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Diabetes Induced Inflammation and Accelerated atherosclerosis.

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Abstract

Monocytes and macrophages are like the body's defence team against inflammation, producing different substances that cause inflammation, like cytokines, chemokines, and lipid mediators. A common problem related to inflammation is cardiovascular disease, which is often made worse by diabetes. New studies have shown that in mice and humans with type 1 diabetes, the monocytes and macrophages become more active in producing an enzyme called acyl-CoA synthetase 1 (ACSL1). This enzyme affects how a certain kind of fat is used in the body. Interestingly, when this enzyme is stopped from working, it helps protect these cells from the harmful effects of inflammation and atherosclerosis (a disease that narrows the arteries) caused by diabetes, at least in mice. This research helps us learn more about how ACSL1 and similar substances in monocytes and macrophages are linked to inflammation and the faster artery-clogging in diabetes-related heart diseases. This information is exciting because it might lead to new ways to treat vascular diseases that are made worse by diabetes.

Keywords: Acyl-CoA synthetase, Arachidonic acid, Eicosanoids, Macrophage, Monocyte

Introduction-

A common chronic inflammatory condition of the artery wall known as atherosclerosis frequently results in impairment and even death. A lesion of the artery wall's intimal layer and a build-up of plaques are the last signs of atherosclerosis. Atherosclerotic plaque erosion or rupture that occurs later results in thrombotic episodes that may be deadly. Years of rigorous study have shown that the pathophysiology of atherosclerosis is complicated, with fat build-up and chronic inflammation in the artery wall serving as its primary drivers. Hypercholesterolemia and abnormal lipid metabolism are conventionally linked to atherosclerosis. As a known risk factor for cardiovascular illnesses, a higher amount of circulating modified low-density lipoprotein (LDL) is seen [i]. However, the pathophysiology of the disease involves several elements, the most important of which is inflammation, and appears to be more complicated than changes in lipid metabolism.

Atherosclerotic plaques can narrow the blood vessel's lumen, causing ischemia and altering the metabolism of the fed tissues. Even more hazardous is thrombogenesis, which can frequently have fatal results and is caused by unstable plaques and, in some cases, on the surface of undamaged plaques.

Diabetes Mellitus

Chronic hyperglycaemia, which is the hallmark of diabetes mellitus, is caused by problems with insulin secretion, action, or a combination of these. Diabetes mellitus is a collection of metabolic disorders that affect how carbohydrates are metabolised.

Diabetes-related metabolic abnormalities can be brought on by low insulin production and/or insulin resistance in the target tissues. At the level of insulin receptors, the signal transduction system, and/or effector enzymes or genes, the disease primarily affects skeletal muscles and adipose tissue, but it can also damage the liver[ii]. Polyuria, polydipsia, weight loss, occasionally coupled with polyphagia, and blurred vision are all signs of hyperglycaemia. Growth impairment and susceptibility to specific diseases are additional potential side effects. The nonketotic hyperosmolar syndrome or hyperglycaemia with ketoacidosis are the primary life-threatening effects of untreated diabetes.

However, certain people, typically those with type 2 diabetes, may experience no symptoms in the first stages of the condition.

Type 1 Diabetes Mellitus

The autoimmune loss of insulin-producing pancreatic -cells results in type 1 diabetes (T1D) [16]. Polydipsia, polyphagia, and polyuria are the traditional trifecta of T1D symptoms. The condition is most frequently discovered in children and teenagers, who typically exhibit the mix of symptoms in addition to a severe hyperglycaemia that requires exogenous insulin supply for the rest of their lives.

T1D patients can experience acute pancreatitis with leukocyte build-up due to pancreatic lesions that can develop. Exocrine and endocrine pancreatic organs are both impacted by the condition.

Diabetes Type 2

The global rise in obesity is a contributing factor to the rising prevalence of type 2 diabetes mellitus (T2D), which today affects more than 370 million individuals. Diabetes is identified by measuring glucose levels at fasting and two hours after a prescribed oral glucose load. The contrast between impaired fasting glucose and/or impaired glucose tolerance is frequently used to identify prediabetes.

Atherosclerosis and Diabetes Mellitus: A Pathophysiological Conjunction

Multiple pathogenic mechanisms seem to link diabetes mellitus and atherosclerosis. Studies on diabetic people have revealed an elevated risk and hastened development of atherosclerosis. For instance, multiple investigations [26,27] have documented the early onset of atherosclerosis in children and adolescents with T1D. Theoretical explanations for this acceleration include dyslipidaemia with elevated levels of atherogenic LDL, hyperglycaemia, oxidative stress, and elevated inflammation (Figure 1).

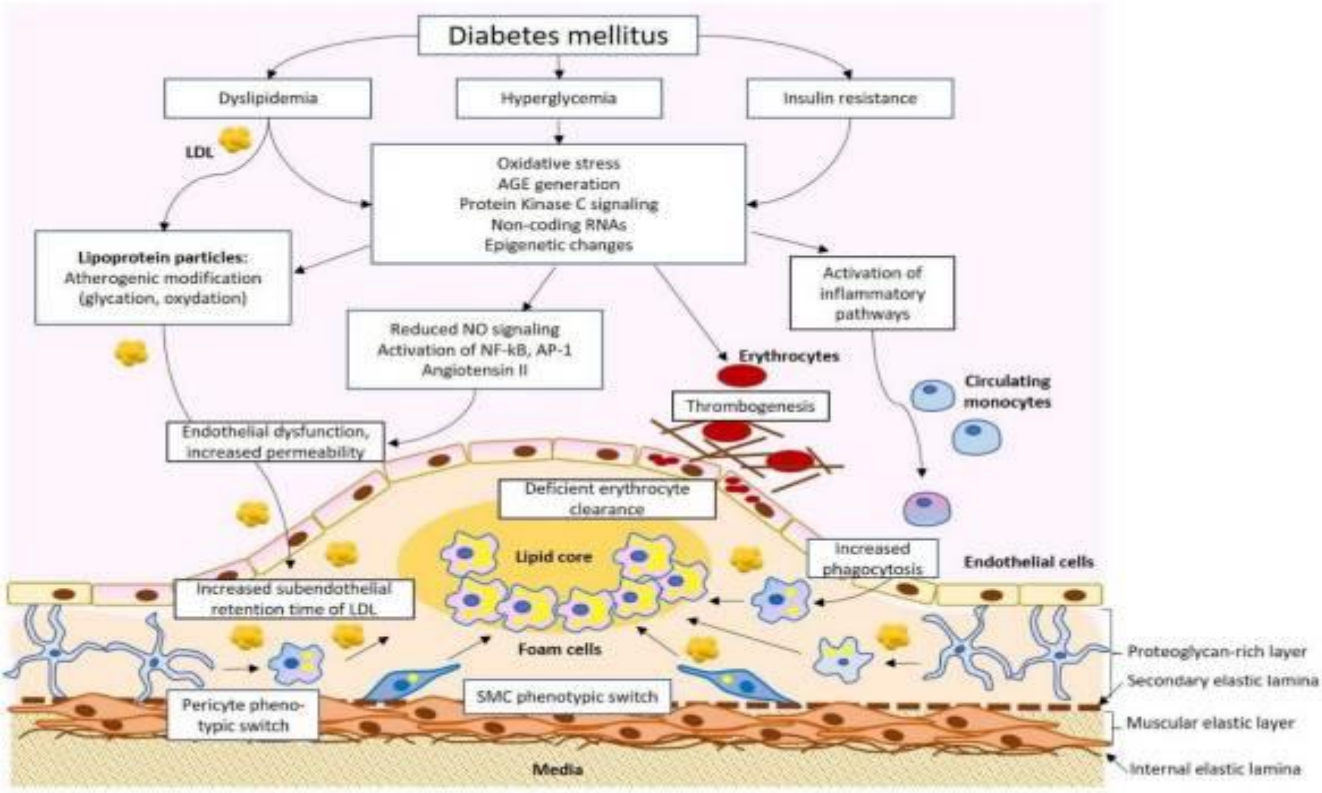

Figure 1 Shows an outline of the pathophysiological relationship between atherosclerosis and diabetes mellitus. A variety of physiological changes brought on by dyslipidaemia, hyperglycaemia, and insulin resistance include the production of atherogenic low-density lipoprotein (LDL), advanced glycation end products (AGE), and the activation of pro-inflammatory signalling, which affect various cell types in the arterial wall and lead to the growth of atherosclerotic lesions. Smooth muscle cells, or SMC.

Dyslipidaemia in Patients with Diabetes

The role of small dense LDL (sdLDL) levels as a prominent risk factor for atherosclerosis has garnered significant attention, particularly in exploring the intricate ties between diabetes and atherosclerosis. Native LDL particles, while not inducing substantial intracellular lipid build-up in cultured cells, exhibit limited atherogenicity. This is intriguing as LDL is conventionally considered a key catalyst in the formation of arterial plaques. The substantial accumulation of lipids is a consequence of atherogenic modifications in LDL, altering their physicochemical attributes.

The prevailing concept postulates a series of modifications that LDL particles undergo in the bloodstream, potentially leading to a cascade of LDL alterations. According to this hypothesis, the initial desalination of an LDL particle is followed by an increase in particle density, reduction in particle size, and the acquisition of a negative charge. These evolving characteristics enable the isolation of these distinct particles. Another subset of modified LDL is the human version of very-low-density LDL (VLDL). Altered lipid composition and diminished antioxidant capacity render small dense lipoprotein particles more susceptible to oxidative processes. It is plausible that the later stages of LDL modification are when oxidation predominantly occurs.

Experiments conducted on a diabetic mouse model provide substantial support for the pivotal role of LDL modification in extending the retention duration of lipoprotein particles beneath the endothelial layer. By extracting LDL fractions from both type 1 diabetes (T1D) patients and healthy individuals, and subsequently administering them to diabetic mice, researchers evaluated their retention within the arterial walls, particularly in regions prone to atherosclerosis. Intriguingly, the LDL obtained from T1D patients exhibited a retention rate over four times higher than that derived from the control group, underscoring the significance of LDL modifications in atherosclerosis progression.

The term "metabolic memory" or "legacy effect" refers to the possibility of developing diabetic cardiovascular problems during a period of prolonged exposure to high glucose levels. The development of advanced glycation end-products (AGE), which take place when the blood glucose level is high, is one of the potential mechanisms of this effect. These substances are difficult to digest and build up in people who have a lengthy history of poor blood glucose control. Such build-up could hasten the vascular disease progression in diabetic people. Numerous studies have proven the connection between poorly regulated blood glucose levels and the microvascular consequences of diabetes, including symptoms in the kidneys and eyes. The connection between high blood sugar and atherosclerosis of the major arteries, however, seems to be less clear-cut. It was not possible to show that high glucose levels had direct pro-atherogenic effects on the cell types that are frequently found in atherosclerotic lesions [38]. It is still plausible that increased glucose preferentially affects certain tissues, such as the liver or adipose tissue, and that these tissues' altered signalling then affects the atherosclerotic lesion cells. Increased flux through cellular metabolic pathways, such as the mitochondrial electron transport system, brought on by a high intracellular glucose level may lead to an overproduction of reactive oxygen species (ROS). Furthermore, by activating protein kinase C-beta and aldose reductase, glucose metabolites might cause pro-inflammatory reactions [iii].

Another explanation is that high blood glucose largely affects extracellular systems, such as by causing protein glycation and glycoxidation, which leads to the production of AGE. When blood glucose levels are raised in diabetic patients, AGE build up and appear to be a major factor in the development of atherosclerosis.

A recent study has demonstrated the direct effect of AGE in activating the development of scavenger receptors and encouraging phagocytosis[iv]. In this study, cultured murine macrophages exposed to AGE-modified bovine serum albumin underwent morphological alterations that elevated their phagocytic activity. A sulphated polysaccharide called fucoidan, which is known to have anti-inflammatory effects, decreased this effect. The pro-inflammatory state that is known to be linked to diabetes is explored in more detail below. Instead of being a direct result of hyperglycaemia, it's probable that higher glucose uptake by lesion cells is encouraged by pro-inflammatory signalling and increased phagocytic activity by lesion macrophages.

What Part Oxidative Stress Plays

Both increased ROS generation and decreased antioxidant system function have been linked to diabetes. Studies conducted in vitro have shown a connection between elevated ROS production and hyperglycaemia[v]. Additional animal investigations have shown that the NADPH oxidase family protein Nox1, which was up regulated in diabetic mice, is involved. In these animals, this protein's knockdown slowed the development of atherosclerosis.

Protein Kinase C (PKC) Activation's Function

One of the important protein kinases that mediates the cellular signalling system, which reacts to cytokines, growth hormones, and other messenger molecules, is protein kinase C (PKC) [53]. Vascular cells that take in more glucose produce more diacylglycerol, which is an activator of PKC. Oxidative stress can also trigger increased PKC activity[vi]. In diabetes animal models, elevated vascular PKC activation was confirmed. Pro-atherogenic consequences of enhanced PKC signalling includes lower NO generation and impaired vasodilation, endothelial dysfunction, and increased permeability, as well as increased production of cytokines and extracellular matrix.

Circulating Non-Coding RNAs: Their Function

Since they have been linked to many human diseases, non-coding RNAs are now thought to be potential biomarkers and disease modifiers. Non-coding RNAs could be investigated in more detail thanks to improvements in genetic techniques, which also revealed their connections to pathogenic processes. Short RNA pieces called microRNA (miRNA) can prevent some genes from being expressed at the mRNA level. These RNA fragments can either circulate freely in the circulation or are contained in membrane macrovesicles, and they can be produced by a variety of cell types and organs. MiRNAs are being highlighted as significant potential biomarkers by mounting evidence. Although the complexity of the miRNA landscape linked to human

diseases, such as diabetes, is so great that studying miRNA signatures (combinations of many miRNA types) rather than individual miRNA types is probably more fruitful.

Conclusions

It has been established that both forms of diabetes mellitus are separate risk factors for accelerated atherosclerosis development. Although it is now well established that atherosclerosis and diabetes mellitus have a common pathophysiology, the mechanisms and molecular interactions underlying this association are still being debated. Dyslipidaemia, hyperglycaemia with AGE formation, increased oxidative stress, and inflammation are a few of the pathogenic factors that link diabetes with atherosclerosis. Few drugs have demonstrated strong positive effects in terms of lowering the risk of atherosclerosis formation in the specific population of diabetes patients, despite the ongoing quest for novel therapeutic options. The most common methods for protecting such patients continue to be adequate glucose control and reducing identified risk factors. More research is required to pinpoint the precise signalling processes that cause diabetes-related macrovascular damage and to choose precise treatment targets.

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