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The Histomorphological and Apoptotic Effects of Diabetic Mellitus in the Pathological Remodiling of the Heart Structures in Cardiovascular Disease – A Systematic Review

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ABSTRACT: Background: Studies have shown that Patients with diabetes mellitus have greater risk of developing heart failure (HFrEF or HFpEF)with worse Cardiovascular outcomes, hospitalization and prognosis.However, the staged histomorphological and apoptotic effects of diabetes mellitus in altering the normal structural organization of the heart wall is not well elucidated. This study set out to undertake a systematic review on the histomorphological and the apoptotic progressive changes that occur on the heart structures leading to development of cardiovascular disease. In carrying the study, databases like, Pubmed, Google were searched for English language publications between 2005-2020 were searched. A total of 439 articles published on diabetes mellitus related structural effects on the heart structures were screened and 230 of these were evaluated and 54 met inclusion criteria. The reviewers independently selected studies that addressed the study questions and met the eligibility criteria. The Information on the study design, experimentation and outcome, the animal characteristics, diabetic effects on cardiovascular disease, metabolic syndrome definition, follow-up duration, and endpoint assessment was abstracted. 54 full text articles were used for systematic review of the established heart wall histomorphological and apoptotic histopathological changes leading to cardiovascular diseases. Conditions like HFrEF and HFpEF were noted to be associated with histopathological signs of congestion and myocardio-endocardial atrophy, as well as nuclear and cellular degeneration of the heart myocardium. In parallel, there is overexpression of proapoptotic Bax protein, release of cytochrome C from the outer mitochondrial membrane into myocardio-cell cytoplasm, and nuclear transfer of activated caspase 3 indicating apoptotic events in the heart myocardial components consistent with what happens in the kidneys injuries induced by diabetes. This was confirmed by DM studies on the ultrastuctural changes of the heart wall sub-cellular structures using electron microscopy that revealed that apoptotic signs in the heart cells resembled what was seen in kidney cells that depicted swollen mitochondria and degenerated nuclei in heart endothelial cell like what was seen in the kidney renal tubular cells. In conclusion, this systematic reviewy provides histomorphological evidence on how the heart wall structures are adversely injured by DM, leading to heart failure which may be due to caspase-mediated apoptosis via overexpression of proapoptotic Bax protein, subsequent mitochondrial cytochrome C release, and final nuclear transfer of activated caspase 3, supporting the notion of a cardio-histomorphological and related renal syndrome. Therefore, system and policy level intervention as well as preventive measures that target individuals with diabetes mellitus are needed in order to improve the outcome of cardiovascular diseases and quality of life in people with diabetes.

KEYWORDS: Diabetes mellitus, histomorphology, apoptosis, structures, cardiovascular system, diseases

I. INTRODUCTION

Structurally, diabetes affects both macroscopic and microscopic structures of the cardiovascular system like the heart muscle (myocardium), the blood vessels, the endothelium among others but the ultimate presentation of all these is the heart failure (Thrainsdottir et al., 2005).

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Heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are common in patients with diabetes mellitus (Al Jaralla et al., 2020). Diabetes, being a major risk factor for cardiovascular disease (CVD) also affects different body structures and organs such as the eyes, kidneys, brain among others. The complications that result from this morphological distortion include coronary artery disease, peripheral vascular disease, stroke, retinopathy, nephropathy and many others (papatheodorou et al., 2018). High blood sugar levels and inadequate blood supply to the heart tissue among other factors have been shown to damage the morphology of the cardiovascular structures like the myocardium and blood vessels (Knudsen et al., 2009). However, the link between morphological effects of diabetes on the cardiovascular system structures is not clear.

The prevalence of diabetes mellitus has been consistently increasing from 108 million in 1980 to 422 million in 2014 posing even greater risk of cardiovascular diseases to these patients (WHO 2021). However, it is still challenging to manage the cardiovascular risk factors alongside the associated complications in patients with diabetes. This review will try to give a description of the current scientific knowledge between diabetes and both macroscopic and microscopic cardiovascular system structures such as the blood vessels, myocardium, endothelium among others.

II. METHODOLOGY

The standard protocol for systematic review was followed.

Study question

Which histomorphological changes influence cardiovascular disease in diabetes mellitus

Data sources and selection

The PUBMED and Google English published articles from the year 2000 to 2022 were searched. The data sources were searched by using Apoptotic, histomorphological, heart, cardiovascular disease and diabetes mellitus as engine words.

III. RESULTS

The screened articles were 439 titles and abstracts and out of which 230 articles were evaluated and 54 met the inclusion criteria.

Arterial narrowing

Diabetes is associated with deposition of fatty material in the wall of the arteries (atherosclerosis) which cause arterial narrowing (Poznyak et al., 2020). Dyslipidemia among people with diabetes has been increasing for approximately last 30 years (pirillo et al., 2021). The fat deposition occurs due to abnormally raised cholesterol or fats (lipids) in blood as well as endothelial dysfunction. Approximately 97% of patients with diabetes have abnormal lipid levels and this is highly linked with atherosclerosis (Mooradian., 2009; Fagot et al., 2000).

There are different types of lipoprotein; low density lipoprotein (LDL) and high density lipoprotein (HDL) (Feingold et al 2021). Further, there is small dense and large LDL cholesterol. However, small LDL dominate among people with diabetes (Krauss et al., 2004). This type of cholesterol is more vulnerable to oxidation, they also infiltrate and attach more to the arterial wall hence they tend to promote more formation of fatty acid in the arteries (Rosenson., 2004). Oxidation of LDL make them obtain different properties which are new to the immune system hence provoke response through production of leukocytes to the innermost lining of the blood vessel wall called endothelium (Bajpai et al., 2018). When these leukocytes ingest the lipids they change to foam cells and this quicken proliferation of leukocytes, cells in the endothelium, smooth muscle cells and all these are involved in the formation of the atherosclerotic plaque (Stone et al., 2011). The presence of the plaque narrows the blood vessel wall hence compromising the arterial functions like supply of nutrients to the tissues and this finally leads to cardiovascular disease in diabetes.

Endothelial dysfunction

The endothelium is the innermost cellular lining of the blood vessels such as the arteries, veins and the capillaries (Kruger et al., 2019). A normal endothelium regulates the tone of the blood vessel, platelet activation, adhesion of the leukocyte, clot formation as well as inflammation (Ait-oufella et al., 2010). Therefore, structurally intact endothelium vasodilate, prevent formation of fatty deposits in the arteries and inhibit inflammation (Hadi et al., 2005). However, when structural integrity of the endothelium is affected as well as its mechanisms for example in patients with diabetes, the process of atherosclerosis is accelerated.

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The endothelium plays a very important role in regulating the vascular tone (Sandoo et al., 2010). It produces nitric oxide which vasodilate and endothelin I which vasoconstrict hence allowing the metabolic products to flow in the tissues appropriately and in a continuous manner depending on the need of these tissues (Nishiyama et al., 2017; Poredos et al., 2021). However, diabetes affects the endothelium hence causing diseases of the small blood vessels due to poorly regulated low production of the vasodilator and high production of the vasoconstrictor substances and this goes a long way in affecting the blood flow to the organs of the cardiovascular system such as the heart hence manifesting inform of cardiovascular disease (Hadi et al., 2007).

The smooth muscle lining the vessels are also continuously regulated by the autonomic nervous system to meet required metabolic needs of the tissues (Sheng & Zhu., 2018). However, Diabetes has been shown to affect the autonomic nervous system (Sucharita et al., 2011) and this end up with various complications such as diabetic neuropathy, retinopathy, nephropathy which compromise the blood flow to the tissues of the cardiovascular system and other vital organs like the kidneys, eye, brain among others (Wang et al., 2017).High blood sugar levels also prevent production of nitric oxide (vasodilator) in the cells of the endothelium of the arteries hence leading to vasoconstriction of the vessels which presents inform of a cardiovascular disease (Hoshiyama et al., 2003).

Thickening of the capillary basement membrane

The microvascular system of the diabetic patients has been shown to have morphological alterations with complications such as nephropathy and retinopathy among others (Tsilibary et al., 2003). Persistent high blood glucose levels among people with diabetes has been shown to cause thickening of the capillary basement membrane and this affect the variety and quantity of nutrients, metabolic products transportation between the cardiovascular system and the tissue (Hayden et al., 2005). The changes in the basement membrane morphology affect the openings in the cells of the endothelium hence abnormally allowing larger molecules to pass through the small vessel wall from the cardiovascular system and this leakage for example of proteins like albumin in the kidneys is a warning sign of diabetic cardiovascular disease (Strain et al., 2018).

Tissue injury

The persistency of high blood glucose levels in diabetic patients has been shown to cause functional decline in neutrophil levels hence infections becomes the main problem in the early stages of the disease (Kawahito et al., 2009). High blood sugar levels have also been shown to increase glucose and fatty acid metabolism which leads to prolonged oxidative stress and mitochondrial dysfunction with increased production of reactive oxygen species involved in destruction of anatomical microscopic structures like the plasma membranes as well as other organelles (Victor et al., 2011)).

Oxidative stress happens when the cellular production of reactive oxygen species surpasses the ability of anti-oxidant defenses within cells (Pizzino et al., 2017). Reactive oxygen species are free radicals with unpaired electron which makes it very reactive leading to attachment with other compounds hence affecting the structure and function of the body tissue (Petersen et al., 2004) . The event in high glucose-induced cell apoptosis is upregulation of voltage-dependent anion channel (VDAC1) because when it is silenced it reduce high glucose-induced upregulation of mitochondrial/cellular Bax hence silencing VDAC1 recovered the high glucose-reduced binding of Bax to VDAC1, which finally reduced the high permeability of the mitochondria (Zhang et al.,2018).

Arterial occlusion

The inflammation process and thrombosis increases the risk of cardiovascular morbidity and mortality in patients with diabetes (Hess et al., 2011). The occlusion of the artery by a blood clot otherwise known as a thrombus is common in diabetic patients due to a hypercoagulable state (Carr. 2001). This has been shown to occur when the atherosclerotic plaque raptures leading to acute coronary syndromes, myocardial infarction, stroke among others (Sugiyama et al., 2018; Gu et al.,2002). This is because patients with diabetes show increased platelet activation and clotting factors in blood. These platelet activation factors include thromboxane, platelet factor, thromboglobulin among others while the clotting factors include fibrinogen, factor VII, VIII, XI, XII, kallikrein, and von Willebrand factor (Ferroni et al., 2004; Prescott et al., 2002). In addition, the anticoagulant factors have been shown to be low in diabetic people, the clots formed in their cardiovascular system are somehow resistant to

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degradation hence fibrinolysis process is slowed (Kim et al., 2014). The endothelium plays a vital role when it comes to clot formation or clot degradation because it is closely associated with factors involved in these processes (Carr., 2001). As described earlier, there is endothelial dysfunction among the diabetics hence these patients are prone to clot formation which leads to cardiovascular diseases like stroke, myocardial infarction among others with high morbidity and mortality.

Myocardial damage

The abnormal events of the cardiovascular system such as ischemia, clot formation in patients with diabetes damage very important heart structures like myocardium and this leads to poor contractility and ventricular diastolic function (Araz et al., 2015). Oxidative stress in diabetes is very key when it comes to tissue damage (Babizhayer et al., 2015). Neutrophil stimulation generates superoxide radical more in diabetic animals (Johnsone et al.,2022). Further, there is accumulation of leukocyte following ischemia and this increase production of reactive oxygen species which in turn cause damage of the cardiovascular tissue like the heart myocardium resulting in vital cardiovascular disease like myocardial infarction (Swirski et al., 2013). In patients with diabetes, there is production of insulin like growth factor binding protein 7, the heart myocytes increase the utilization of the free fatty acid and altered glucose hence causing HFpEF (Gandhi et al.,2016). Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products (AGEs) ,cell death which cause HFrEF (Van et al.,2008).

Effects on Cardiovascular autonomic system

The autonomic nervous system plays a vital role in sustaining the heart activities such as the sinus node, end systolic and diastolic volume (prince et al 2010). The interference of its functions directly affects the morphology of the cardiovascular structures causing stiffness of the arteries and enlargement of the left ventricles posing even a higher risk of developing cardiovascular disease (Vinik et al 2021). Diabetes mellitus commonly cause cardiovascular autonomic neuropathy which is a microvascular complication of sympathetic and parasympathetic nerve fibers supplying the heart and blood vessels among diabetic mellitus patients. Its reduced clinical investigation raises the risk of silent myocardial ischemia, myocardial dysfunction, cardiac arrhythmias and sudden death among diabetic patients (Duque et al 2021).

Myocardial hypertrophy and fibrosis

The enlargement of the heart wall alongside formation of the fibrous tissue in the interstitium lead to increase in the size of the heart, myocardial dysfunction and finally heart failure in diabetes which in most cases it is not related to hypertension or coronary artery disease and it is commonly known as diabetic cardiomyopathy (Maisch et al.,2011). Type 2 diabetes was related with the enlargement of the left ventricles and reduced function of the myocardial in both gender.

Data synthesis

blood sugar levels in diabetic patients is associated with progression of cardiovascular diseases through morphological modification from normal to abnormal cardiovascular system structures. These mechanisms include; myocardial injury and endothelial dysfunction due to high oxidative stress which in turn produce raised levels of reactive oxygen species and low amount of nitric oxide (Napoli et al.,2009).

The large elastic arteries in people who live with diabetes become stiff and this majorly contribute to vascular damage and atherosclerosis (Niiranen et al., 2016). Other studies attribute arterial stiffness and the thickening of the carotid intima media among the diabetes to increased level of glucose hence leading to abnormal cardiovascular events (Tropeano et al., 2004; Rubin et al.,2012). Prolong high glucose levels cause accumulation of glycation end products hence leading to arteriosclerosis according to a study done by Stirban et al 2013. In diabetic patients, some studies have shown to cause structural loss and reduction in the number of vessels in the tissues with reduced perfusion commonly portrayed in myocardial blood vessels (Levy et al., 2008).The endothelial dysfunction or systemic inflammation are structural abnormalities that also contribute to reduced blood flow and subsequent cardiovascular events (Von et al.,2016).

IV. CONCLUSION

The cardiovascular diseases accounts for the majority of the morbidity and mortality in people with diabetes due to histomorphological and apoptotic modification of the cardiovascular structures. These structural changes include narrowing of the arterial lumen due to

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atherosclerosis, arterial occlusion because of clot formation due to hypercoagulability state, heart failure due to apoptotic myocardial damage, endothelial dysfunction, thickening of the basement membrane in small vessels. These events are the major contributors to the cardiovascular diseases seen in patients with diabetes mellitus.

As we ascertain further on the link between diabetes and the cardiovascular disease which is a vital health care problem globally, more studies on preventive and treatment measures need to be done. These review will improve the clinical monitoring and approach of cardiovascular problems by redefining our knowledge of vascular disease, particularly in people with diabetes.

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