Abstract

Earlier we had reviewed the role of micro RNA’s in obesity as well as diabetes mellitus and importance of treating both together with the term diabesity coined along with the role of various transcription factors in lipid metabolism. Further we had evaluated the role of developing drugs for brown adipose tissue thermogenesis (BAT) along with mirabegron in obesity as well as macrophage polarization in Non-alcoholic Fatty Liver Disease (NAFLD) along with various transcription factors in macrophage polarization, besides reviewing the role of macrophage polarization in tackling obesity as well as diabetes mellitus [91-96]. Here we have further tried to summarize the correlation among diabetes mellitus as well as atherosclerosis. Diabetes Mellitus is a well known disorder of the carbohydrate metabolism occurring secondary to defects in insulin liberation, insulin action or both. Atherosclerosis forms secondary to a multiple steps or events that finally culminates in cardiovascular disease (CVD) that is associated with great morbidity as well as mortality. Here we conducted a systematic review to find the correlation among diabetes mellitus as well as atherosclerosis utilizing the pubmed search engine with the MeSH terms like DM; atherosclerosis; Obesity; NAFLD; microRNA; inflammation; macrophage polarization; epigenetics; therapy. We found a total of 26,137 articles out of which we selected 97 articles for this review. It was seen that both type 1 (T1D) as well as type2 diabetes (T2D) can stimulate atherosclerosis formation or increased rate of propagation. Escalated glucose amounts, dyslipidaemia as well as other metabolic derangements have a close role in the etiopathogenesis of atherosclerosis at every step of atherogenic event. Chronic inflammation is believed to be a crucial factor in atherosclerosis formation, being present right from the initiation of the pathology. It might be thought to be a connection among atherosclerosis as well as diabetes mellitus. Inspite of the insight efficacious inflammatory treatments that would halt atherosclerosis generation or decrease further propagation have not been generated. Here we have tried to comprehensively summarize the various aetiopathogenetic pathways including roles of micro RNA as well as epigenetic events, as well as oxidative stress, changed PKC signaling, roles of various transcription factors to help form some effective anti-inflammatory therapies.

Keywords: Diabetes Mellitus; Atherosclerosis; Chronic Inflammation; Micro RNA; Epigenetic Events; Transcription Factors; PKC Signaling; Oxidative Stress
Introduction

Atherosclerosis represents a chronic inflammatory problem of the arterial wall which commonly causes disability as well as death in some cases ultimately. In its final stages atherosclerosis presents as a lesion of the intimal layer of the arterial wall along with collection of plaques. Erosion or rupture of plaques triggers thrombotic processes which can prove to be fatal. A lot of research in the past decades has clarified the complicated etiopathogenesis, the major parts of which are lipid collection as well as chronic inflammation in the arterial wall [1]. Classically Atherosclerosis correlates with changes in lipid metabolism as well as hypercholesteremia [2]. Nevertheless, an enhanced amount of circulating modified lipodensity lipoprotein (LDL) is an accepted risk factor of cardiovascular disease (CVD) [3]. But the pathogenesis seems to be complicated than lipid metabolism alterations, involving lot of factors, of which the commonest one is inflammation [4].

The chain of these processes culminating in atherosclerosis formation is thought to get started by local endothelial impairment, that might lead to blood flow turbulence near the areas of artery bends or bifurcations. The blood vessel endothelium responds to mechanical stress resulting in activation that is followed by recruitment of circulating immune cells. Circulating monocytes stick to the damaged site of the arterial wall and invade inside followed by differentiation into macrophages which actively take a part in the lipid uptake via phagocytosis and result in foam cells generation which are present in massive amounts in atherosclerotic plaques [5]. Nevertheless, the basic ways of the events could be found out.

Studying the atherosclerotic lesion formation extensively is complex due to the reason that events might vary in humans as well as animal models [6]. The early stages of atherosclerotic lesion formation is called “fatty streak”, an area within the vascular wall which has the properties of intracellular lipid collection by foam cells, that also possesses vascular smooth muscle cells (VSMCs) as well as T lymphocytes. Fatty streaks can then move to atherosclerotic lesion once chronic damage of the endothelium continues. In the enlarging lesion intracellular lipid collection is related to multiple cell kinds. The macrophages that get recruited internalize lipid particles through phagocytosis and aid in the local generation of inflammatory mediators. Resident intimal cells further actively take part in this event. The stellar shaped macrovascular pericytes develop a 3 dimensional cellular network in the sub endothelial intimal layer, that form contacts with one another as well as endothelial cells and seeing that tissue homeostasis is maintained. This network gets disturbed in atherosclerotic plaques in view of pericyte phenotype alterations, resulting in a loss of intercellular contacts as well as escalated synthesis of extra cellular matrix (ECM) components [7]. VSMCs that participate in the pathological event might further undergo a phenotypic shift, probably achieving a proliferation as well as secretory characteristics [8]. Once reach the later stages of disease formation, plaques can get a stable fibrous cap which segregates them from the vessel milieu. On destabilizing the plaques takes place via depletion as well as rupture of the fibrous cap that is aided by matrix metalloproteinases (MMP) which stimulates ECM degradation. Macrophages as well as other inflammatory cells can act as significant contributors of these enzymes in the plaque [9]. The modes causing plaque erosion require future evaluation. These events are tough especially for modelling in atherosclerotic animals [6]. Inflammatory processes like local platelet modulated neutrophil activation, liberation of myeloperoxidase, toll like receptors 2 (TLR2) signaling as well as neutrophil modulated damage, seem to have their parts in this event [10]. Atherosclerotic plaques can decrease the lumen blood vessels causing ischemia as well as metabolic alteration in the alimented tissues [11]. Further scary is thrombogenesis caused via unstable plaques as well as in certain cases, on the surface of the uninjured plaques can commonly result in fatalities [12].

Diabetes mellitus

Diabetes mellitus (DM) represents a group of carbohydrate metabolic disorders, with their major presentation being chronic hyperglycemia that occurs secondary to defects in insulin liberation, or a combination of these. Metabolic aberrations seen during DM can be secondary to the insulin synthesis as well as/ or insulin resistance (IR) of the target tissues. The disease initially involves skeletal muscle’s
as well as adipose tissue (AT), as well as liver, at the insulin receptor level, signal transduction system as well as/or effector enzymes or genes [13]. Hyperglycemia symptomatology includes polyuria, polydipsia, weight loss, associated with polyphagia at certain times as well as blurring of vision. It might be associated with growth impairments as well as tendency towards particular infections. The direct life threatening sequences of uncontrolled DM are constituted by hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome [14]. Nevertheless, certain patients, usually with type 2 DM, might remain asymptomatic in the early years of the disease.

Type 1 diabetes

Type 1 diabetes (T1D) results secondary to the autoimmune damage of insulin synthesizing pancreatic β-cells [15]. The typical triad of T1D symptomatology comprises of polyuria, polydipsia as well as polyphagia. Usually the disease gets diagnosed in childhood as well as adolescence, who usually show these combination of symptomatology as well as severe hyperglycemia which makes it essential that lifelong exogenous insulin replacement is done. Research for T1D etiopathogenesis was generally on the basis of 2 animal models of the disease, the non-obese diabetic (NOD) mouse as well as Biobreeding-diabetes prone rat, both of which have the properties of propagating β-cells destruction modulated via Tcells [16,17]. Nevertheless, the variations among rodent models as well as human condition caused limitation of transferring these outcomes received. In case of humans, autoantibodies were there in 70 - 80% of subjects when the diagnosis was made [18]. Immunosuppressive as well as immuno-interventive treatment targeting for avoiding T1D did not aid in the preservation of β-cell function or worked just temporarily [19].

Subjects with T1D formed pancreatitis along with leukocyte collection [16]. This disease involves both exocrine as well as endocrine parts of the pancreas.

Type 2 diabetes

The escalation of prevalence of type 2 diabetes (T2D) involving 370 million people currently, is secondary to the global escalation of the obesity enhancement. For the diagnosis of T2D facing as well as 2h glucose amounts after a standardized oral glucose load. Pre Diabetes is found out usually with the separation among impaired fasting glucose as well as/or impaired glucose tolerance [20]. Nevertheless, one should consider T2D as a continuation of disease stages with escalating severity where the amount of plasma glucose enhancement depends on the degree of β-cells decline. IR has been well established once impaired GTT is present and escalation of glucose, even across the normal amount is secondary to a continuum of reduction in β-cells function [21]. This disease was demonstrated to be heritable in certain cases and persons having 1st degree relatives affected by DM are at an enhanced risk of its formation [22]. It was shown that in β-cells function is heritable [23], as well as that β-cells function determines glucose intolerance as well as T2D in various racial as well as ethnic groups [24]. At present it is realized that the etiopathogenesis of T2D is heterogenous and events other than IR as well as β-cells dysfunction are influential in its formation.

Atherosclerosis as well as diabetes mellitus-similar pathophysiology

Atherosclerosis as well as diabetes mellitus seem to have a connection via various pathophysiological pathways. Escalated risk as well as exaggerated formation of Atherosclerosis have been demonstrated in variety of studies on diabetic subjects. Like, various studies documented that the early formation of atherosclerosis in adolescents as well as children with T1D [25]. Of the factors explaining these exaggeration, dyslipidemia with enhanced amounts of atherogenic LDL, hyperglycemia, oxidative stress as well as escalated inflammation have been posited (Figure 1) [26].

Diabetes mellitus and dyslipidaemia

Of the maximum studied links among atherosclerosis as well as diabetes is the amount of small dense LDL (sd LDL), that is a recognized factor of atherosclerosis. Though at present LDL is known to be the major source of intracellular lipids collection in the plaques,
Figure 1: Courtesy ref no-26. A simplified scheme of the pathophysiological connection of diabetes mellitus and atherosclerosis. Dyslipidemia, hyperglycemia, and insulin resistance result in a spectrum of physiological changes, including the formation of atherogenic low-density lipoprotein (LDL), advanced glycation end products (AGE) and activation of pro-inflammatory signaling that impact different cell types of the arterial wall, resulting in atherosclerotic lesion development. SMC: Smooth Muscular Cells.

native LDL particles don’t result in prominent lipids collection within cultured cells, thus they do not have atherogenicity. The atherogenic manipulation of LDL, is the one that causes changes in the physical-chemical properties of these LDL particles as well as triggers mammoth lipid collection [3]. A cascade of lot of manipulation of LDL has been posited as a probable model of LDL atherogenic manipulation in the blood. As per this model, an LDL particle initially gets desialyated, that is followed by the escalation of particle density, reduction of its size as well as acquiring of negative charges [27]. These particles might get identified on the basis of their physical characteristics. Very low density lipoproteins (VLDL) represents another subfraction of changed LDL that has been detailed in humans. sd LDL particles have susceptibility to oxidation in view of decreased antioxidant amount as well as changes in lipid composition. It is plausible that oxidation occurs at the end stages of LDL atherogenic manipulation [28].

Following penetration into the subendothelial space at the Atherosclerotic lesion area, manipulated LDL particles lodge there for a time in view of crosstalk with proteoglycans and hence have escalated chances of getting internalized via the lesion cells. Furthermore, these modified LDL possesses affinity for the LDL receptor (LDLR) and is hence internalized by major unspecific phagocytosis, that causes intracellular cholesterol collection, instead of normal breakdown of lipoprotein particles. These events cause the development of foam
cells with the cytoplasm full of collected lipid droplets [29].

On a murine model of DM, studies carried out show the importance of LDL manipulation for the escalation of subendothelial retention time of lipoprotein particles. Extraction of LDL fraction was done by Hegensen, et al. from the blood of T1D patients as well as healthy controls and injected in the Atherosclerosis prone sites of the arterial wall. It was found that the retention of LDL received from T1D patients was 4 times higher as compared to LDL received from control subjects [30].

Changes in lipoprotein amounts was observed in a cross sectional study conducted in young adolescents with T1D as well as T2D. Escalation of amounts of apolipoprotein B, sd LDL as well as LDL cholesterol were not prevalent in high amounts in young subjects with T1D but the prevalence was escalated in T2D subjects [31]. Significant studies that did not check atherogenic LDL subfractions and only evaluated total amount of circulating LDL might have missed the chances in a DM patient, as the latter might remain in the normal range inspite of sd LDL being abnormally enhanced.

Indirectly the epidemiological studies showed the action of T1D as well as T2D correlated metabolic alterations in atherosclerosis formation. Like, the diabetes control and complications trial in patients with T1D in the United Kingdom prospective diabetes study in patients with T2D showed that patients who could not manage enough blood glucose regulation had a risk of vascular complications than the ones getting intensive therapy for seeing to it that strict glucose regulation was achieved [32,33].

Diabetes-correlated dyslipidemia got a lot of emphasis in recent years and became the reason for umpteen review papers [34,35]. Changes in the blood lipid profile in DM is related to enhanced hepatic synthesis of triglycerides-rich proteins, causing escalated generation of atherogenic very low density lipoproteins (VLDL). This change can be rectified partly via insulin therapy.

Hyperglycaemia and advanced glycation end-products-Role in atherosclerosis

High glucose amounts for a particular time period, the risk of cardiovascular system (CVS) complications is known as “metabolic memory” or “legacy effect”. One of the probable mode of action is the Advanced glycation Products (AGE) that takes place when the blood glucose amounts are high. These compounds are difficult to metabolize, thus collecting in patients having a long history of incomplete blood glucose regulation. This collection might exaggerate the propagation of vascular disease in DM patients. A lot of studies have shown the correlation among improperly regulated blood glucose as well as micro vascular complications of DM, like renal as well as retinal symptoms. Nevertheless, the correlation among enhanced blood glucose as well as atherosclerosis of large arteries seems to be simple. Direct pro atherogenic action of glucose amounts on the cell kinds that are there in atherosclerotic lesions could not be shown [36]. It is probable that escalated blood glucose acts mainly on tissues like liver, or adipose tissue (AT) as well as the action on atherosclerotic lesions cells is modulated by changes in signaling from these tissues. An escalated intracellular glucose amounts enhances the flux via cellular metabolic pathways, like the mitochondrial electron transport system that might cause ROS oversynthesis. Further glucose metabolites can produce proinflammatory responses via activation of protein kinase C-beta as well as aldose reductase [37].

Other possibility is that enhanced glucose works mainly via extracellular modes, like, by stimulation of glycation as well as glycoxidation of proteins, causing AGE synthesis. AGE collection in diabetics when the blood glucose amount is escalated, seems to be significant in the atherosclerosis synthesis. These molecules effect endothelium activation as well as surface expression of adhesion molecules, thus facilitating adhesion as well as entrance of monocytes/macrophages into the sub endothelium space at the initial stages of plaque synthesis. Further these molecules elevate cytokine liberation by macrophages, thus sustaining a proinflammatory context in the forming plaque. A separate mode is glycation of LDL particles, that can be considered as one of the atherogenic manipulation of LDL. It was further demonstrated that AGE might inhibit reverse cholesterol by decreasing the expression of ATP- binding membrane cassette transporters A1 as well as G1 (ABCA1 as well as ABCG1 on monocytes, to increase vasoconstriction by enhancing endothelin 1 amounts, as well as decrease vasodilation by decreasing nitric oxide (NO) amounts. Ultimately, AGE takes part in the manipulation of ECM molecules that also facili-
The Role of Diabetes Mellitus (Both T1D and T2D) in the Atherosclerosis Development-A Systematic Review with Part of Inflammation along with Altered Glucose and Lipid Metabolism for Forming Therapeutic Approaches

Figure 2: Courtesy ref no-97. Metabolic mechanisms of macrophage polarization. M1 macrophages are characterized by predominantly glycolytic metabolism. Glycolysis consists of breaking down a 6-carbon glucose molecule (where each carbon is depicted as a blue circle, white when phosphorylated) into 3-carbon sugars then into pyruvate, ATP, NADH and H+. The transcriptional programme that supports glycolysis is mediated by HIF1 and at least in part by IRF5. A Glucose substrate is provided by increased expression of the glucose transporter GLUT1. Meanwhile several glycolytic enzymes undertake non-canonical roles to support M1 effector functions. The mitochondrial tricarboxylic acid (TCA) cycle is disrupted, leading to accumulation of citrate and succinate which also enhance M1 effector function. The M2 macrophage has a fully intact TCA cycle, enhanced OXPHOS and increased mitochondrial biogenesis. ATP citrate lyase (ACLY) is activated downstream of IL4 signaling and enhances M2 effector functions through epigenetic mechanisms and producing substrates for lipogenesis. The sedoheptulose kinase (CARKL) represses the pentose phosphate pathway (PPP). Transcriptional programmes for M2 macrophage metabolism are mediated by PPARγ and LXR. GLUT1: Glucose Transporter-1; HK: Hexokinase; NLRP3, NACHT, LRR, and PYD domains-containing protein; OXPHOS: Oxidative Phosphorylation; TCA: Tricarboxylic Acid Cycle; PPP: Pentose Phosphate Pathway; aPFK2: Ubiquitous Phosphofructokinase2; PKM2: Pyruvate Kinase Isozyme 2; G6P: Glucose-6-Phosphate; F6P: Fructose-6-Phosphate; F1,6BisF: Fructose-1,6-Bisphosphate; G3P: Glyceraldehyde-3-Phosphate; DHAP: Dihydroxyacetone Phosphate; NO: Nitrous Oxide; ROS: Reactive Oxygen Species; CoA: Coenzyme A; HIF1: Hypoxia-Inducible Factor 1; IRFs: Interferon Regulatory Factor 5; IL-4: Interleukin 4; IL-4Rα: IL-4 Receptor Alpha; ACLY: ATP-Citrate Lyase; CARKL: Carbohydrate Kinase Like/Sedoheptulose Kinase; Ac: Acetylation Mark; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; LXR: Liver X Receptor; SREBP: Sterol Regulatory Element Binding Protein; PGC-1β: PPARγ Coactivator 1-Beta.

induced obesity (DIO), protection conferred by ABCA1/APOA1 action are STATs 3-based, like the anti-inflammatory AT phenotype of mice with a myeloid deficiency of janus kinase (JAK) [42] (Figure 2).

In case of mouse models of atherosclerosis, like apolipoprotein E-deficient (apo E-) mice with chemically stimulated diabetes, RAGE deficiency was demonstrated to ameliorate atherosclerotic lesions formation [43]. These observations enhance the feasibility of utilizing receptor for RAGE inhibitors for decreasing atherosclerosis formation in diabetic patients.

Direct part of AGE in inducing the expression of scavenger receptors as well as facilitating phagocytosis has been illustrated in a study recently [44]. Here AGE-modulated bovine serum albumin caused morphological alterations in cultured murine macrophages, enhanced their phagocytic action. This action got ameliorated by a fructose containing sulphated polysaccharide, fucoidan that has revealed anti-inflammatory characteristics. DM correlates with a pro inflammatory state. It is probable that increased glucose uptake via lesional cells gets facilitated by pro inflammatory signalling as well as phagocytic action by lesion macrophages instead of the direct action of hyperglycemia.

More understanding on probable relation among hyperglycemia as well as atherosclerosis was disclosed through animal studies. Hyperglycemia's action on vascular lesions in the apo E-/- mouse model showed that advanced lesions occur in hyperglycaemic mice earlier as compared to normo glycaemic controls. Further, exaggerated atherogenesis was seen earlier than any changes that could be found in the plasma lipid levels of normo glycaemic mice [45]. By crossing apo E-/- or LDLR-deficient mouse strains with mice carrying a point mutation in the gene encoding insulin (Ins 2+/+Akita; apo E-/- mice) a novel model of hyperglycemia- exaggerated atherosclerosis was formed [45]. These animals possessed the property of spontaneously forming DM as well as atherosclerosis, thus presenting with insulin deficiency, hypercholesteremia (mainly via LDL-cholesterol escalation), as well as increased rate of atherosclerotic plaque development when kept on a regular chow diet. Deficient lipoprotein clearance was documented by Jun., et al [46] via lipolysis-induced lipoprotein receptors as well as changed lipoprotein composition. This animals model was anticipated to be of use for evaluating atherosclerosis in relation to T1D as well as examining probable therapeutic methods. Like Ins 2+/+Akita; apo E-/- mice were utilized to show the advantage of leptin on atherosclerotic plaques propagation [46].

Escalated glycation might further have a part at later stages of atherosclerosis formation. As shown in a recent evaluation, glycation of erythrocytes in T2D patients might favour their internalization by the endothelial cells through phagocytosis, that prevents endothelial function. This process is going to aid in unstable plaque formation with following thrombosis in pts with T2D as well as atherosclerosis [47].

The amounts of AGE might also be utilized for diagnosis as well as assessing the chances of atherosclerosis formation as well as vascular complications. Recently evaluation of skin AGE amounts via autofluorescence (AF) in case of patients with type 1 diabetes from Japan along with their gender as well as age matched controls showed that escalated AF in Diabetes seemed to be an independent causative factor for carotid atherosclerosis [48].

Part of oxidative stress

Diabetes is understood to be correlated with escalated amounts of reactive oxygen species (ROS) synthesis as well as decreased action of antioxidant systems [49]. In vitro studies have shown that escalated ROS synthesis is associated with hyperglycemia [50]. More studies in animals have shown the association of NADPH Oxidase family protein Nox1 that was upregulated in diabetic mice. Knockdown of this particular protein ameliorated atherosclerosis propagation in these animals [51]. Part of Oxidative Stress in Diabetes-related atherosclerosis got corroborated in evaluation in apo E-/- mice deficient for 1 of the major controllers of antioxidant enzymes, glutathione

peroxidase 1 (Gpx1). On streptozotocin induced diabetes animals that had deficiency for Gpx1 as well had exaggerated atherogenesis, with escalated plaque size, macrophage infiltration as well as enhanced expression of inflammatory markers, whereas restoring Gpx1 decreased atherogenesis [52]. In total vascular ROS escalation seems to be associated with atherosclerosis in relation to Diabetes, and antioxidant treatment might be thought of in managing the disease, though more selective methods are required to get needed outcomes with antioxidant drugs [40].

### Part of protein kinase C activation

Protein kinase C (PKC) is one of the crucial Protein kinases modulating the cellular signalling pathway that responds to cytokines, growth factors, as well as other messenger molecules [53]. Escalated glucose uptake by vascular cells causes enhanced production of diacyl glycerol (DAG), that is an activator of PKC. Increased PKC activation can also occur following Oxidative Stress [54]. Escalated vascular PKC activation was corroborated in animal models of Diabetes. Increased PKC signaling causes multiple proatherogenic actions that are decreased synthesis of nitric oxide (NO) as well as disturbed vasodilation, endothelial dysfunction as well as enhanced permeability as well as synthesis of cytokines as well as extracellular matrix (ECM) [42]. The complicated intracellular signalling cascades that get activated through PKC make it tough to exactly suggest the true mode of its proatherogenic actions. Nevertheless, studies in apo E-/- mice have demonstrated that chemical or genetic inhibition of PKCβ caused a decrease in development of atherosclerotic lesions [56]. These observations point that PKC might be thought of as a potential treatment target.

### Diabetes-related chronic inflammation as well as atherosclerosis

Chronic Inflammation is a characteristic that both Atherosclerosis as well as Diabetes mellitus share. At present Atherosclerosis is thought to be a Chronic Inflammatory problem. In cases of T2D, enhanced action of inflammasome as well as escalated amounts of nucleotide-binding oligomerization domain-like receptor 3 (NLRP3) were shown, along with escalated amounts of pro Inflammatory cytokines IL-1β as well as IL-18 [57]. One of the direct connections among atherosclerosis as well as Diabetes mellitus found in the inflammatory pathways is neutrophil extracellular trap formation or NETosis [58], that is a special type of cell death of macrophages, at the time when cells liberate chromatin into the extracellular space for trapping as well as killing bacteria. This event is believed to be escalated in chronic sterile inflammation as well as autoimmune situations where it aids in the pathology formation [40]. Elevated amounts of NETosis markers were observed in patients of T2D [58]. Further it was demonstrated that NETosis might be elevated in hyperglycemic situations [59]. The probable part of elevated NETosis in atherosclerosis formation was corroborated in animal models. The atherosclerotic apo E-/- mice which also don’t possess neutrophil elastase as well as proteinase 3 essential for NETosis had decreased atherosclerotic lesion development as compared to single knockout animals [60].

An active lookout for anti-inflammatory drugs naturally which could decrease the chance of atherosclerotic cardiovascular disease in diabetic patients was carried out in recent years [54]. Of the anti-inflammatory drugs utilized for treating diabetic patients are salicylates, that were demonstrated to lower the glucose amounts while being efficacious for cardiovascular disease avoidance as well as decrease the risk of thrombosis [61]. Utilization of Inflammatory cytokine inhibitors seemed to be a favourable approach for decreasing cardiovascular risk in diabetic patients. It was demonstrated that canakinumab, a monoclonal antibody which binds as well as neutralizes interleukin-1beta, markedly decrease markers of Inflammation in patient having controlled diabetes mellitus as well as high cardiovascular risk, but did not have any main action on LDL cholesterol [62]. One more study demonstrated that canakinumab, had a similar advantage for decreasing cardiovascular risk in patients with and without diabetes mellitus, but had no action on de novo diabetes mellitus incidence [63]. The search for efficacious anti Inflammatory treatments decrease atherosclerosis in diabetic patients is on [64].

### Part of circulating non coding RNAs

Non coding RNAs were demonstrated to be involved in multiple human disorders and are at present thought of as probable biological...
markers as well as disease modifiers. Genetic methods update allowed study of non coding RNAs and demonstrated their correlation with pathogenic events. Micro RNA are short RNAs fragments which can inhibit the expression of some genes at the mRNA level. These RNAs fragments can be synthesized via numerous cell kinds as well as tissues and can be seen circulating in the blood either free or limited to membrane microvesicles. Collecting proof shows Micro RNA are significantly probable biological markers. Nevertheless, the complicated nature of the mi RNAs landscape that correlates with human diseases, like DM, is so large that it is possibly more favourable to examine mi RNAs signatures (combination of numerous mi RNAs) instead of single mi RNA kind [65].

In humans 2500 mi RNAs have been isolated and lot of them were demonstrated to have a part in DM pathogenesis. Especially Micro RNA-146 as well as Micro RNA-126 have got focus, of these mi RNAs that have importance in atherosclerosis as well as diabetes mellitus. Micro RNA-146 as well as Micro RNA-126 have a significant part in the endothelial cells, where their expression gets induced through inflammatory cytokine signalling and causes negative feedback loop for regulating inflammatory endothelial activation [67]. Hence control of these mi RNAs has chances of being involved in the early stages of atherosclerosis lesion formation in diabetic patients. Micro RNA-126 expression was demonstrated to be a risk factor for T2D formation, as well as it has a protective part in a mouse model of atherosclerosis [68,69].

Another significant mi RNAs, mi RNA-378a was demonstrated to have a significant part in the metabolism, that includes energy as well as glucose homeostasis [70]. A very recent research by Chen., et al. [71] showed that this mi RNAs has role in atherosclerosis formation. They demonstrated that mi RNA-378a targets signal regulatory protein alpha (SIRPα), thus controlling phagocytosis as well as polarization of macrophage. Further, the amounts of this mi RNAs was decreased in aorta of apo E⁻/- mice as compared to controls, emphasizing its significant part in the control of Atherosclerosis-related events [71].

Following noncoding RNA that probably participates in diabetes-related atherosclerosis is a long noncoding RNA Dnm3os (dynamic 3 opposite strand). This RNA was demonstrated to be escalated in macrophages from diabetic mice including apo E⁻/- diabetic mice, along with monocytes from T2D patients. Overexpression of this RNA facilitated inflammatory gene expression as well as phagocytosis by macrophages and caused chromatin epigenetic alterations, further facilitating the inflammatory response [72]. Greater studies are required for isolation of as well as characterisation of noncoding RNAs that might have derogatory or were advantageous for cardiovascular (CVS) risks in diabetic patients.

Part of epigenetic manipulation

Persistent as well as temporal hyperglycaemic exposure were demonstrated to effect various important cellular signaling pathways, that included PKC activation as well as, Oxidative Stress as well as Transforming growth factor beta (TGFβ)-SMD-MAPK signalling [73,74]. Further hyperglycaemia escalated the flux into the polyol as well as hexosamine pathways as well as escalated the development of AGE which are also correlated with changes in signaling pathways [75]. All these different actions make hyperglycaemia a big risk for diabetic complications as well as vascular processes. Chromatin alterations have a significant controlling part in the correlation of glycaemia as well as vascular complications.

Hyperglycaemia gets correlated with a wide range of Chromatin alterations which influence the genetic signatures of vascular endothelial cells. Like genome wide sequencing study of aortic endothelial cells that were exposed to a high amount of glucose showed histone H3K9/K14 hyperacetylation patterns which were inversely correlated with DNA methylation in CpG clusters. This finding correlates with the activation of transcription pathways associated with atherogenic actions as well as vascular diseases. This study showed that hyperglycaemia is capable of stimulating various Epigenetic alterations in the vascular endothelium as well as atherosclerosis pathogenesis [76].

Transient hyperglycaemia further triggers mono methylation of H3 histones at lysine 4 (H3K4m1) as well as other histones lysine modulations. H3K4m1 was demonstrated to be written by the Ser 7 lysine methyl transferase. The changes seen at the promoter of the RELA gene that encodes the NFκB-p65 subunit remained for 5 - 6 days following the cells were returned to a normoglycaemic state [77].
Hence cytokines, chemokines as well as adhesion molecules get influenced by hyperglycaemia via the controller of one of the key pro inflammatory transcription factors associated with vascular as well as metabolic complications, of which one is atherosclerosis [78]. Of these molecules, vascular cell adhesion molecules (VCAM-1), that facilitates adhesion of monocytes to the arterial endothelial cells, as well as monocyte chemoattractant protein-1 (MCP-1), that cause macrophage infiltration, needs to be emphasized [79]. The escalated expression of both NFκB-dependent MCP-1 as well as VCAM-1 as well as genes encoding NFκB-p65 itself was seen in aorta of apolipoprotein A knockdown mice that were earlier exposed to hyperglycaemia.

Further these results of hyperglycaemia stimulated alterations in the transcriptional activation of genes which are correlated with endothelial dysfunction [80]. Acetylation as well as hyper Acetylation, is also feasible and can result in escalated expression of the following genes for atherosclerotic lesion formation at various stages via the inflammatory response as well as ECM degradation; MCP-1, MMP10, ICAM, HMOX1 as well as SLC7A11 [75] (Figure 3).

![Figure 3: Courtesy ref no-97. Epigenetics of macrophage polarization in T2D. Epigenetic mechanisms that modulate transcription act on chromatin remodeling and altering DNA accessibility to transcriptional machinery. Modifications are in dynamic exchange where methylation and acetylation status of H3K27 dictate repression or activation of transcription, respectively. When chromatin is closed, methylation is dynamically altered by EZH2 (adding methyl groups) and KDM6B (removing methyl groups), and the active transcription mark (H3K27ac) is removed through HDAC3 activity. GPS2-SMRT also participate in gene repression. During active transcription, the active transcription mark (H3K27ac) is maintained whilst EZH2-KDM6B play smaller roles. GPS2-SMRT are not present to exert repressive effects.](image-url)
Future research showed the role of Set 7/9, that probably coactivates NFκB transcriptional activation in monocytes in response to inflammation via the activation of the H3K4dem promoter; as well as the analogous action was seen in endothelial cells in response to hyperglycaemia [79,80]. Further the induction of Set 7-mediated upregulation of HMOX1 was demonstrated that early intrusive monitoring of the glycaemic profile in diabetic patients can have a significant role of hyperglycaemia in the long term outlook resulting in a phenomena known as metabolic memory [80].

In case of M1 macrophages PPAR α inhibits the expression of proinflammatory mediators via negative control of AP1 as well as NFκB. Various studies documented the advantage of PPAR α activation in T2D as well as its sequelae. PPAR α agonists have been used in T2D patients as well as effective in atherosclerosis, via inhibition of foam cell development as well as inflammatory signaling. The advantage is got via interference with c-Jun as well as c-Fos interactions as well as by limiting lipid collection via repression of FA transport protein (FATP)-1 [81,82].

All these observations point that there are multiple links among hyperglycaemia, Epigenetic alterations as well as cardiovascular risk that can't be overlooked. Nevertheless, there are still many blind areas in the insight of underlying molecular modes as well as their connections. In in vitro as well as ex vivo modeling, PPAR γ inhibits M1 signaling related to LPS +IFNγ stimulation, that includes iNOS, COX-2 as well as a 1L-2 [83-87]. Significantly macrophages, PPAR γ is also downstream target of internalized lipids, as well as modulates expression of scavenger receptors for foam cell development [88]. Hence PPAR γ deficient mice show impaired M2 maturation as well as develop accelerated IR as well as metabolic inflammation in DIO [89]. Notably, overexpression of PPAR γ show that mature adipocyte PPAR γ in fact is the major insulin sensitizing part (overexpression phenotype is comparable to TZD therapy [90]. Little or nil benefit is seen in DIO if PPAR γ overexpression is there in macrophages [90]. These over/under-expression studies show diverging functions of PPAR γ. More work is needed in mode to find exact role as well as control of nuclear receptors as well as different isoforms in separate cell kinds as well as microenvironment. In in vitro as well as ex vivo modeling.

Conclusion

Earlier we had reviewed the role of micro RNA's in obesity as well as diabetes mellitus and importance of treating both together with the term diabesity coined along with the role of various transcription factors in lipid metabolism. Further we had evaluated the role of developing drugs for brown adipose tissue thermogenesis (BAT) along with mirabegron in obesity as well as macrophage polarization in Non-alcoholic Fatty Liver Disease (NAFLD) along with various transcription factors in macrophage polarization, besides reviewing the role of macrophage polarization in tackling obesity as well as diabetes mellitus [91-96]. Here we have further tried to summarize the correlation among diabetes mellitus as well as atherosclerosis. Both kinds of diabetes mellitus have been demonstrated to be independent risk factors for escalated rate of atherosclerosis formation. Now it is seen that the pathogenesis of diabetes mellitus as well as atherosclerosis are closely related, but the mode, as well as molecular crosstalk is still getting evaluated. Of the known etiopathogenesis that links DM, as well as atherosclerosis represent dyslipidaemia, hyperglycaemia correlated with AGE synthesis, enhanced oxidative stress as well as inflammation. Inspite of the continuous look out for innovative treatment methods, small amount of medicines have demonstrated strong efficacy in relation to decrease the chance of atherosclerosis formation in the particular population of diabetic patients. Enough glycemic regulation as well as decrease of known risk factors continue to be maximum utilized methods to protect these patients. Further we have tried to summarize how salsalates might work in the inflammatory cause besides role of the monoclonal antibody canakinumab. Moreover we have summarized that how metformin acts with STAT3 as the downstream target and further utilizing the APCB1 pathway and how PPAR γ as well as PPARα influence lipid metabolism and influence atherosclerosis of the known antidiabetic drugs that might be useful anti-diabetics in therapy of DM for the prevention of atherosclerosis. Further role of developing RAGE inhibitors might be helpful in tackling the AGE components in diabetes, preventing atherosclerosis. Greater studies are required for showing the precise signalling modes of DM-related macrovascular injury as well as to pinpoint the particular therapeutic targets.
The Role of Diabetes Mellitus (Both T1D and T2D) in the Atherosclerosis Development-A Systematic Review with Part of Inflammation along with Altered Glucose and Lipid Metabolism for Forming Therapeutic Approaches

Bibliography


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