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MODERN VIEWS ON THE PATHOGENESIS OF ATHEROTROMBOSIS IN TYPE II DIABETES

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Abstract

Worldwide, the incidence of diabetes mellitus is increasing due to the interaction of obesity, inflammation, and hyperglycemia. Immune activation and cytokine production lead to insulin resistance and other components of metabolic syndrome, establishing a link between diabetes and atherosclerosis. Endothelial dysfunction induced by hyperglycemia is associated with adventitious inflammation in experimental models of diabetic atherosclerosis and increased oxidative stress stimulating vascular vascular neovascularization. Recent studies have shown increased inflammation, neovascularization, and intraplatelet bleeding in human diabetic atherosclerosis. This is an inflammatory microangiopathic process associated with plaque rupture leading to coronary thrombosis on its own. The tissue factor, which is the most potent trigger of the coagulation cascade, increases in patients with diabetes mellitus and without glycemic control. Circulating tissue factor microparticles are also associated with platelet macrophage apoptosis, establishing a link between inflammation, platelet rupture, and blood thrombogenicity. High-density lipoproteins responsible for free cholesterol uptake are reduced in patients with insulin resistance and diabetes mellitus. Treatment with high-density lipoproteins leads to a significant reduction in platelet macrophages and an increase in smooth muscle cells. These effective effects may be responsible for the stabilization of coronary plaques in patients receiving the recombinant apolipoprotein AI Milano/phospholipid complex. Finally, peroxisomal proliferator-activated receptors (PPARs) are now considered regulators of nuclear transcription in atherosclerosis. Three subgroups have been identified: PPAR-alpha, -delta, and -gamma, which play an important role in the regulation of lipid metabolism, platelet inflammation, adhesion molecules, cytokine expression, and matrix metalloproteinases. Numerous experimental

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studies have confirmed plaque stability with PPAR-gamma agonists—a group of drugs that show great promise in the treatment of diabetic atherosclerosis.

Diabetes affects 150 million people worldwide and about 20 million in the United States. The prevalence of diabetes among adults in the United States has increased by 40% over the last decade and is expected to increase by 165% between 2000 and 2050 (A.H. Mokdad, B.A. Bowman, 2001). Furthermore, one-third of the population born in 2000 will suffer from diabetes mellitus, resulting in a 30% reduction in life expectancy, which is primarily associated with atherosclerosis, accounting for 80% of deaths among diabetic patients in North America (K.M. Narayan, J.P. Boyle, 2003). The mortality rate from myocardial infarction in patients with diabetes mellitus is significantly higher than in patients without diabetes (W. Otter, S. Claybrink, 2004). As a result, diabetes imposes a significant economic cost on society, estimated at $100 billion annually in the USA alone (L. Ettaro, T.J. Songer, 2004).

This article focuses on the pathophysiology of diabetic atherosclerosis, ranging from metabolic syndrome to advanced diseases, plaque rupture, and coronary thrombosis. A state of inflammation, neovascularization, apoptosis, and disease-associated hypercoagulation is considered. Finally, new experimental treatment methods are presented.

Metabolic syndrome

Previously known as a prediabetic condition, metabolic syndrome is characterised by at least two of the following conditions: abdominal obesity, insulin resistance (increased fasting glucose levels), hypertension, dyslipidemia (increased triglycerides, decreased cholesterol and high-density lipoproteins [HDL]) and microalbuminuria (P. Zimmet, 2001).

Epidemiological studies have identified the significance of metabolic syndrome in diabetes mellitus. As is commonly observed, when both diseases coexist, the prevalence of cardiovascular diseases reaches 19.2% of the population. However, in the absence of metabolic syndrome, the prevalence of cardiovascular diseases in patients with diabetes mellitus is as low (8.7%) as in the non-diabetic population (7.5%) (C.M. Alexander, P.B. Landsman, 2003).

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Congenital immunity and inflammation play an important role in the development of insulin resistance and diabetes mellitus. Since this hypothesis was proposed in 1997, at least 12 studies have shown that circulating inflammatory markers, acute-phase reagents, or interleukin-6 (a key cytokine mediator of the acute-phase response) are strong predictors of the development of type 2 diabetes mellitus reactions (J.C. Pickup, 2004). Thus, the pathophysiology of insulin resistance, metabolic syndrome, and atherosclerosis may have a common proximal inflammatory basis.

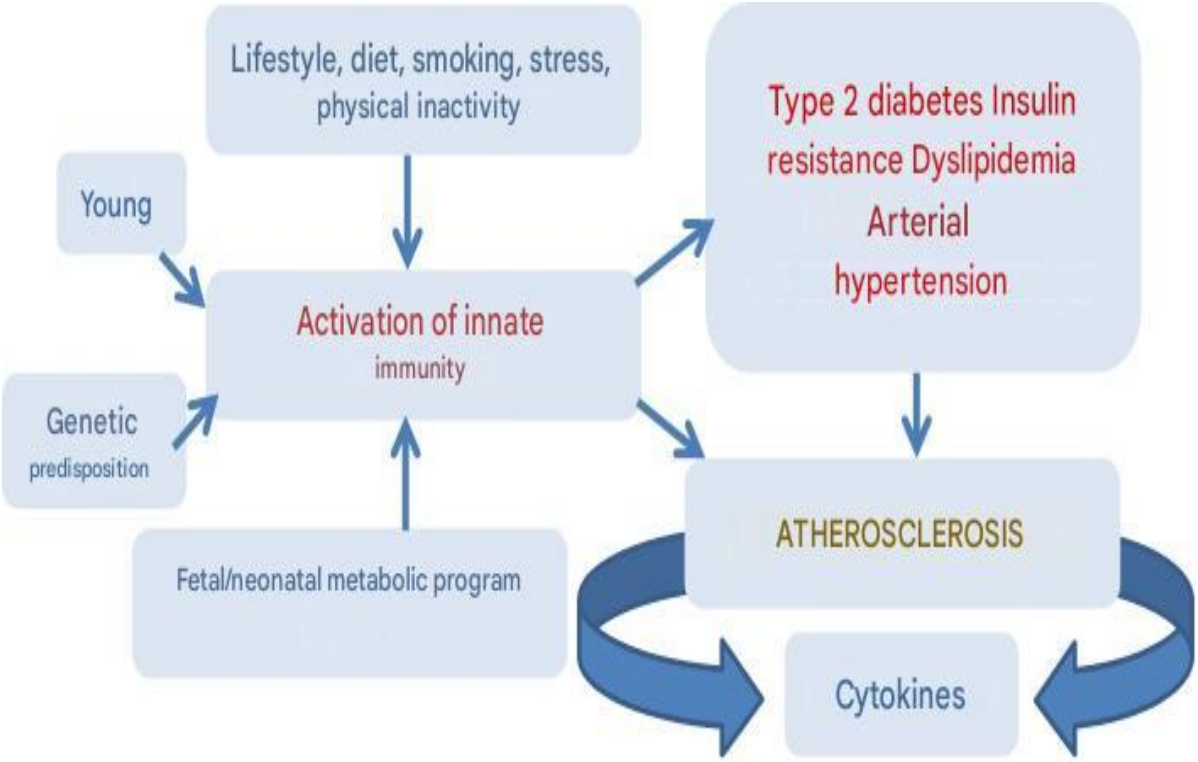

Photo 1. A number of factors, such as dietary changes, sedentary lifestyle, age, metabolic program during pregnancy, and genetic predisposition, are known activators of the innate immune system. Cytokin production leads to insulin resistance, type 2 diabetes, and other components of metabolic syndrome such as dyslipidemia. Activated innate immunity is a possible common precursor to type 2 diabetes and atherosclerosis. IL-6 = interleukin-6; TNFα = tumor necrosis factor-alpha. (J.C. Pickup, 2014).

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Early stages of diabetic atherosclerosis

Five main molecular mechanisms are involved in endothelial damage caused by hyperglycemia: activation of protein kinase C isoforms through the de novo synthesis of the lipid second messenger diacylglycerol, increased flow of hexosamine pathways, increased formation of the end product of glycation (AGE), increased flow of polyol pathways, and activation of the anti-inflammatory nuclear transcription factor, nuclear factor kappa B (M.A. Creager, T.F. Luscher, 2014). All these mechanisms are independently associated with the excessive production of superoxide by the mitochondrial electron transport chain (M. Brownlee, 2020). The formation of oxygen-activated species (OAP) resulting from hyperglycemia can lead to endothelial dysfunction, a decrease in the bioavailability of nitric oxide and prostacycline, increased synthesis of vasoconstrictor prostanoids and endothelin, and the formation of atherosclerotic plaques (A. Ceriello, E. Motz, 2014). This hypothesis requires further testing to fully determine the role of GFR in the pathogenesis of diabetic atherosclerosis.

Diabetic endothelial dysfunction also increases vascular permeability associated with GFR production, which is associated with hyperglycemia two weeks after the onset of diabetes (A.B. El-Remessy, M.A. Behzadian, 2013). Recently, it has been proven that endothelial dysfunction in children with diabetes mellitus is associated with a decrease in brachial artery flow-mediated dilation, leading to early atherosclerosis, which is confirmed by an increase in the intimomedial thickness of the carotid arteries (M.J. Jarvisalo, M. Raitakari, 2014). Furthermore, diabetes-induced microvascular conduction is responsible for the expression of endothelial mitogenic vascular endothelial growth factor, which is a key promoter of angiogenesis and neovascularization, responsible for diabetic microangiopathy (H.P. Hammes, J. Lin, 2010).

Late stages of diabetic atherosclerosis

Insulin resistance is associated with an increase in macrophages of the CD36 protein with an increase in oxidized low-density lipoproteins in experimental obesity (Liang C.P., Han S., 2014). Hyperglycemia increases the expression of macrophage matrix metalloproteinase (MMP) (A.K. Death, E.J. Fisher, 2013), which is enhanced in the fibroblasts of patients with diabetes mellitus (S.J. Wall,

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M.J. Sampson, 2013). Furthermore, MMP-2 is a marker of microangiopathy in children with type 1 diabetes (G. Derosa, M.A. Avanzini, 2014), indicating the primary role of macrophages in the pathogenesis of diabetic atherosclerosis. However, the absence of an animal model of atherosclerosis in type 2 diabetes mellitus may limit these observations.

Recently, new structural and functional features characterizing diabetic atherosclerosis have been identified, including adventitial inflammation and neovascularization of the vas vasorum, leading to intraplaque hemorrhage, activation of macrophages, and enlargement of the lipid nucleus, leading to high-risk atherosclerotic lesions. The mechanical role of diabetic oxidative stress in adventitious inflammation and neovascularization provides new pathogenic links between hyperglycemia and atherosclerosis.

Adventitial inflammation

In patients with unstable angina and acute myocardial infarction, adventitious inflammation around the vas vasorum is often observed in the ruptured plaques (P. Laine, M. Kaartinen, 2015). To assess oxidative stress and adventitious inflammation caused by diabetes mellitus, Zhang et al. (2019) observed increasing levels of cytokines (interleukin-6 and tumor necrosis omli-alpha), chemokines (macrophage chemotactic protein-1), and adhesive molecules in the adventitial fibroblasts of pigs with streptozoticin-induced diabetes. Oxidative stress is responsible for this inflammatory response and is associated with the activation of transcription factor kappa B by AGE in coronary adventitious fibroblasts (L. Zhang, A. Zalewski, 2019), providing a mechanical link between diabetes, oxidative stress, and adventitious inflammation.

Adventitial inflammation can also spread to the middle layer, causing atrophy and fibrosis. An increase in the levels of MMP-2 and -9, originating from macrophages, is described at the intimomeal interface of complex plaques (G. Pasterkamp, A.H. Schoneveld, 2020). This increased MMP activity is an independent predictor of plaque rupture and is associated with the disruption of the internal elastic plate (P.R. Moreno, K.R. Purushothaman, 2022).

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Adventitious inflammation is also associated with neovascularization of the vasa vasorum, leading to the extravasation of red blood cells, the formation of foam cells, and the expansion of the lipid nucleus (M.M. Kockx, K.M. Cromheeke, 2020).

Neovascularization of vasa vasorum

Neovascularization of the vascular wall is a permanent sign of the development of atherosclerotic plaques. New vessels can serve as an entry port for blood cells, providing nutrients to aerobic cells such as macrophages and smooth muscle cells. Vasa vasorum neovascularization develops during the first two to four weeks of a hypercholesterolemic diet, preceding endothelial dysfunction (J. Herrmann, L.O. Lerman, 2021). Furthermore, the new vessels are involved in plaque bleeding and the development of symptoms of cerebrovascular disease, and may also play a role in plaque rupture (A.N. Tenaglia, K.G. Peters, 2018). In ruptured plaques, the total and local microvascular density increases compared to non-ruptured plaques. Furthermore, microvascular density increases in inflammatory lesions, intraplatelet hemorrhages, and thin-capsule fibroatheromas. The presence of microvessels at the base of the plaque is independently associated with plaque rupture, indicating the contribution of microvessels to plaque instability (P.R. Moreno, K.R. Purushothaman, 2014).
Purushothaman et al. (2014) examined the composition of microvascular and inflammatory cells in 230 plaques of patients with diabetes mellitus. In the plaques of patients with diabetes mellitus, there is an increase in microvascular content, macrophages/T-lymphocytes, and intraplaque hemorrhage. These differences in plaque composition can increase the risk of plaque rupture in diabetic atherosclerosis.

Coronary thrombosis

Diabetes mellitus is characterized by an increase in the concentration of procoagulant factors, including fibrinogen, von Willebrand factor, and factor VII, and a decrease in the concentration of antithrombotic factors, including antithrombin III and protein C (Schneider D.J., Sobel B.E., 2021). Arterial

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thrombosis is mediated by tissue factor (TF), which is the most potent pathogen of the coagulation cascade. Rauch et al. reported that polymorphonuclear leukocytes may be involved in transporting circulating TF to platelets via a CD15-dependent mechanism. In patients with acute coronary syndrome, high levels of circulating TF-positive microparticles with plasma TF antigen and procoagulant activity have been described. Mallat and Tedgi linked apoptosis events to atherothrombosis and TF production. Recently, Hutter et al. have shown that apoptosis of platelet macrophages combines with TF expression, suggesting a potential pathogenic mechanism leading to increased platelet thrombogenicity.
Tissue factor increases in patients with diabetes mellitus. Recently, Tsukino et al. found a significant decrease in TF activity and blood thrombogenicity in patients with diabetes mellitus with improved glycemic control. These observations emphasize the concept of high-risk blood in the pathophysiology of diabetic atherosclerosis, which leads to coronary thrombosis (A. Sander, W. Fuster, 2020).

Conclusion

Diabetic atherosclerosis is an aggressive disease that causes serious health problems in modern society. Metabolic syndrome is an inflammatory disorder that plays a key role in the development of atherosclerosis and requires serious attention for adequate treatment. A new understanding of the complex pathophysiology of atherosclerosis is a disease involving all three layers of the vascular wall and associated with the active involvement of the adventitial vasa vasorum, which is responsible for the rupture of the internal elastic layer, the environment, and the neovascularization of plaques. This microangiopathic process is exacerbated in diabetes mellitus and is associated with increased inflammation and intraplatelet hemorrhage. Atherosclerotic microvasculature enlarges in the middle layer and at the base of the plaque. Furthermore, microvasculature also proliferates in ruptured plaques in patients with diabetes mellitus. Coronary thrombosis mediates the interaction of systemic procoagulant factors, the activity of which increases in patients with diabetes mellitus. The tissue factor, which is the most potent trigger of the coagulation cascade, increases in diabetes mellitus with poor glycemic control.

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