The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1236-1240

Relationship of Diabetes Mellitus (DM) and Ischemic Heart Disease: Review Article

Mohamed Ibrahim Mustafa Al Awadi, Mohamed Samy Mohamed Abd El Aziz, Abdulrahman Faraj Ali Alhuwayj*, Ibtesam Ibrahim El Dosouky

Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Abdulrahman Faraj Ali Alhuwayj, **Mobile:** (+20)01005157826, **E-Mail:** dr.erhoma85@gmail.com

ABSTRACT

Background: Diabetes mellitus (DM) is one the strongest risk factors for cardiovascular disease and, in particular, for ischemic heart disease (IHD). The pathophysiology of myocardial ischemia in diabetic patients is complex and not fully understood. Some diabetic patients have mainly coronary stenosis obstructing blood flow to the myocardium and others present with coronary microvascular disease with an absence of plaques in the epicardial vessels.

Objective: This review article aimed to study diabetes mellitus in order to reduce the high morbidity and mortality due to cardiovascular disease in diabetic patients.

Methods: These databases were searched for articles published in English in 3 data bases [PubMed – Google scholar-science direct] and Boolean operators (AND, OR, NOT) had been used such as diabetes mellitus and ischemic heart disease or coronary artery disease and in peer-reviewed articles between July 1998 and April 2021. A 23-year date range was selected without language limitations, and filtered in selected data basis for the last 23 years. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded (documents unavailable as total written text, conversation, conference abstract papers and dissertations).

Conclusion: Diabetes mellitus, a simultaneously endocrine and metabolic disease, is an especially aggressive process leading to vascular lesions. In order to reduce the high morbidity and mortality due to cardiovascular disease in diabetic patients the goals of prevention must be maximal on non-diabetic persons who already have ischemic heart disease.

Keywords: Diabetes mellitus, Ischemic heart disease, CAD, CVD.

INTRODUCTION

Diabetes mellitus (DM) affects 180 million patients worldwide. It is present in up to 25% to 30% of all patients undergoing percutaneous coronary intervention (PCI) [(1)]. Diabetes mellitus (DM) is associated with increased cardiovascular risk and mortality, and has long been recognized as an independent risk factor for cardiovascular disease (CVD) and is also an independent predictor of adverse clinical outcomes after PCI [(2)]. Diabetes mellitus is regarded as a coronary heart disease risk equivalent and an important factor when planning for treatment strategies for coronary artery disease as well as evaluating clinical outcomes after PCI [(3)]. DM markedly impaired myocardial microvascular perfusion, which is regarded a clinically significant predictive marker of plaque progression in coronary artery disease (CAD) [(4)].

Relationship effect between diabetes mellitus and coronary artery disease patients:

Epidemiological data suggest a reliable relationship between the level of glycosylated hemoglobin (HbA1c) and the risk of cardiovascular morbidity and mortality. With an increase in the level of HbA1c by 1%, the risk of cardiovascular morbidity increases by 10% [(5)].

DM is a complex and heterogeneous chronic metabolic disease caused by elevated levels of blood glucose. DM has a great impact worldwide that will probably increase in the next decades. DM is classified into four different etiological categories: type 1, type 2, "other specific types", and "gestational DM". Type 1 DM (T1DM) is due to T-cell–mediated autoimmune destruction of pancreatic-cells that leads to insulin deficiency; T1DM occurs mostly in young people, generally up to 30 years of age. Type 2 DM (T2DM) is characterized by both insulin resistance and failure of pancreatic-cells. Other specific types of DM are due to either single genetic mutations, to other pathological diseases of the pancreas, or to drugs. Gestational diabetes develops during pregnancy [(6)].

Insulin resistance also plays a critical role in the pathogenesis of type II DM. Hyperinsulinemia is closely related to the metabolic syndrome, which includes insulin resistance, arterial hypertension and obesity, and is accompanied by a high risk of coronary artery disease (CAD). The change in the concentration of plasma lipids in type II DM is a predictor of CAD. It was established that in persons with high blood glucose level in the blood on an empty stomach and after a load significantly higher cardiovascular morbidity and mortality rate was noted [(7)]. Asymptomatic hyperglycemia, especially in women, is an important risk factor for the development of CAD [(8)].

The effect of hyperinsulinemia and insulin resistance on the development of atherosclerosis is associated with the impact on blood coagulation processes. Hypercoagulation and depression of fibrinolysis are noted, which can contribute to intracoronary thrombosis. In patients with DM type II,

Received: 10/10/2021
Accepted: 8/12/2021

damage to the endothelium and its dysfunction are detected, which is an additional factor in the increased risk of developing CAD [9].

Clinical features of CAD in patients with DM are as follows [6]:

- The same frequency in men and women
- High incidence of painless forms of CAD (painless myocardial ischemia, painless myocardial infarction)
- Frequent development of postinfarction complications;
- Mortality in acute (10 days) and subacute (4-8 weeks) periods myocardial infarction is 2 times higher than that in persons without DM.

Cardiovascular Risk Factors and Ischemic Heart Disease in diabetic patients:

Among cardiovascular diseases represented by a group of disorders of the heart and blood vessels such as IHD, cerebrovascular diseases, and peripheral arterial disease, IHD represents the most frequent cause of mortality in the world. IHD consists of several clinical conditions characterized by myocardial ischemia, which is a situation of cardiomyocyte damage due to a reduced blood supply compared to their metabolic demand [6].

IHD is classically attributable to CAD, a condition characterized by the presence of an atherosclerotic plaque that causes a vascular obstruction of more than 50%. On the other hand, coronary microvascular dysfunction, which is a condition of impaired vasomotor tone due to several mechanisms, is able to provoke IHD, independently from the presence of an atherosclerotic plaque. In fact, clinical, angiographic, and autopsy findings suggest a multifaceted pathophysiology of IHD that should not be associated only with CAD [10]. Several cardiovascular risk factors are involved in the pathogenesis of IHD. DM is considered one of the strongest risk factors for cardiovascular disease, including IHD, cerebrovascular disease, and peripheral arterial disease [11].

The risk of increased cardiovascular morbidity and mortality has been well described and, because of this, diabetes has been named a "cardiovascular disease equivalent". Long-term risk of myocardial infarction in patients with DM was similar to that of patients with a previous myocardial infarction. Moreover, one-year mortality in patients with myocardial infarction is higher in diabetic patients compared to those without it. It has been noted that patients who develop DM at a younger age present more cardiovascular complications [6].

CVD is the long-term complication of T1DM as well as of T2DM with the greatest impact on prognosis both in terms of mortality and morbidity. T1DM is associated with a markedly increased risk for IHD compared to the general population, similar to the increased risk associated with T2DM. CVD in T1DM differs from that in T2DM, mostly in terms of age and gender difference. Risk factors have different influences in T1DM versus them in T2DM on susceptibility to cardiovascular disease. There are several potential pathophysiological mechanisms through which DM causes CVD. Usually, subjects with T2DM have other risk factors, such as hypertension as well as dyslipidemia that are linked with increased cardiovascular risk [12].

DM determines a pathophysiological continuum, characterized by a state of long-standing insulin resistance with a compensatory hyperinsulinemia. Initially, the hyperglycemia remains under the threshold for the diagnosis of DM and it describes impaired glucose tolerance. Glucose metabolism impairment and endothelial dysfunction, mediated by oxidative stress and inflammation, are the main substrates of coronary atherosclerosis in DM [13].

A complex network of signaling pathways is involved in the multistage pathological condition leading to atherosclerosis. Imbalanced lipid metabolism and immune response lead to chronic inflammation of the arterial wall, with growth of atherosclerotic plaque. The nature of the hyperglycemic damage in patients affected by DM lies in the accumulation of superoxide anions, which are free radicals capable of activating cellular pathways that includes advanced glycation end products (AGEs), polyol and hexosamine flux, PKC, and vascular inflammation mediated by nuclear factor-B. Hyperglycemia itself also increases oxidative stress through greater glucose oxidation in the citric acid cycle [14]. All these different hyperglycemia consequences lead to decreased cellular resistance to oxidative stress, amplification of the proinflammatory response, and apoptosis of endothelial cells and their overall dysfunction. These mechanisms, together with the alterations in mineral metabolism induced by renal dysfunction and the release of osteoprogenitor cells into the circulation, increase the development of vessel calcification, which is a complication of atherosclerosis in diabetic patients and correlates to increased plaque burden [15].

Diabetic patients present wide calcium deposits in coronary arteries and, thus, a bigger atherosclerotic plaque burden with a higher resulting mortality risk than in non-diabetic patients (Figure 1). Using computed tomography coronary angiography (CTCA), a higher calcium score and plaque burden in patients with DM were demonstrated [16]. In addition to this, studies using autopsy showed larger necrotic cores and more significant inflammation in patients with DM and ACS [6].

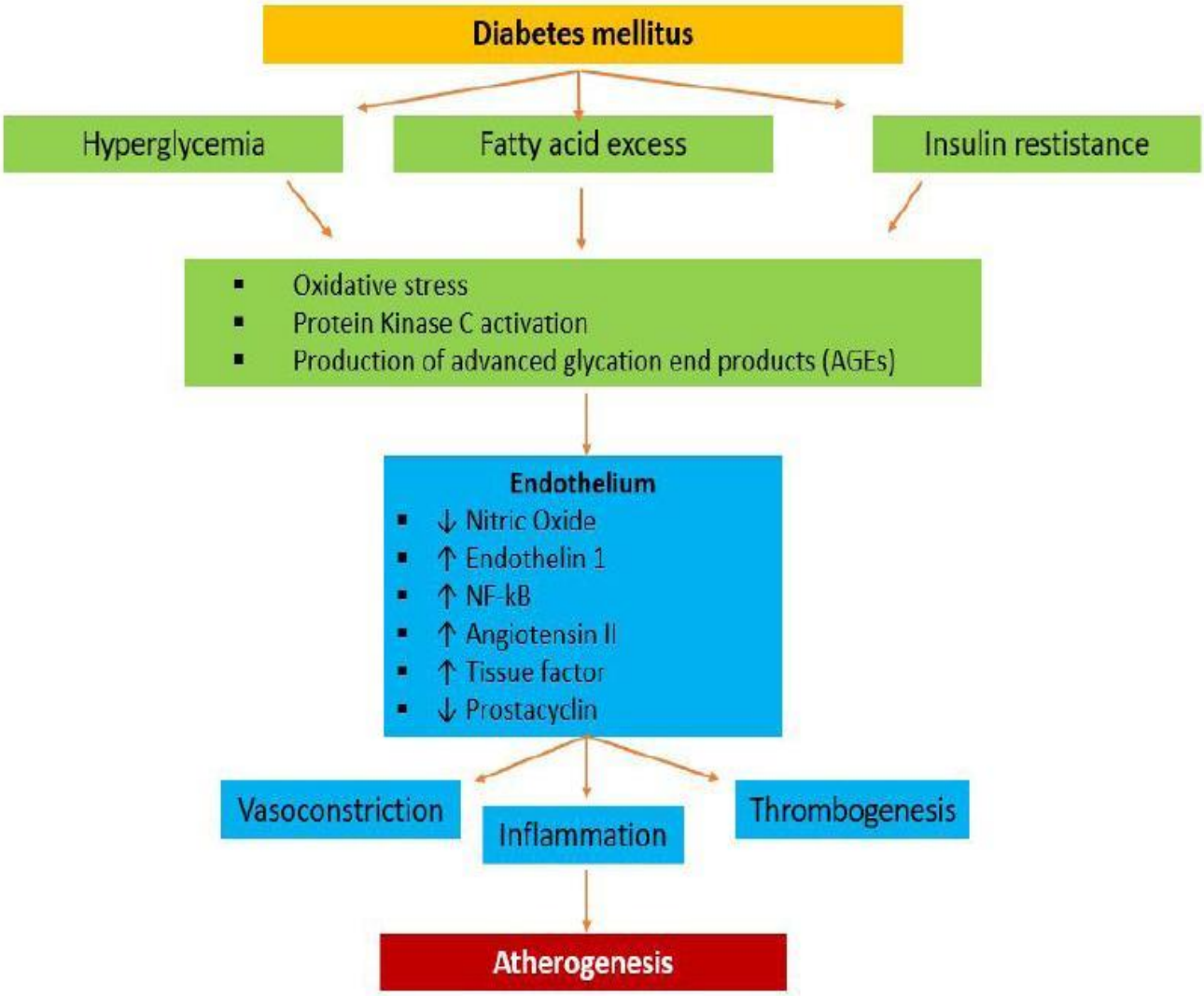

Figure (1): Pathophysiology of atherogenesis in patients affected by diabetes mellitus [6]

In diabetic patients the pathophysiology of myocardial ischemia is complex and not fully understood. Some diabetic patients have coronary stenosis obstructing blood flow to the myocardium and others have coronary microvascular disease with absence of plaques in the epicardial vessels with or without endothelial dysfunction. It is important to underline that myocardial ischemia is not synonymous with atherosclerotic CAD. In the absence of coronary large vessel disease, ischemia is determined by impaired coronary vasodilator reserve and coronary microvascular disease **[17].**

However, little is known about the basic aspects of diabetic coronary microvascular dysfunction. The impaired coronary arteriole vasomotion, including reduced endothelial mediated vasodilation, hypoxia-induced vasodilation, and myogenic response, are the proposed pathophysiologic processes of diabetes-induced coronary microvascular dysfunction. Both hyperglycemia and insulin resistance, besides tumor necrosis factor-B overexpression and inflammation interfere with flow-mediated endothelial-dependent vasodilation through nitric oxide (NO) level decrease and endothelin-1 level increase, which are associated with acute intracellular changes **[18]**.

By using positron emission tomography, various studies have confirmed the reduction of endothelium-dependent and -independent vasodilator function in coronary arteries in diabetic subjects compared to control group. These results suggest the role that chronic hyperglycemia might play in the pathogenesis of coronary microvascular dysfunction in diabetes. Furthermore, an inverse correlation was shown between myocardial flow reserve and average levels of HbA1c for five years and fasting plasma glucose concentration, underlining how glycemic control is significantly related to coronary microvascular function **[6]**. Moreover, altered Ca^{+2} regulation with impaired myofilament function, increased reactive oxygen species formation with decreased antioxidant defenses, raised lipotoxicity, endomyocardial fibrosis, endothelial and cardiomyocyte cell necrosis and apoptosis, and autonomic dysfunction are additional mechanisms responsible for cardiomyocyte changes in DM. In DM

Received: 10/10/2021
Accepted: 8/12/2021

chronic hyperglycemia plays a main role in the onset and progression of autonomic neuropathy, which may reduce the vasodilator effect of sympathetic stimulation on coronary resistance vessels [19].

As previously described, CAD represents the most frequent condition that leads to IHD. The presence of a coronary atherosclerotic plaque represents a pathological process that is not uniquely associated with DM. In fact, other cardiovascular risk factors are involved in its pathogenesis. Although they all lead to the same final condition, they act in a different way compared to DM, for the purposes of atherosclerosis pathogenesis. DM and all the consequences of the associated hyperglycaemic condition usually combine their effects with other atherosclerotic risk factors, which add their own contribution to the pathogenesis of atherosclerosis. First, hypertension is responsible for increased vascular resistance and endothelial dysfunction in small-resistance vessels, producing a vascular remodeling. This seems to be due to the reduction of NO release, which is caused by the abnormal production of reactive oxygen species (ROS) resultant from the cyclooxygenase (COX) activity [20].

The impaired NO availability has a negative impact on vasodilation, platelet adhesion and aggregation, and leukocyte migration contributing to atherosclerotic events. Besides, this atherosclerosis is closely linked to the physiological changes of aging. Growing evidence confirms that cellular senescence promotes atherosclerosis [21]. In particular, senescent Endothelial Cells (ECs) show a reduction in NO production and at the same time, augment endothelin-1 secretion and alter expression of the adhesion molecules VCAM-1 and ICAM-1. Moreover, late-passage ECs increase the activation of nuclear factor (NF)-B and susceptibility to apoptosis, leading to a shift toward a proinflammatory and proapoptotic state. These conditions contribute to and facilitate the succession of atherosclerotic phenomena [22].

Systemic inflammation represents a condition, which is strictly associated with all the steps of atherosclerosis and sometimes, such as in autoimmune disease, could be the trigger of atherosclerosis independently from other risk factors. Premature atherosclerosis is demonstrated in patients with autoimmune diseases and represents the main death cause in these patients. The dysregulation of cytokine production, mainly of IL-17, IL-6, tumor necrosis factor-α, and interferon-γ, is induced by the autoimmune response and represents the main cause of systemic inflammation and atherogenesis [21].

In patients with systemic inflammatory disorders the risk of developing atherosclerosis is also increased because the chronic inflammatory state modifies the physical features of blood, making it more viscous. In these mechanisms, different molecules have a main role, such as lupus anticoagulant and anticardiolipinic antibodies in lupus erythematosus through the binding of several cell and tissue antigens. Innate immunity seems to have a main role in the initiation of atherosclerosis through the toll-like receptor (TLR) pathways. Indeed, TLR4, which is highly expressed in fragile areas of plaques, binds the oxidized low density lipoproteins (ox-LDL) supporting foam cell formation and their proinflammatory role. Ox-LDL stimulates the endothelial cells to produce chemokines which recruit other leucocytes around the plaque [21].

Patients with both diabetes and ischemic heart disease are supposed to have more aggressive coronary artery disease and poorer cardiovascular outcomes. However, this is controversial, because of the great variability in disease states regarding diabetes and its association with other cardiovascular risk factors. Moreover, the causes of this supposed worse prognosis are not well understood and impairment in myocardial protective mechanisms is supposed to be one of the possible explanations [23].

CONCLUSION

Diabetes mellitus, a simultaneously endocrine and metabolic disease, is an especially aggressive process leading to vascular lesions. In order to reduce the high morbidity and mortality due to cardiovascular disease in diabetic patients the goals of prevention must be maximal on non-diabetic persons who already have ischemic heart disease.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Jensen R, Støttrup N, Kristiansen S *et al.* (2012):** Release of a humoral circulating cardioprotective factor by remote ischemic preconditioning is dependent on preserved neural pathways in diabetic patients. Basic Res Cardiol., 107: 285-89.
2. **Haffner S, Lehto S, Rönnemaa T *et al.* (1998):** Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med., 339: 229-34.
3. **Mashaly A, Rha S, Choi B *et al.* (2018):** Impact of diabetes mellitus on 5-year clinical outcomes in patients with chronic total occlusion lesions. Coronary Artery Disease, 29 (2): 119-126.
4. **Shi R, Shi K, Yang Z *et al.* (2019):** Serial coronary computed tomography angiography-verified coronary plaque progression: comparison of stented patients with or without diabetes. Cardiovascular Diabetology, 18 (1): 1-10.
5. **Barrett E (2015)** Does hyperglycemia really cause coronary heart disease? Diabetes Care, 20: 1620–1623
6. **Severino P, D'Amato A, Netti L *et al.* (2018):** Diabetes mellitus and ischemic heart disease: the role of ion channels. International Journal of Molecular Sciences, 19 (3): 802-6.

7. **Balkou B, Shipley M, Jarrett R *et al.* (2014):** High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. Diabetes Care, 21: 360-65.
8. **Pyorala K, Pederson T, Kjekshus J *et al.* (2014):** The Scandinavian Simvastatin Survival Study (4S) Group. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care, 20: 614–620.
9. **Sobel B (2015):** Coronary artery disease and fibrinolysis: from the blood to the vessel wall. Thromb Haemost., 82: 8–13.
10. **Piccini J, Schulte P, Pieper K *et al.* (2011):** Antiarrhythmic drug therapy for sustained ventricular arrhythmias complicating acute myocardial infarction. Critical Care Medicine, 39 (1): 78-83.
11. **Wang C, Hess C, Hiatt W *et al.* (2016):** Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus–mechanisms, management, and clinical considerations. Circulation, 133 (24): 2459-2502.
12. **Einarson T, Acs A, Ludwig C *et al.* (2018):** Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular Diabetology, 17 (1): 1-19.
13. **Chatterjee S, Khunti K, Davies M (2017):** Type 2 diabetes. The lancet, 389 (10085): 2239-2251.
14. **Scărlătescu A, Micheu M, Popa-Fotea N *et al.* (2021):** MicroRNAs in Acute ST Elevation Myocardial Infarction—A New Tool for Diagnosis and Prognosis: Therapeutic Implications. International Journal of Molecular Sciences, 22 (9): 4799-4803.
15. **Yahagi K, Kolodgie F, Lutter C *et al.* (2017):** Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. Arteriosclerosis, Thrombosis, and Vascular Biology, 37 (2): 191-204.
16. **Van Werkhoven J, Cademartiri F, Seitun S *et al.* (2010):** Diabetes: Prognostic value of CT coronary angiography—Comparison with a nondiabetic population. Radiology, 256: 83–92.
17. **Murthy V, Naya M, Foster C *et al.* (2012):** Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation, 126 (15): 1858-1868.
18. **Pucci M, Severino P, D'Amato A *et al.* (2019):** P874 Role of Genetic Polymorphisms of ion channels in the pathophysiology of coronary microvascular dysfunction and ischemic heart disease: an update. European Heart Journal, 40 (1): 747-752.
19. **Joshi M, Kotha S, Malireddy S *et al.* (2014):** Conundrum of pathogenesis of diabetic cardiomyopathy: role of vascular endothelial dysfunction, reactive oxygen species, and mitochondria. Molecular and Cellular Biochemistry, 386 (1): 233-249.
20. **Virdis A, Taddei S (2016):** Endothelial dysfunction in resistance arteries of hypertensive humans: old and new conspirators. Journal of Cardiovascular Pharmacology, 67 (6): 451-457.
21. **Wang J, Bennett M (2012):** Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circulation Research, 111 (2): 245-259.
22. **Khaidakov M, Wang X, Mehta J (2011):** Potential involvement of LOX-1 in functional consequences of endothelial senescence. PLoS One, 6 (6): 964-69.
23. **Rezende P, Rahmi R, Hueb W (2016):** The influence of diabetes mellitus in myocardial ischemic preconditioning. Journal of Diabetes Research, 8201: 1-6.