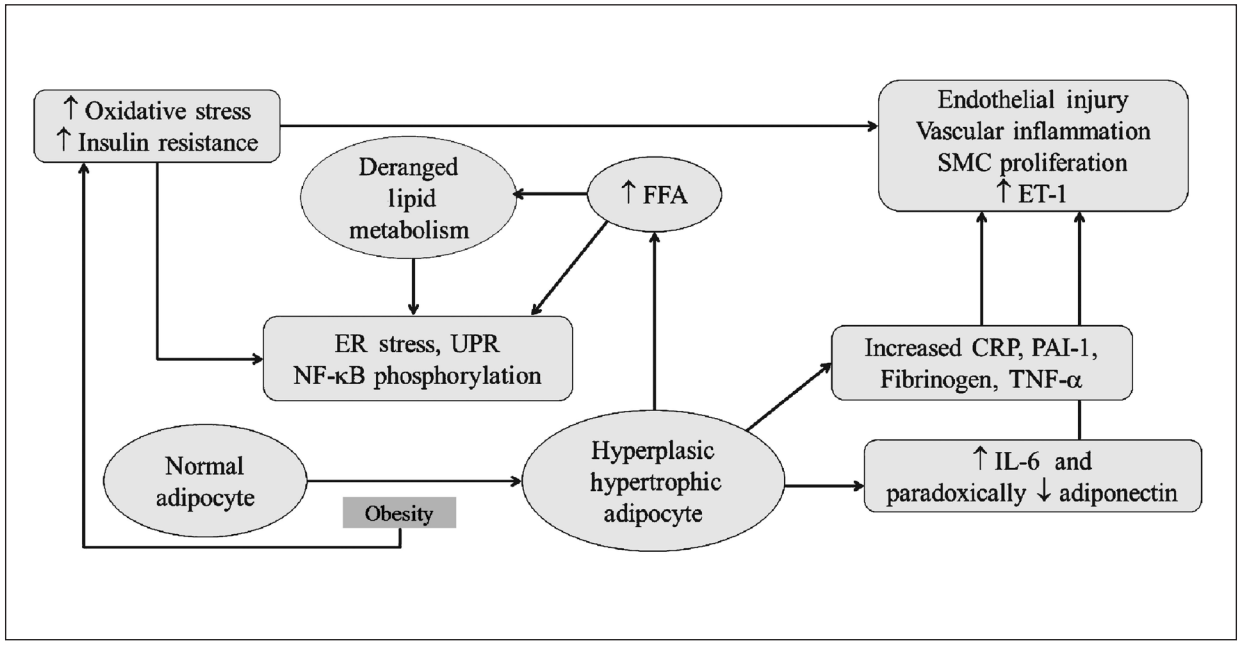

Fig. 2. Model for obesity, inflammation and vascular endothelial changes. ER, endoplasmic reticulum; NFκβ, nuclear factor kappa beta; IL-6, interleukin-6; CRP, C-receptive protein; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumour necrosis factor-alpha; FFA, free fatty acids; SMC, smooth muscle cells; UPR, unfolded protein response.

a decrease in body weight. Serum total cholesterol, LDL cholesterol and triglyceride levels showed greater reductions as compared to control group[112]. Importantly, even short-term yoga based comprehensive lifestyle intervention led to notable reduction in body mass index, blood pressure, and blood glucose with a clinically meaningful improvement in lipid profile[20,118]. A recent study suggested that a yoga-based, residential weight loss programme may foster psychological well-being, improved nutrition behaviours, and weight loss[119]. Similar reduction in weight was observed in another study that included an 8-week of yoga training that resulted in an improvement in body composition and total cholesterol levels in obese adolescent boys[120].

Another study showed that yoga postures (specifically *suryanamaskar*) resulted in improved cardiorespiratory fitness[121]. In a previous study in young hypertensive and pre-hypertensive patients, it was observed that there was a significant reduction in BP (SBP/DBP: 2.0/2.6 mm Hg) following yoga[122]. Similarly, a yoga-based lifestyle intervention resulted in a decrease in all lipid parameters except HDL. The effect started from four weeks and lasted for 14 weeks[21]. Together, these results indicate that a yoga-based lifestyle intervention may have an effect on some of the modifiable risk factors, which could probably explain the preventive and therapeutic beneficial effects of yoga observed in CVD. Overall, lifestyle intervention can modulate progression of the vascular inflammation at various steps of pathogenesis, thus counteracting causation/progression of CVD (Fig. 3).

A yoga-based lifestyle intervention is efficacious in weight-loss[123], and it also prevents weight-gain, especially amongst those who are overweight[124]. Besides this lifestyle intervention also reduces inflammation as shown by a reduction in the levels of IL-6, IL-18, and CRP and increased adiponectin in obese and post-menopausal women[35]. Similar benefit was observed in another study where yoga improved adiponectin level, serum lipids, and metabolic syndrome risk factors in obese postmenopausal women[125]. A short-term yoga-based lifestyle intervention has been shown to decrease IL-6 and TNF-α in obese and normal weight individuals[126], and increase adiponectin and decrease IL-6 in obese males[127]. IL-6, hs-CRP, extracellular superoxide dismutase levels were significantly decreased in heart failure patients after short term yogic exercises[128]. Also, a diet- induced weight loss led to a decrease in ET-1 and this decrease was correlated with a decrease in systolic BP[129]. It has been shown that an intensive lifestyle modification leads to a significant increase in plasma total antioxidants, plasma vitamin

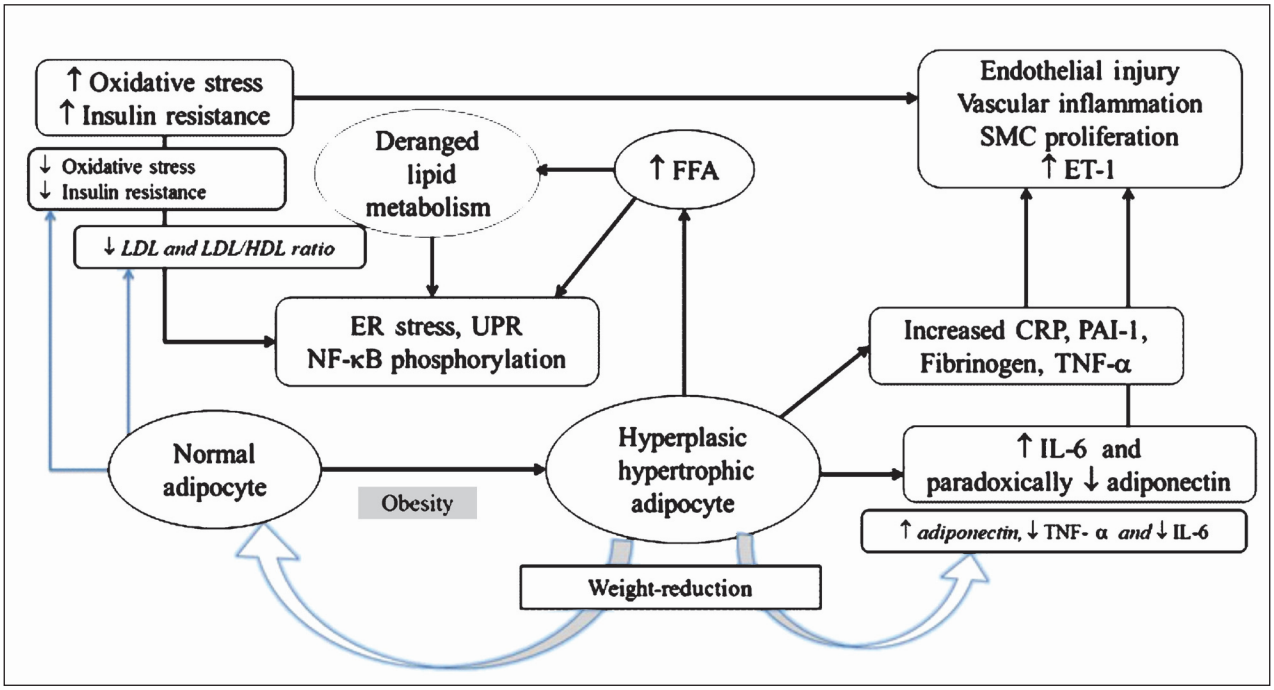

Fig. 3. Lifestyle intervention modifies various steps of vascular inflammation and pathogenesis of cardiovascular disease. ER, endoplasmic. ER, endoplasmic reticulum; NFκβ, nuclear factor kappa beta; IL-6, interleukin-6; CRP, C-receptive protein; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumour necrosis factor-alpha; FFA, free fatty acids; SMC, smooth muscle cells; UPR, unfolded protein response.

E and erythrocyte glutathione (GSH) in patients with CAD[130].

Psychoneuroimmunological effects of yoga: The beneficial effects of yoga in reduction of inflammation appear to be related to reduction in stress as shown previously[126]. These effects of yoga can be explained using the concept of psychoneuroimmunology, which is a relatively new field of science that investigates multidirectional interactions between behaviour and immune system, mediated by nervous system and clinical implications of these linkages[131]. Yoga is known to induce relaxation via lowering of cortisol, and increasing the levels of beta-endorphins[126]. This results in lowered levels of cytokines[126], as also observed in patients with hypertension[132]. as well as those who experienced heart failure[133]. A plausible reason for stress reduction by yoga is increased mindfulness[134], however, there may be several other complex activities in brain that may combine to produce the relaxing effect. This is especially important in obese and overweight patients who often exhibit a low grade ongoing inflammation[23] and may later culminate in a chronic disorder if goes untreated. IL-6 is a known predictor of all-cause mortality as reported in a study with a 9-year follow up in men[135], and its reduction by a yoga-based lifestyle intervention may, therefore, be beneficial in reducing all-cause mortality.

Conclusion

Obesity, especially visceral adiposity, upregulates various inflammatory cytokines and other biomolecules. Chronic elevation of these inflammatory mediators leads to cardiovascular morbidity and mortality. Yoga-based lifestyle intervention can effectively prevent and retard the progression of cardiovascular and metabolic disorders. The mechanism of action of such benefit may be attributed to a reduction in weight and stress, networking at mind and body levels, thereby leading to a reduction in inflammation, and causation and progression of the disease.

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