



Role of obesity related inflammation in pathogenesis of peripheral artery disease in patients of type 2 diabetes mellitus

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Abstract

Objective Type 2 diabetes mellitus (T2DM) has emerged as one of the greatest global health challenges of twenty-first century. Visceral obesity is one of the most important determinant of insulin resistance (IR) as well as T2DM complications. Therefore this review focuses on the molecular mechanism of obesity induced inflammation, signaling pathways contributing to diabetes, as well as role of lifestyle interventions and medical therapies in the prevention and management of T2DM.

Method Articles were searched on digital data base PubMed, Cochrane Library, and Web of Science. The key words used for search included Type 2 diabetes mellitus, obesity, insulin resistance, vascular inflammation and peripheral arterial disease.

Result Visceral obesity is associated with chronic low grade inflammation and activation of immune systems which are involved in pathogenesis of obesity related IR and T2DM.

Conclusion Metabolic dysregulation of adipose tissue leads to local hypoxia, misfolded/unfolded protein response and increased circulating free fatty acids, which in turn initiate inflammatory signaling cascades in the population of infiltrating cells. Mechanism that relates the role of adipocytokines with insulin sensitivity and glucose homeostasis might throw a light on the development of therapeutic interventions and subsequently might result in the reduction of vascular complications.

Keywords Type 2 diabetes mellitus · Obesity · Insulin resistance · Vascular inflammation · Peripheral arterial disease

Introduction

Diabetes is a clinical syndrome, characterized by hyperglycemia, polyuria, and polydipsia. It is due to absolute or relative deficiency of insulin or both. On the basis of pathogenesis there are four classes of diabetes mellitus namely type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types [1]. Insulin resistance and abnormal insulin secretion are the two most important factors that are responsible for the development of type 2 diabetes. In T2DM beta cells of pancreas are able to produce insulin in excess but insulin is not able to carry out its function [2]. Even though the prevalence of both type 1 and type 2 DM are increasing worldwide, the prevalence

of type 2 is expected to increase with a rapid rate in the future due to changing life style. Currently India (31.7 million) has the highest number of people with diabetes mellitus followed by China (20.8 million) and United States of America (17.7 million) [3]. According to international diabetes foundation (IDF) 415 million people worldwide have been diagnosed with diabetes. It is estimated to increase over 600 million people by 2040 [4]. Studies suggest that the developed countries represents around 87% to 91% of the diagnosed patients with type 2 diabetes and 7% to 12% with type 1 diabetes, while 1% to 3% have other types of diabetes. Reportedly, in developed countries around 87% to 91% of the diagnosed diabetic people have type 2 diabetes, 7% to 12% have type 1 diabetes while 1% to 3% have other types of diabetes [2]. There are various risk factors which are associated with the development of DM viz genetic susceptibility, age, ethnic background, HDL cholesterol level ≤ 35 mg/dl or triglycerides level ≥ 250 mg/dL. Besides this, variety of life style factors like physical inactivity, sedentary lifestyle, smoking, and alcohol consumption are also associated with the development of T2DM [5]. Studies have shown that overweight or obesity

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is the most important modifiable risk factor for the progression of T2DM [6]. According to the World Health Organization, 2011 about 90% of the diabetic patients develop T2DM mostly relating to the overweight.

Impaired insulin secretion, peripheral insulin resistance, and excessive hepatic gluconeogenesis are the three pathophysiological abnormalities that characterize T2DM. To carry out the function properly every cell within the human body, requires a regular source of energy and glucose is the primary source of energy, which circulates in the blood as a mobilizable fuel source for cells [7], and the regulation of the blood glucose level is done by insulin [1]. The elevated levels of blood glucose stimulate the secretion of insulin by the pancreatic beta cells. Insulin receptors are found primarily on hepatic cells, muscles, and adipocytes. The binding of insulin to its receptor triggers a conformational change that leads to the autophosphorylation of tyrosine residue in the carboxy-terminal domain of the receptor. The phosphorylated insulin receptor in turn phosphorylates insulin receptor substrates (IRS) on tyrosine residue. Phosphorylated IRS molecule act as docking site for enzyme PI-3 kinase. PI-3 kinase then phosphorylates PI 3, 4 bisphosphate (PIP2) leading to the formation of PI3, 4, 5- trisphosphate (PIP3) [8]. Binding of PIP3 with PKB leads to activation of PKB [9]. The activated PKB stimulates recruitment of glucose transporter (GLUT4) from internal membrane vesicles to the plasma membrane, causing rapid uptake of glucose from bloodstream to the peripheral tissues [10, 12]. In T2DM, these signaling pathways may get dysfunctional leading to insulin resistance, so even in presence of insulin there is decreased peripheral uptake of glucose which may lead to hyperglycemia. High glucose level causes further release of insulin from beta cells of pancreas by feedback mechanism which may lead to compensatory hyperinsulinemia. Insulin hypersecretion is followed by beta cells exhaustion resulting in beta cells failure and in long term T2DM is associated with reduced insulin secretion along with insulin resistance.

Obesity is characterized by increased fat deposition in adipocytes which may induce chronic low grade inflammation of adipocytes and other cells. This chronic low grade inflammation plays an important role in pathogenesis of T2DM. In addition many studies have showed that increased free fatty acids in obesity can induce ER stress in many cells, including adipocytes. Increased ER stress has been observed in the subcutaneous and visceral adipose tissues of the patients who are either overweight or obese. The ER stress markers have also been shown to be upregulated in the obese diabetic mice. In this review we have discussed how obesity contributes to development of T2DM and how altered AT macrophage phenotype impact on inflammation and trigger IR. We also discussed the complications that arise due to diabetes such as peripheral artery disease (PAD) and its pathophysiology. Further the role of lifestyle modifications

and medical therapies in the management of diabetes has been discussed.

Obesity: risk factor for diabetes

Obese subjects show a high risk of developing T2DM because 80–90% of T2DM patients are either overweight or obese [6]. The term “diabesity” has been coined considering the role of obesity in pathogenesis of T2DM [13]. Prevalence of obesity particularly abdominal obesity has been on rise in subsequent years. Prevalence of both forms of obesity (generalized as well as abdominal obesity) is higher in urban population compared to rural population [14]. According to WHO in 2016, more than 1.9 billion adults aged 18 years and older were overweight and over 650 million adults among these were obese. In 2016, 39% of the adults aged 18 years and over (39% men and 40% of women) were overweight. Overall about 13% of the world’s adult population (11% of men and 15% of women) were obese in 2016. The prevalence of overweight and obesity among children and adolescents aged 5–19 years has risen dramatically from just 4% in 1975 to over 18% in 2016. This rise has been observed similarly among both boys and girls: in 2016, 18% of girls and 19% of boys were overweight [15]. Globally there are more obese people than underweight irrespective of region except some parts of sub-Saharan Africa and Asia. According to WHO the BMI cutoff for obesity is 25 kg/m², while in Indian population there is revision of BMI criteria i.e. it has been fixed to 23 kg/m² [16].

Obesity induced changes in adipose tissue microenvironment:

Obesity is the accumulation of abnormal or excessive fat that may interfere with maintenance of an optimal state of health. It is the result of chronic imbalance between energy intake and energy expenditure [17]. There are two distinct types of adipose tissue, brown adipose tissue (BAT) and white adipose tissue (WAT). BAT mainly specialized in heat production, earlier it was thought, in humans, soon after birth BAT disappear, but now there are evidences to suggest that BAT is present in adult humans in the supraclavical and paraspinal regions [18]. BAT level and activity are inversely correlated with BMI, and loss of BAT activity may be associated with deposition of WAT [19–21]. Lipid storage is the primary functions of WAT. Depending on its anatomical location, WAT is subdivided into two categories: Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). All fat depots are not equally deleterious for health, like subcutaneous adipose tissue (SAT) may not be a risk factor for metabolic disorder, while visceral adipose tissue (VAT) and

ectopic fat deposition in or around the heart, muscles or liver is related to insulin resistance, impaired glucose homeostasis and vascular complications [22–24]. Visceral adiposity is strongly correlated with metabolic abnormalities and vascular diseases than subcutaneous adipose tissue [25–27]. Normal weight individuals with increased level of abdominal obesity could genetically predispose to the development of DM as well as vascular diseases [28]. Vascular complications are particularly common with obesity, but there are group of individuals who are phenotypically obese but may not be at an increased risk for vascular complications, are said to have metabolically healthy obese (MHO) [29, 30]. On the other side metabolically unhealthy obese individuals (MUO) are at increased risk of vascular complications irrespective of BMI, this group may include individuals within normal weight category with a BMI of 18.5–24.9 kg/m² [31, 32]. MHO individuals have less VAT and more SAT and low fat deposition in peripheral tissues as compared to MUO individuals [33–35]. During energy excess, free fatty acids (FFA) are stored in the form of triglycerides (TG) and during the nutrients deprivation, these stored fat are released from TG by the process of lipolysis [36]. The enzymatic control of rate limiting step for TG mobilization is hormonally regulated [37] and insulin is the main hormone which is involved in this regulatory process [38]. In case of obesity and insulin resistance, the adipocytes sensitivity to insulin is lost that results in increased FFA [39, 40], which is a characteristics feature of type 2 DM.

Adipose tissue stays in dynamic state, in both physiological as well as in pathological conditions. WAT has ability to change its characteristics, which directly influences its functionality [41]. The hyperplasia and hypertrophy of adipocytes causes WAT to expand which may lead to obesity [42]. In humans adipocyte size is positively correlated with glucose intolerance and hyper insulinemia [43]. During the advancement from normal weight to obese and then to overt diabetes, adipocytes derived factors contribute to the occurrence and development of β cell dysfunction and type 2 diabetes [44]. Macrophages are the innate immune cells, constitute 5 to 10% of stromal cells of lean steady state adipose tissue, regulating tissue homeostasis. During nutritional overload because of increased FFA, the numbers of macrophages increase and reach upto < 40–50% of stromal cells in human and mouse [45]. On the basis of functions there are two subtypes of macrophages, namely M1 macrophages and M2 macrophages. Normal weight and MHO tissues are rich in M2 macrophages that are anti-inflammatory in nature and known to secrete anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and IL-33 which assist in regulating physiological processes, and controlling insulin sensitivity. Obese tissues are rich in M1 macrophages which are induced by proinflammatory

factors, and secrete inflammatory cytokines such as IL-6, TNF- α , IL-1 β , IL-12, IL-23, and monocyte chemoattractant protein 1 (MCP-1) [46] (Fig. 1). In a study no macrophage accumulation and inflammatory response has been observed in mice, deficient in MCP-1 and MCP-1 receptor CCR-2, and also these mice were found to have resistance against diet induced insulin resistance [47]. For rapid ATP formation M1 macrophages use the glycolysis pathway whereas M2 macrophages use oxidative phosphorylation. Furthermore M1 macrophages also utilize oxidative pentose phosphate pathway for ATP as well as NADPH generation, leading to ROS generation and glutathione reduction [48]. These macrophages can be distinguished on the basis of the expression of their surface markers. F4/80 + CD206 + CD301 + CD11c- expressed by M2 macrophages while M1 macrophages express F4/80 + CD11c + [47].

The M1 macrophages activation, stimulated by lipopolysaccharides and interferon gamma (IFN- γ), that is largely expressed in T helper-1 and CD8 T cells. In the AT of obese individuals increased amount of these cells were observed [46, 48]. Rupture of hypertrophied adipocytes leads to release of FFA, which in turn interacts with Toll like receptor (TLR) 4 and 2, and activate proinflammatory response and increased accumulation of local inflammatory cells [5, 49]). This condition leads to the release of various active molecules by adipocytes (Table 1). The interactions of FFA with TLR-2 stimulate the cyclo-oxygenase 2 and iNOS expression by macrophages. According to a study inflammatory response and obesity induced insulin resistance was prevented in TLR-4 and TLR-2 knockout mice [45]. Increased expression of inflammatory mediators has also been observed in visceral fat of obese individuals. Proteomic analysis showed mitochondrial impairment and decreased adipocyte differentiation in the visceral adipose tissue of metabolically unhealthy obese T2DM patients, which augment the M1 macrophages [49, 52]. Increased M1 macrophages also, cause the release of nitric oxide which may lead to the AT fibrosis by mitochondrial dysfunction of preadipocytes and excess collagen deposition [53]. Compared to healthy lean subjects, the adipose matrix metalloprotease-9 expression was found to be increased in metabolically unhealthy obese subjects [54, 55]. In obese individuals the increased AT MMP-9 positively correlates with homeostatis model assessment for insulin resistance (HOMA-IR) [54]. Also the ATM produces a metalloelastase MMP-12 and its activation leads to lipolysis [53]. Individuals having poor glycemic control, showed excess AT accumulation of collagen I, III, IV, VI [49, 56]. With proinflammatory accumulation and increased visceral fat mass collagen VI gene expression was found to be increased [57, 58].

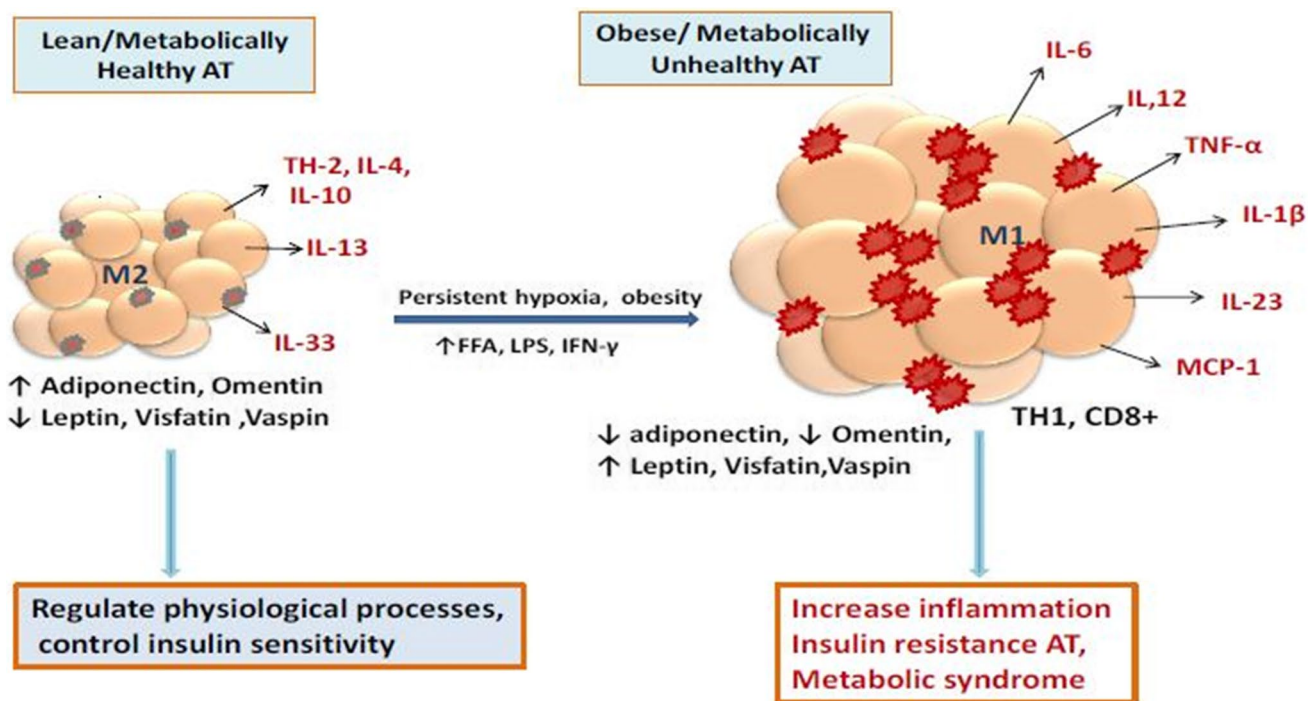


Fig. 1 Macrophages in lean and obese adipose tissue: TH-2 cytokines such as IL-4 and IL-10, IL-13 promote differentiation of macrophages to M2 phenotype. TH1 cytokines in the presence of \uparrow FFA, LPS, IFN- γ causes differentiation of macrophages into M1 phenotype

Table 1 Immune cells involve in AT remodeling during metabolic disturbances:

Immune cells	Action/observations	References
Eosinophils	Involve in M2 macrophage polarization, by releasing IL-4 Mice deficient in eosinophils showed: impaired adipocyte maturation and glucose tolerance	[59, 60]
Mast cells	Compared to lean subjects increased amount of mast cells have been observed in obese subjects Deficiency associated with improved insulin sensitivity	[50, 61]
Th1	With increase obesity amount of Th1 also increases Increased Th1 found to be positively correlated with HOMAIR in obese individuals	[62, 63]
Th2	Causes differentiation of quiescent (M0) macrophages to M2 macrophages Helps in maintaining insulin sensitivity by producing anti inflammatory cytokines like IL-10 and transcription factor STAT-3	[46]
Tc	Compared to SAT increased amount of Tc were observed in VAT Produces IFN- γ , IL-12 and IL-18, creating pro- inflammatory environment	[64]
NK cells	Increased accumulation in VAT of obese individuals and its depletion was associated with better insulin sensitivity and reduction in macrophages	[65]
NK T cells	Produce IL-4, IL-10, IL-12 cytokines, which protect against diet induced obesity in mice as well as in human Obesity reduces the population of NK T cells	[46, 66]
Dendritic cells	HFD increases AT Dc recruitments HFD induced inflammation was protected in VAT of cDC depleted mouse	[67, 68]
B cells	Cause T cell activation and pro – inflammatory cytokines production that increases the M1 macrophages polarization and insulin resistance	[69]

Pathway linking obesity induced inflammation and insulin resistance:

The link between the obesity and diabetes has been

attributed to the inflammatory pathways [78]. In obesity, due to adipocyte hypertrophy and excess release of free fatty acids (FFA), increased ROS generation has been observed in AT of mice. This excess FFA further deteriorate the local adipose tissue inflammation, also the

constant demand for lipid processing and storage leads to organellar stress, with maximum stress to endoplasmic reticulum (ER) [79–81]. In addition, the poor oxygenation of AT in obesity causes AT hypoxia, which also results in ER stress. ER stress is accompanied by accumulation of unfolded and misfolded proteins which lead to activation of specific cellular process called unfolded protein response (UPR) [82]. Transmembrane proteins namely inositol requiring enzyme 1 (IRE1), PKR – like ER kinase (PERK), and activating transcription factor 6 (ATF6) are involved in mediating UPR. These proteins remain inactive by binding with ER chaperons at basal state. During stress IRE1 becomes active and interacts with tumor necrosis factor receptor-associated factor 2 (TRAF2) which leads to activation of c-jun N-terminal kinase (JNK) and nuclear factor kappa β (NF- $\text{K}\beta$) [83]. It disrupts the insulin signaling by phosphorylating IRS1 on serine residue. JNK phosphorylates S307 in murine IRS1 and S312 in human IRS1. In a study JNK activation are reported to increase in AT of patients with obesity and T2DM [75]. In absence of any stimulus inhibitory protein named inhibitor of $\text{K}\beta$ ($\text{IK}\beta$) remain associated with NF- $\text{K}\beta$ inside the cytosol. In the presence of proinflammatory stimulus, $\text{IK}\beta$ is phosphorylated at two serine residue by inhibitory kinase $\text{K}\beta$ ($\text{IKK}\beta$). After phosphorylation $\text{IK}\beta$ is rapidly degraded by proteasomes, releasing NF- $\text{K}\beta$ for translocation to the nucleus where it activates transcription of target gene; this will lead to increased production of various cytokines including IL-6 and decrease in adiponectin [84] (Table 2). The increased production of these inflammatory cytokines leads to chronic low grade inflammation (Fig. 2). According to a study in a mouse model of obesity deletion of $\text{IK}\beta$ or neutralization of TNF- α [88] or IL-1 β [89], leads to improvement in insulin sensitivity and glucose tolerance. Chronic inflammation decreases the lipid storage capacity

of the adipose tissue by inhibiting preadipocytes differentiation and increases lipolysis. Increased FFA reduces the IRS-1 and PI3-K-AKT expression in the liver as well as in skeletal muscles which in turn causes IR in liver and muscles. In a study it was observed that the FFA induced expression of IL-6 and TNF- α was prevented in adipocytes by inhibition of $\text{IKK}\beta$ [50].

Every type 2 diabetic patient does not show similar IR and vascular risk factor profile. There is significantly decreased insulin stimulated glucose disposal and insulin sensitivity index in obese type 2 diabetic, confirming that IR is the major contributor to the pathogenesis of hyperglycemia in obese diabetic, whereas normal weight type 2 diabetic are characterized primarily by defect in insulin secretion [90, 91].

Complications of diabetes mellitus:

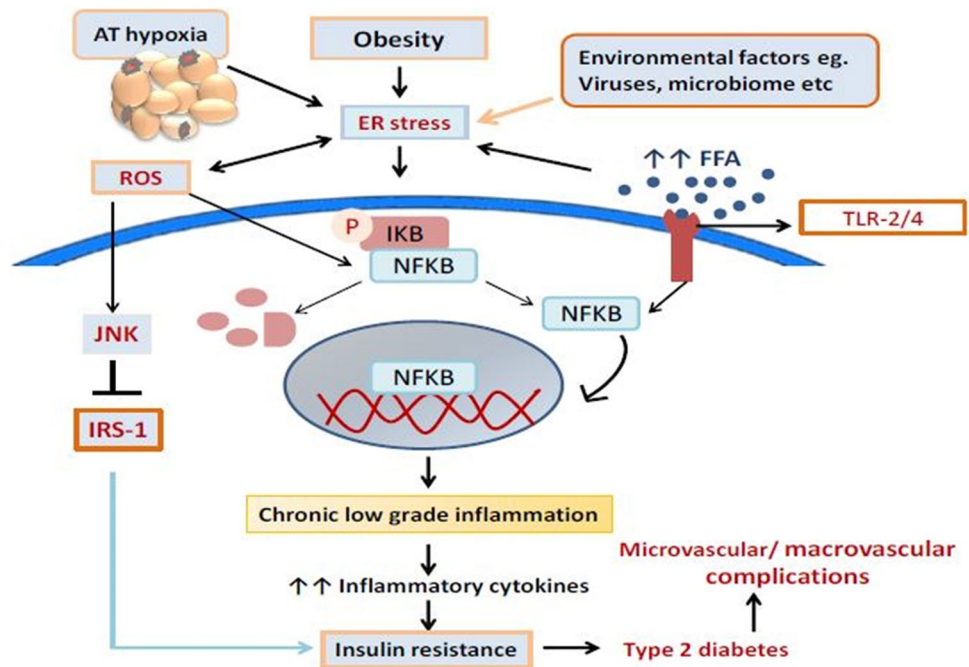
Chronic hyperglycemia that arises from DM causes long term damage, dysfunction and failure of various organs, mainly the eyes, kidneys, nerves, heart and blood vessels [92]. This high accumulation of glucose inside the bloodstream not only damage the cells, but also leads to the several other complications, such as development of atherosclerosis, where artery gets narrowed and blocked due to deposition of fat inside it, which further increase the risk of MI or stroke. Peripheral artery disease (PAD) is also one of the major atherosclerotic complications of diabetes.

Diabetes mellitus greatly increases the risk of PAD, as well as it accelerates its course [93]. Patient with PAD therefore have an increased risk of MI, stroke and death [94]. It is a risk factors for foot ulceration and amputation [95] and increases the risk of coronary artery disease as well [96]. The prevalence of PAD is estimated to be 10%- 25% in

Table 2 Adipokines in relation to obesity, T2 DM, and vascular complications

Adipokines	Action/ observations	Reference
Adiponectin	Insulin sensitizing, anti-atherogenic and anti-inflammatory property Reduced plasma level in obese individuals Low plasma level significantly correlated with endothelial dysfunction, increased intima-media thickness and progression of coronary artery calcification	[70, 71]
Omentin	Negatively associated with IR, diabetes, and obesity Highly expressed in visceral fat serum levels are significantly lower in Type 2 DM patients with PAD than in diabetic patients without PAD	[72, 73]
Leptin	Increased leptin level were correlated with BMI, IR in type 2 DM Increases platelets aggregation, hypertrophy and proliferation of vascular smooth cells	[71, 74, 75]
Visfatin	Positive correlation between plasma visfatin and visceral adipose tissue visfatin mRNA expression, whereas negative correlation between plasma visfatin and subcutaneous adipose tissue visfatin mRNA expression Negatively associated with endothelial function in diabetic patients	[71, 76]
Resistin	Increased circulating concentration in mouse model of obesity Increased in human obesity and correlated with IR in diabetic patients	[71, 77]
Vaspin	Increased in obesity and type 2 DM patients	[77]

Fig. 2 Obesity and environmental factors such as viruses and pathogens cause ER stress, which lead to activation of NF- κ B, which in turn initiates a cascade of signaling activities, which leads to chronic low grade inflammation, and development of insulin resistance, eventually resulting in type 2 diabetes mellitus



people aged ≥ 55 years [97]. After coronary artery disease and stroke, PAD is the third most common clinical manifestation of the atherosclerosis [98]. Diabetes is not only qualitative risk factors, but also a quantitative risk factor, as each 1% increase in glycosylated hemoglobin is associated with a 25% increase in the risk for PAD [99].

According to Beckman et al. glucose intolerance is associated with a more than 20% prevalence of an abnormal ankle—brachial pressure index (ABI) relative to 7% in those with normal glucose tolerance [100]. Atherosclerosis induced chronic limb ischemia (CLI) has been associated with a mortality rate of 20%–25% in the first year after presentation and a survival rate of less than 30% at five years [97]. In year 2015, in individuals aged 25 years and older the global prevalence of PAD was 5.56% [101].

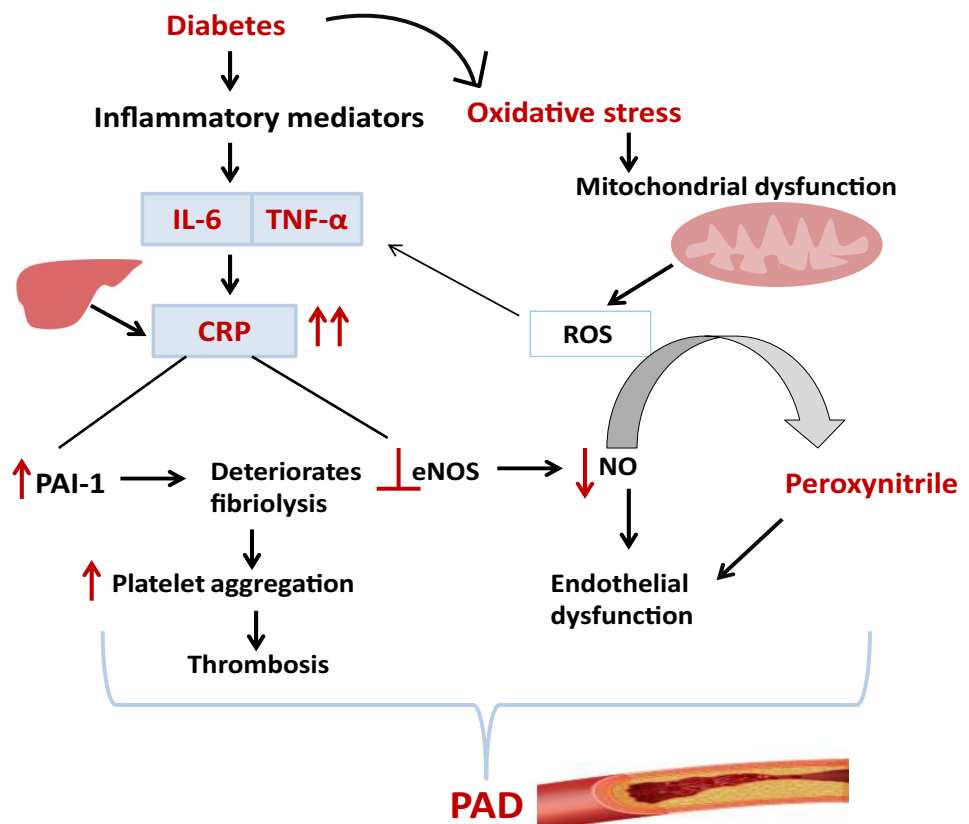
Pathophysiology of PAD in diabetes mellitus:

PAD is characterized by reduction of blood flow to the lower limb [102, 103]. It can be asymptomatic or symptomatic like intermittent claudication, a typical leg pain and critical limb ischemia [104–106]. Hypertension, smoking, age, obesity are important risk factors for the PAD [107]. Hyperglycemia, insulin resistance, and dyslipidemia are mainly responsible for the progression of PAD in diabetic patients [108–110]. Prolonged hyperglycemia favors atherosclerosis and thrombosis by increasing platelet activity and modifications in the vascular endothelium and coagulating factors [111–114].

The concentrations of C – reactive protein (CRP), an acute phase protein synthesized by liver increases in response to inflammation and it is strongly associated with the progression of PAD [115]. It has been reported that in patients with impaired glucose tolerance or diabetes there is increased plasma concentration of CRP [116]. Endothelial cell nitric oxide synthase (eNOS) is inhibited by CRP that results in the abnormalities in the regulation of vascular tone [117]. CRP also augments the release of plasminogen activator inhibitor (PAI)-1, that vitiates fibrinolysis [96]. Oxidative stress increases vascular endothelial cells permeability and promote leukocyte adhesion, these molecules cause internalization of monocyte, that change into macrophages, which stimulate the production of CRP by releasing IL-6, which further lead to reduction of nitric oxide (NO) [114]. NO is a signaling molecule that diffuses from endothelial cells to neighboring smooth muscle cells in the wall of the blood vessels, where it interacts with iron bound to the active site of the enzyme guanylyl cyclase (NO receptor), resulting in the synthesis of cGMP, which leads to blood vessel dilation and relaxation of smooth muscle cells. NO also inhibits the aggregation of platelets within the vessels and prevents thrombotic events [96]. The elevated levels of CRP inhibit the NO mediated vasodilation as well as enhance the platelet aggregation and therefore result in thrombotic events (Fig. 3).

In comparison to non-diabetic individuals severity and prevalence of PAD is higher in diabetic individuals [118–121]. According to a study obese diabetic patients had higher chances of vascular events, as well as hypertension and target organ lesions than normal weight diabetic

Fig. 3 Pathophysiology of peripheral artery disease in type 2 diabetes mellitus. CRP: c reactive protein, IL-6: Interleukin-6, TNF- α : Tumor necrosis factor alpha, ROS: Reactive oxygen species, PAI-1: Plasminogen activator inhibitor – 1, eNOS: Endothelial nitric oxide synthase, NO: Nitric oxide, PAD: Peripheral artery disease



patients [122]. There are some studies according to which there is no any association between BMI and PAD [123, 124], while other studies have shown that a high BMI [125, 126] or low BMI [127, 128] are associated with PAD. According to Tseng et al. lower BMI (≤ 23 kg/m²) is a major risk factor for PAD [128]. In a study researcher noted a J- shaped association of BMI with prevalent PAD. This relationship was most robust in women with only a slight association of increasing BMI and PAD in men. Underweight and normal BMI men exhibited a higher prevalence of PAD than overweight and obese men, with a positive association of prevalent PAD with increasing BMI evident only in severe class III obesity (BMI ≥ 40 kg/m²) [129].

There are various invasive and non- invasive methods for the assessment of PAD substantiated with clinical findings. Ankle brachial pressure index (ABPI) is a non- invasive test for detection of earlier occurrence of PAD. It claims 98% overall accuracy (sensitivity 97%, accuracy 100%) against angiography using an ABPI threshold of 1.0 as being normal. The most important utility of ABPI is at primary health care setting for the early detection and cost effective treatment of PAD. The ABPI is used to diagnose patients for PAD as a fall in blood pressure in an artery at the ankle relative to the central blood pressure would suggest a stenosis in the arterial conduits somewhere between the aorta and the

ankle [130]. It is calculated as-ABPI = Ankle systolic blood pressure/ Brachial systolic blood pressure.

Peripheral artery disease and risk of cardiovascular events and mortality:

Clinical studies describing PAD is a strong prognostic marker of future cardiovascular events. In a study conducted in our lab we found there was an inverse correlation between anthropometric parameters and obesity indices in healthy obese subjects [131]. In a prospective cohort study cardiovascular events were recorded in 1049 subjects divided into four groups: 558 with neither diabetes nor PAD, 192 with PAD but without T2DM, 153 with T2DM but without PAD, and 146 with T2DM and PAD. It was observed that the cardiovascular event rate was lowest in subjects with neither PAD nor T2DM. Non diabetic PAD patients were at higher cardiovascular risk than T2DM patients without PAD [132]. Furthermore, a total 289 diabetic subjects, 27 of whom had already been diagnosed with PAD, and remaining 262 asymptomatic patients without Known PAD were followed up for 10 years. In patients with abnormal ABI the cardiovascular mortality was higher ($p < 0.05$). A significantly higher survival was observed among patients with normal baseline ABI as compared to patients with

an abnormal baseline ABI ($P < 0.001$) [133]. In a community based study, in White and African American men and women ($N = 12,186$) of age range 45–65 years ABI was measured and were followed up for median of 13.1 years. It was observed that risk of coronary heart disease increased exponentially with decreasing ABI in African American, White men and women [134].

The prevalence of coronary artery disease varies from 10.5% to 71% among PAD patients while it is 5.3% to 45.4% among subjects without PAD. Decreased ABI is also associated with prevalent cerebrovascular disease with odd ratios in the range of 1.3 to 4.2 [135]. These findings clearly point out that PAD is strongly associated with cardiovascular and cerebrovascular disease which contributes to a high risk of morbidity and mortality.

Management of diabetes:

Lifestyle modifications:

Most of the people with diabetes are either overweight or obese, therefore weight reduction is seen as the key therapeutic goal in the prevention and management of type 2 diabetes. Lifestyle modification is the first line intervention for weight loss [136–140]. Reduction in weight due to physical activity and decreased calorie intake or both, involve a significant decrease in VAT in obese individuals [141–143]. Evidences suggest that with regular exercise person can reduce the risk of cardiovascular disease and also improve the whole body blood glucose levels [144]. Reduced mortality risk was found in physically active individuals with type 2 DM as compared to physically inactive groups. According to studies, intra-abdominal fat mass significantly increase after reduction in daily foot-steps from 10,000 to 1500 even without a change in total fat mass [145]. Physical exercise helps to control risk factors for vascular complications [146]. Mechanistically, lifestyle might modulate whole body energy metabolism, as evidences suggest that during intake of high calorie diet concurrent physical activity increases fatty acid oxidation [42]. Various forms of physical activities like aerobic exercises (swimming, bicycling, walking or jogging), resistance exercises (push – ups), and flexibility exercises can help individuals to improve their metabolic status as well as prevention of chronic diseases. In a study cardiorespiratory fitness was found to be increased in both type 1 and type 2DM by aerobic exercise training [147]. Aerobic exercise can increase the heart rate upto 65%–90% of maximum, known to be associated with substantial reduction in cardiovascular mortality in T2DM patients [148]. In a meta- analysis HbA1c level was greatly reduced in subjects performing aerobic exercise with greater intensity compared to those with lower intensity [149]. Overweight

T2DM treated with 6 month aerobic exercise programme, it was observed that compared with baseline and control group, patients treated with exercise have improved glycaemic control, decreased insulin resistance and blood pressure, with reduced level of CRP and IL-18 [150]. A significant reduction in plasma P-selectin and ICAM-1 levels as well as increased plasma HDL levels were observed in sedentary older T2 DM participated in aerobic exercise [151]. Resistance training also has beneficial effect on glycaemic control also it increases muscular strength. Patients with peripheral neuropathy or severely obese for whom aerobic exercise may be physically challenging, resistance training may be helpful. Erikson et al. observed that improvement in glycaemic control was strongly correlated with muscles size after 3 month of resistance training programme in type 2 DM patients [152]. The effects of resistance exercise and aerobic exercise on glycaemic control are additive as 40% reduction in HbA1c level was observed in the combined resistance and aerobic exercise group in comparison to non- exercise group [153]. Exercise also have beneficial role in improving metabolic homeostasis of adipose tissue. Exercise may improve metabolic function and cellularity of adipose tissue by promoting lipolysis and decreasing lipogenic gene expression in AT. According to study endurance exercise increases the triglycerides lipase activity in AT [154]. Exercise may also inhibit the hypoxic condition of AT by stimulating angiogenesis [155]. Exercise induced weight reduction in obese elderly men and women resulted in decreased insulin resistance, which was correlated with change in VAT [156]. Studies have suggested that exercise may improve adipocyte function by reducing inflammatory cytokines production. The increment of CD8 + T cells in AT reduces with physical exercise in obesity and thus exercise could be helpful in changing the M1 phenotype of AT to M2 phenotype [157]. In addition, cigarette smoking and alcohol consumption can also increase the risk of vascular complications in T2DM patients. Regular consumption of alcohol can interfere with blood sugar control in diabetic person [158]. According to studies risk of peripheral artery disease was double in diabetic patients who smoke than the non- smokers [159]. Therefore quitting smoking and alcohol consumption person may reduce the risk of T2DM as well as its complications.

Pharmacological therapy:

Metformin: It works by inhibiting glucose production from liver [160]. A large meta-analysis [161] supports the use of metformin monotherapy as first-line therapy. Within adipose tissues positive effect of metformin has also been observed [162]. With the use of metformin, the modest reduction in body weight [163], is associated with redistribution of fat

from visceral depots to subcutaneous depots, which carry lesser cardiovascular risk [164].

Sulphonylureas: work by triggering insulin release from pancreatic β – cell [165]. Gliclazide, glipizide, glibenclamide and glimepiride are second generation sulphonylureas currently used, while first generation drugs are no longer used. It reduces glycosylated hemoglobin HbA1C level by 0.8 to 2.0% and fasting plasma glucose concentration (FPG) by 60 to 70 mg/dl, with the greatest reductions observed in patients with the high FPG concentration at the initiation of therapy [166–168].

Meglitinides: Like sulphonylureas increases insulin secretion from pancreatic β cells. Studies have suggested that meglitinides reduces hemoglobin A1C by 0.5% to 1.5% [169]. **Alpha – glucosidase inhibitors:** Acarbose and miglitol are the two drugs available in this class. It works by inhibiting the enzyme alpha—glucosidase, found on the brush border cells that line the small intestine [165].

Glucagon like peptide – 1 (GLP-1) receptor agonists: GLP-1 is a hormone that plays an important role in regulating appetite and blood sugar levels. GLP-1 receptor agonists mimic the action of this hormone. Its administration stimulates GLP-1 receptors, thereby increasing insulin secretion in response to oral and intravenous glucose to similar extent [170]. It includes exenatide and liraglutide and can reduce HbA1C level by 0.8% to 1.5% [171]. **Dipeptidyl peptidase (DPP) – 4 inhibitors:** DPP- 4 is a ubiquitous enzyme found in soluble form in plasma, or as a membrane component of many cells [172], including endothelial cell [173]. It inhibits the activity of incretin hormones, glucose – dependent insulinotropic polypeptide (GIP) and GLP-1. DPP-4 inhibitors can improve the activity of endogenously active GLP-1 and GIP by blocking its degradation by enzyme DPP – 4.

The biological half-life of circulating GLP-1 and GIP is very short hence the therapeutic use of native GLP-1 is very limited but DPP-4 inhibition offers a novel way to increase endogenous incretin concentration as a treatment.

Orlistat and sibutramine are the two drugs approved by Food and Drug Administration (FDA) for long term treatment of obesity. Orlistat via inhibition of lipase activity prevent the absorption of 30% dietary fat [174]. A study shows that orlistat causes weight loss of 9 to 10% compared with a 4 to 6% in placebo group [175, 176]. Sibutramine is a nor-epinephrine and serotonin reuptake inhibitor that acts as an appetite suppressant and increases thermogenesis [177]. It also improves lipid profile and glucose control, with a reduction of cardiovascular risk factors [178]. A clinical study demonstrated that there is significant reduction in weight and waist circumference with the use of sibutramine compared with placebo in obese type 2 diabetic patients, and it was associated with significant improvement in metabolic control such as reduction in HbA1C, fasting glucose and triglycerides levels [178].

Conclusion:

Diabetes is the fastest growing disease which affects millions of people worldwide. Behavioral changes that lead to increased body weight is a major contributing factor to the rising incidence of diabetes. Apart from genetic factor sedentary life style and unhealthy diet pattern play a major role in causation of obesity and T2DM. Adopting healthy lifestyle which includes increased physical activity and healthy diet can result in preventing diabetes. Excessive fat accumulation and subsequently might result in the reduction of vascular complications in T2DM patients. can trigger pro-inflammatory state, as well as increases the substrate load in the adipocytes which may further lead to ER stress. Suppression of ER stress may reduce the risk of obesity and its complications. Further the mechanism that can relate the role of adipocytokines with insulin sensitivity and glucose homeostasis might throw a light on the development of therapeutic interventions.

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Data Availability Data supporting the findings of the study were derived from resources which are in public domain (<https://www.ncbi.nlm.nih.gov/pmc/>, <https://scholar.google.com/>) and included with doi along with references.

Declarations

Conflict of Interest There is no conflict of Interest.

Consent to participate Not applicable.

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