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CONCEPT AND DEVELOPMENT OF DIABETESMELLITUSANDDIABETICCARDIOMYOPATHY

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ABSTRACT

This review explores the fundamental concepts and developmental aspects of Diabetes Mellitus (DM) and its intricate association with Diabetic Cardiomyopathy (DCM). Diabetes Mellitus, a chronic metabolic disorder, is examined in terms of its etiology, classifications, and impact on cardiovascular health, leading to the development of Diabetic Cardiomyopathy. The abstract also delves into the underlying mechanisms linking DM and DCM, emphasizing the importance of early detection, prevention, and comprehensive management strategies to mitigate cardiovascular complications. A comprehensive exploration of the underlying mechanisms linking DM and DCM is presented. This includes detailed insights into insulin resistance, microvascular dysfunction, myocardial fibrosis, mitochondrial dysfunction, and impaired calcium handling, all contributing to the structural and functional changes observed in DCM. In conclusion, this abstract shed light on the intricate relationship between Diabetes Mellitus and Diabetic Cardiomyopathy. Understanding the mechanisms underlying the development of DCM provides a foundation for early detection, prevention, and management strategies. A holistic approach encompassing medical interventions, lifestyle modifications, and interdisciplinary collaboration is pivotal in minimizing the impact of DM on cardiovascular health and improving the quality of life for affected individuals.

Keywords: Diabetic, Cardiomyopathy, Mellitus, mitochondrial, dysfunction

INTRODUCTION

The metabolic disease known as diabetes mellitus is characterized by chronically elevated blood glucose levels. High blood glucose levels due to insulin insufficiency and frequently insulin resistance define diabetes mellitus, a chronic condition (Dzeufiet et al., 2006). One of the most common metabolic diseases affecting people today is diabetes. It's a widespread problem with serious health consequences. Anyone, from newborns as young as two weeks old to the elderly, may have it. Polyuria, polydipsia, and polyphagia are the hallmark signs of high hyperglycemia. Secondary problems of diabetes result from long-term glucose in the circulation, which damages several organs (Mealey and Ocampo, 2007). The exact cause of this illness is unknown, however research has pointed to viral infection, autoimmune disease, and environmental factors. Numerous issues affecting the vascular system, kidney, retina, lens, peripheral nerves, and skin are prevalent and exceedingly expensive in terms of lifespan and quality of life in people with diabetes (Martim et al., 2003). Polyuria (excessive urine), polydipsia (increased thirst), and polyphagia (increased hunger) are the three hallmarks of diabetes (Alberti and Zimmet, 1998). While symptoms of type 1 diabetes might appear suddenly (within weeks or months), those of type 2 diabetes tend to emerge gradually and subtly, if at all. Diabetic ketoacidosis is a metabolic dysregulation that causes the patient to smell like acetone, breathe rapidly and deeply (Kussmaul breathing), have nausea, vomiting,

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abdominal pain, and possibly lose consciousness (Nair et al., 2000). Hyperosmolar nonketotic condition, which occurs more often in type 2 diabetes and is usually the consequence of dehydration, is an uncommon but very serious complication.

Historyandterminology

Ancient cultures such as Greece, China, Egypt, and India were already aware of diabetes. (Yasuhara and Seino, 2012). One of the most noticeable signs of diabetes is frequent urination, hence the Greek term diabainein refers to this condition. English used the Medieval Latin term diabetes, and the resulting noun was given the medical term "diabetes" (Pavy, 1890). Aretaaeus, a physician from Cappadocia, is credited with coining the name "diabetes," while Thomas Willis ellitus added the "Mellitus" suffix in 1675 from the Latin word for honey (Mel - in the sense of "honey sweet") It was proven in 1776 that the sweet taste was due to a kind of sugar in the urine of persons with diabetes. According to Clark and Dodge (1957), ancient Indians diagnosed diabetes by seeing whether ants were drawn to a person's urine and called it "sweet urine disease" (Madhumeha).

The pathophysiology of diabetes was mostly uncovered in the 20th century. Sir Frederick Grant Banting and Charles Herbert Best replicated the work of Von Mering and Minkowski in 1921 (Rosenfeld, 2002) and showed that they could reverse diabetes induced in dogs by treating them with an extract from the pancreatic islets of Langerhans of healthy dogs, demonstrating the endocrine role of the pancreas in metabolism and the existence of insulin. Later, at the University of Toronto in Canada, Banting, Best, and their coworkers isolated insulin from bovine pancreas. As a result, insulin injections (an successful therapy) were readily available, and the first clinical patient was cared for in 1922. In 1923, they shared the Nobel Prize in Physiology or Medicine for their efforts. There has been a tremendous increase in cellular and clinical research on diabetes since the discovery of insulin.

Incidenceandepidemiology-Globalprevalenceofdiabetes

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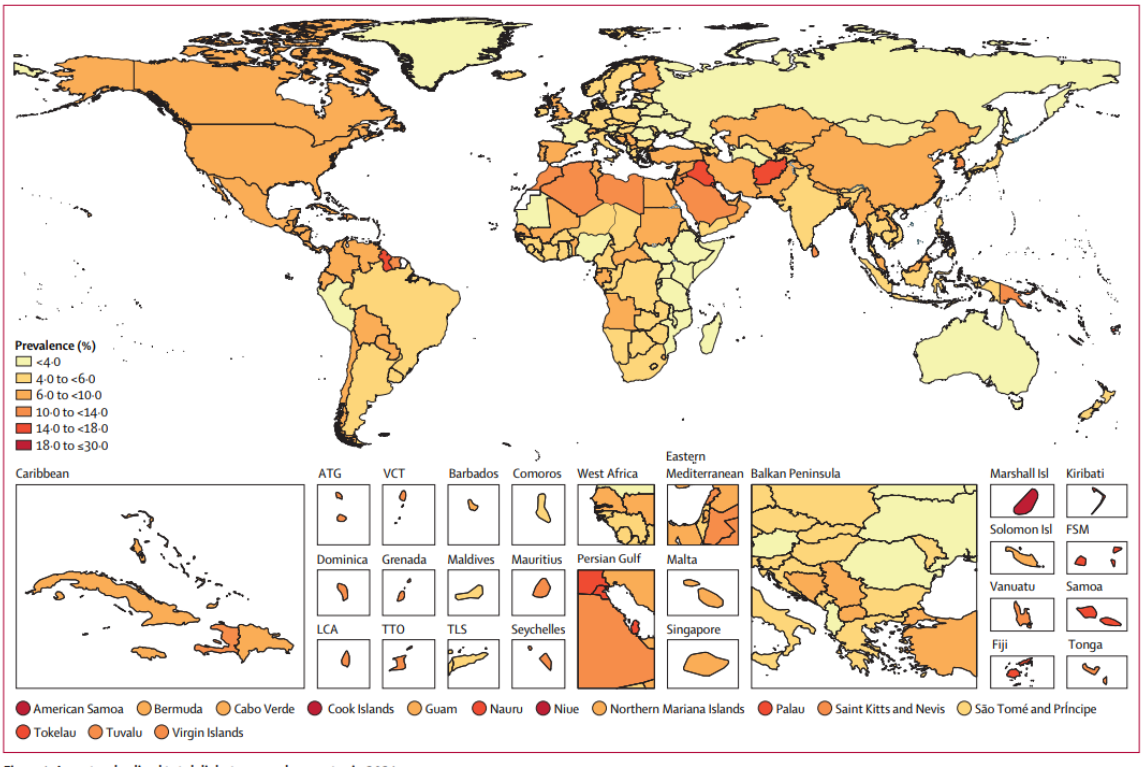

Complications from diabetes are responsible for over 3.2 million fatalities annually, or six deaths each minute. India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh are among the top 10 nations with the most victims. People in India, a country with a population of over a billion, have a higher risk of getting type 2 diabetes later in life and are more likely to suffer from diabetes-related problems such high blood pressure and heart disease. At least 240 million people throughout the globe already suffer from diabetes, and this number is expected to more than quadruple by 2030 (Onitilo et al., 2012); hyperglycemia, the major clinical manifestation of diabetes, is considered to lead to diabetic complications.

In 2021, there were 529 million (95% UI 500–564) peopleof all ages, worldwide, living with diabetes, yielding a global age-standardised prevalence of 6·1% (figure 1) (Chan et al., 2006).

Classificationandtypesofdiabetes

There are four major forms of diabetes mellitus, including type 1, type 2, gestational, and "other specific types" (Zinman, 2006). The "other specific types" include several dozen unique factors. Without further clarification, the word diabetes typically refers to diabetes mellitus. The term "type 1-diabetes" has superseded numerous others, such as "childhood-onset diabetes," "juvenile diabetes," and "insulin-dependent diabetes mellitus." Non-insulin-dependent diabetes mellitus (NIDDM), adult-onset diabetes, and obesity-related diabetes are all terminology that have been superseded by "type 2 diabetes." Diabetes during pregnancy has been described as "type 3 diabetes" by a number of different authors. Despite sharing many of the same symptoms as diabetes mellitus, the metabolic disorder diabetes insipidus (from the Latin for "without taste") is very uncommon.

Type-IdiabetesmellitusorInsulindependentdiabetes

When the insulin-producing -cells of the pancreatic islets of Langerhans are destroyed, type 1

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diabetes mellitus develops. In the early phases, insulin sensitivity and response are often normal. Type 1 diabetes, formerly known as juvenile diabetes, occurs when the immune system of the body attacks and kills the pancreatic cells responsible for making insulin. T-cell-mediated autoimmune attacks on beta cells account for the vast majority of cases of type 1 diabetes (Zinman, 2006). Historically, type 1 diabetes was referred to as "juvenile diabetes" since it accounts for the vast majority of occurrences of diabetes in children. An impaired counter regulatory response to hypoglycemia, occult infection, and gastroparesis (which leads to erratic absorption of dietary carbohydrates) are just a few of the causes of type 1 diabetes' frequent and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemias(Zinman, 2006).

Non-insulin dependent diabetic mellitus, often known as type-2 diabetes

Ninety percent to ninety-five percent of all patients who have diabetes have type 2 diabetes. Type 2 diabetes is characterized by impaired insulin sensitivity in its first stages (Onitilo et al., 2012). Medications and lifestyle changes that increase insulin sensitivity or decrease glucose synthesis by the liver may correct hyperglycemia at this point. The insulin receptor is thought to be involved in the poor responsiveness of body tissues to insulin, which is a hallmark of type 2 diabetes mellitus (Onitilo et al., 2012). Insulin resistance may occur in conjunction with somewhat lower insulin production. However, the nature of the faults is yet unknown. Cases of diabetes mellitus caused by a genetic anomaly are separated apart.

Diabetic Pregnancy

About 2-5% of all pregnant women develop gestational diabetes mellitus (GDM), which often improves or goes away after the baby is born. Similar to type 2 diabetes, GDM is characterized by both insufficient insulin production and insulin responsiveness. Treatment for GDM is possible, but it requires close medical monitoring during pregnancy. Type 2 diabetes develops in between 20%-50% of afflicted women (Schwar et al., 2010). Untreated gestational diabetes may compromise the health of the mother or baby, despite the condition being temporary. Malformations of the skeletal muscles, heart defects, and the central nervous system, as well as a high birth weight, are all potential dangers to the newborn. Fetal insulin elevation has been linked to respiratory distress syndrome by decreasing fetal surfactant synthesis. This is a major concern since having diabetes during pregnancy increases the likelihood of problems and also makes the offspring more likely to have diabetes themselves in the future.

Insulin's role in regulating glucose metabolism in the blood

Diabetes mellitus, is caused by peripheral tissue becoming less responsive to insulin owing to either insulin shortage or insulin resistance. Hyperglycemia is the hallmark of this condition, which is caused by insulin regulatory anomalies and consequent changes in the metabolism of carbs, lipids, ketones, and amino acids. Despite large shifts in both energy intake and expenditure, plasma glucose concentrations are efficiently controlled within a small range (Roberts and Rosenberg, 2006). The liver, particularly in response to insulin and glucagon, was responsible for regulating plasma blood glucose levels. The liver's glycogenolysis and gluconeogenesis are both influenced by insulin (Assimacopoulos-Jeannet et al., 1982).

The hormone insulin, produced by the pancreatic -cells, reduces blood sugar levels by blocking glucose synthesis in the liver and boosting glucose absorption and utilisation in muscle and fat. Hepatic net extraction of glucogenic amino acids, lactate, and glycerol is

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increased in insulin deficiency, and gluconeogenesis enzymes like glucose-6-phosphatase (Glc-6-Pase), fructose-1,6-bisphosphatase, and pyruvate carboxylase are stimulated in both quantity and activity (Foufelle and Ferre, 2002). Both endogenously generated triglycerides and those obtained exogenously are stored as fat and muscle when insulin is present (Faraj and Cianflon, 2004). Hydrolysis of triglycerides stored in the adipocytes is also reduced because it blocks the hormone-sensitive lipase in adipose tissue. In animals with diabetes, both plasma triglycerides and cholesterol levels rise (Ginsberg & Zhang, 2005).

Diabetes-related complications

The risk of developing long-term problems is elevated in all types of diabetes. Usually, they appear after ten to twenty years have passed. Vascular injury is a primary cause of long-term problems.

Neuropathy due to Diabetes

Numbness, tingling, and pain in the feet are typical symptoms of diabetic neuropathy, a condition in which the nerve system is negatively impacted by diabetes. Neuropathy, in conjunction with vascular disease in the legs, increases the likelihood of developing diabetes-related foot complications (such as diabetic foot ulcers), which may be difficult to treat and may even need amputation. The most common consequence of long-term diabetes is diabetic neuropathy. Diabetic neuropathy may cause loss of peripheral nerve function, tingling, numbness, discomfort, muscular weakness, and parasthesias (Aring et al., 2005). Diabetic neuropathy may sometimes spread to deeper nerves can lead to cardiac dysfunction, diarrhea, constipation, urinary retention, and impotence (Vinik & Erbas, 2001).

Disease of the retina caused by diabetes

Visual discomfort, decreased vision, and even blindness may result from diabetic retinopathy, a disease that damages blood vessels in the retina. One of the most common reasons diabetics become blind is diabetic retinopathy, which is the most specific consequence of diabetes. In those aged 20-74, diabetes is the single most common cause of blindness. Nearly 0.7 million persons with diabetes (4.4% of those with diabetes) had advanced diabetic retinopathy in 2005-2008, and this condition may cause serious vision loss if left untreated (Fong et al., 2004). Non-enzymatic glycation, glycoxidation, buildup of advanced glycation end products, free radical-mediated protein damage, and upregulation of matrix metalloproteinases are all involved in the etiology of diabetic retinopathy (Basta, Schmidt, & De Caterina, 2004).

Nephropathy from Diabetes

The effects of diabetes on the kidneys, known as diabetic nephropathy, may cause pathological changes in kidney tissue, the loss of trace quantities of protein in the urine, and ultimately, chronic kidney disease that necessitates dialysis. Fourty-four percent of all new instances of renal failure in 2008 were brought on by diabetes. Treatment for renal failure due to diabetes was started in 48,374 Americans in 2008. According to the Report of the Committee on Statistics of the American Diabetes Association (1969), in 2008, 202,290 Americans were surviving on continuous dialysis or a kidney transplant owing to end-stage renal disease caused by diabetes. Renal failure is the leading cause of mortality in people with diabetes, responsible for 14% of all diabetes-related fatalities failure. Lesions include peritubular fat, glycogen, and mucopolysaccharide deposition, glomerulosclerosis, arteriosclerosis of efferent and afferent arterioles, arteriosclerosis of renal arteries and its

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intra-renal branches, and glomerulosclerosis (Opitz and von Dorsche, 1975).

Foot ulcers due to diabetes

The primary risk factors for the development of foot ulcers in diabetics are ischemia and peripheral neuropathy. An open sore on the foot caused by diabetes is a serious consequence. Fifteen percent of diabetic people experience this (Rollins, 2000). All skin injuries, whether open or closed, trigger a'make-up' phenomena known as wound healing. However, foot ulcers may be avoided with attentive care, protection from damage, and enhancement of local blood flow.

Ketoacidosis due to diabetes

Patients with diabetes mellitus have a significant risk of developing diabetic ketoacidosis. Because of insufficient insulin production, the body instead uses fat for fuel, which causes an increase in the production of ketones (Beech et al., 1989). Without therapy, the extra ketones might cause ketoacidosis. If left untreated, ketoacidosis may cause a cascade of metabolic complications and possibly coma. Abdominal discomfort, vomiting, fast breathing, intense fatigue, and sleepiness are among symptoms of ketoacidosis (Lambermont et al., 1996).

Disorders of the Blood Vessels

Diabetic people often succumb to cardiovascular problems. The danger of developing cardiovascular disease is increased by a factor of two in those with diabetes. Ischemic heart disease (atherosclerosis of bigger arteries, angina, and myocardial infarction) and stroke are the most common "macrovascular" disorders circulatory problems in the extremities. Having diabetes mellitus raises your chances of developing cardiovascular disease, thrombosis, and atherosclerosis. According to Cade (2008), vascular disease accounts for around 70% to 80% of mortality in diabetes individuals. Death rates from heart disease in individuals with diabetes are around two to four times greater than in those without diabetes. Diabetics have a two- to fourfold increased risk for stroke. Damage to the tiny blood vessels, known as microvascular problems, is a direct effect of diabetes. Clinical studies confirmed the link between diabetes and left ventricular dysfunction, which leads to myocardial structural and functional changes, independently of hypertension, coronary artery disease, and other heart disease (Frohlich, 1999). Diabetic cardiomyopathy is a kind of heart disease that affects people with diabetes but cannot be traced to other causes, such as high blood pressure, coronary artery disease, or obesity.

Cardiomyopathy due to Diabetes

Independent ventricular failure due to factors other than coronary artery disease or hypertension characterizes diabetic cardiomyopathy (From et al., 2010). However, the idea of diabetic cardiomyopathy indicates a direct cellular insult to the myocardium, even if diabetics are at higher risk of structural heart disease owing to vascular problems. Myocardial fibrosis (associated with elevated levels of angiotensin II, insulin-like growth factor I, and inflammatory cytokines; myocytes are lost and replaced with extracellular matrix protein like collagen); metabolic disturbances (increased free fatty acids, carnitine deficiency, changes in calcium homeostasis, and depletion of glucose transporter); and small vessel disease (microangiopathy, impaired coronary blood flow) are the most important mechanisms of diabet

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Stages of Diabetic cardiomyopathy

Both a short-term, physiological response to metabolic abnormalities and longer-term, degenerative changes that the heart can only partially heal seem to be key components of diabetic cardiomyopathy. As a result, interventions made during the early stages of diabetes may prevent or limit the development of long-term complications. It is important to remember that not all diabetic patients are affected by the same factors or to the same degree, so there may be marked variability in the clinical manifestations of diabetic cardiomyopathy. These factors include treatments, metabolic characteristics, lipid profile, and other individual differences.

Start-up phase

Metabolic abnormalities such as GLUT4 depletion, increased FFAs, carnitine insufficiency, calcium homeostasis alterations, and insulin resistance are hallmarks of type 2 diabetes and its associated cardiomyopathy (Stanley, 2005). Minor alterations in cardiac structure (normal LV dimensions, wall thickness, and mass) or merely substructural alterations in myocytes characterize these phases of diabetic cardiomyopathy. Sensitive measures like strain, strain rate, and myocardial tissue velocity are often required to diagnose cardiac dysfunction. Early-stage endothelial dysfunction develops.

Between Phase

Increases in myocyte apoptosis and necrosis, angiotensin II, and transforming growth factor beta may occur from cellular alterations such abnormalities in calcium transport and fatty acid metabolism, producing myocyte damage, loss, and myocardial fibrosis and initially generating aberrant mitral inputs which may progress to a low ejection percent. Myocellular hypertrophy and cardiac fibrosis are the most prominent features of this stage of diabetic cardiomyopathy. Conventional echocardiography may identify subtle changes in structure (such as LV size, wall thickness, or mass) and major alterations in diastolic and systolic performance in patients at this stage (Aurigemma, 2006). Lesions in the structural integrity of the myocardial blood vessels are often minor at this time.

Later Phase

At this point, diabetic cardiomyopathy is often linked to hypertension and the onset of ischemic heart disease in people with diabetes. cardiac microvascular changes are a consequence of the ongoing metabolic alterations and the progression of cardiac fibrosis (Hayat et al., 2004). Myocardial microvascular structural and functional alterations, most often accompanied by recurrent microvascular spasm, define this stage of diabetic cardiomyopathy. There have been noticeable alterations in heart anatomy and function.

Diabetic cardiomyopathy: pathophysiology

- **Fibrosis of the myocardium**

Many researchers believe that diabetic cardiomyopathy's cardiac alterations may be explained by myocardial fibrosis and myocyte hypertrophy. The pathologic process of myocardial fibrosis has a significant role in the development of cardiac dysfunction and failure in DCM hearts. According to previous research, aberrant deposition leading to reduced ventricular contractile performance in DCM hearts may be caused by an imbalance in the production or

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breakdown of collagen, an extracellular matrix (ECM) component (Spinale, 2007). Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) make up the enzyme systems principally responsible for ECM turnover.

According to certain studies (Hayden et al., 2005), aberrant ECM turnover is caused by a dysregulation of MMP-2 and MMP-9. The morphological abnormalities in diabetic myocardium are thought to be linked to the functional abnormality, and they may contribute to the worsening of cardiac haemodynamics over time.

- **Calcium homeostasis disturbances**

Diabetics often have slower diastolic rates because their sarcoplasmic reticular calcium pump functions are impaired. Diabetic cardiomyopathy is characterized by an increase in diastolic stiffness, which may be caused by these modifications (Kain, 2011). Calcium sensitivity of regulatory proteins is altered due to an accumulation of harmful compounds such long chain acylcarnitine and free radicals. Deranged cardiac mechanics in diabetics may result from myocardial calcium handling abnormalities.

- **Accumulation of advanced glycation end products**

Non-enzymatic glycation of macromolecules occurs in diabetes due to hyperglycemia. Advanced glycation end products (AGEs) are the structures formed when glucose is metabolized (Basta, 2004). These AGEs may accumulate in tissues and have been associated to morphological alterations in the diabetic heart (Leslie and Cohen, 2009). They are formed when sugars attached to macromolecules undergo a complicated process that condenses them into massive heterocyclic derivatives. Collagen and elastin, two long-lived extracellular proteins, are especially susceptible to the buildup of AGE cross linkages. Collagen buildup or fibrosis may result if this process is hampered (Wang et al., 2006). Myocardial stiffness is elevated, and cardiac relaxation is hindered, when structural components like collagen and elastin form cross connections with one another (Zibadi et al., 2009). Intracellular auto-oxidation of glucose to glyoxal, breakdown of the Amadori product, and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal are all sources of AGEs. These Matrix components that cause long-term physiological alterations have their functional characteristics modified by reactive dicarbonyls via interactions with amino acid residues (Bierhaus et al., 1998). Changes in myocardial calcium handling, and hence contractility, have been linked to the advanced glycation process. Changes in myocardial contractility may be attributed to a transition in gene expression from the a-MHC to the -MHC isoform of cardiac myosin heavy chain (MHC) caused by oxidative stress (Aragno et al., 2006). In addition to potentially interfering with the contractile function of the myocardium, AGE buildup also alters the extra-cellular matrix, leading to decreased elasticity of the artery wall.

Disorders of metabolism

Hyperglycemia may directly induce metabolic alterations in diabetes. The pathophysiology of diabetic cardio-myopathy may begin with a change in the supply and use of substrates by cardiac myocytes. Slow glucose transport through the sarcolemmal membrane into the myocardium owing to cellular depletion of glucose transporters (GLUT) 1 and 4 is a key limitation to glucose utilization in the diabetic heart (Kilhovd et al., 1999). One of the main causes of diabetic cardiomyopathy is the impairment of glucose oxidation caused by FFAs. An increase in free fatty acid (FFA) concentrations and an increase in myocardial FFA

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absorption and oxidation are major metabolic alterations in diabetes (Fragasso et al., 2009). High levels of circulating free fatty acid (FFA) have been shown to decrease glucose oxidation by inhibiting the pyruvate dehydrogenase complex, leading to lower ATP availability. Accumulation of glycolytic intermediates and intracellular lipids occurs as a result of FFA inhibition of pyruvate dehydrogenase, which in turn reduces energy generation in the myocardium. Toxic lipid byproducts known as ceramides might be produced in greater quantities through nonoxidative pathways as a consequence of this buildup (Lee, 2011).

It has been established in experimental models that an increase in FFA usage and oxidation by the heart raises ischemia risk, lipid buildup, energy deficit, insulin resistance, and the risk of developing cardiomyopathy.

Diabetic cardiomyopathy: factors in its pathophysiology

Multiple factors contribute to the development of diabetic cardiomyopathy. Omar Asghar et al. (2009) identified many components, including excessive glucose, the Renin-Angiotensin-Aldosterone System (RAAS), and Protein kinase-C (PKC), as probable processes underlying the development of diabetic cardiomyopathy. Interstitial and perivascular fibrosis, interstitial inflammation, an activated cardiac renin-angiotensin-system, oxidative stress, and altered Ca2+ homeostasis are all factors in the development of diabetic cardiomyopathy (Van Linthout et al., 2008).

- **Hyperglycemia**

Several secondary transducers, including reactive oxygen species (ROS) and advanced glycation end products (AGEs), may be involved in the pathological consequences of hyperglycemia (Naudi et al., 2012). Highly reactive oxygen species (ROS) include both free radicals (superoxide) and free radical-generating compounds (hydrogen peroxide). When reactive oxygen species (ROS) production exceeds their degradation by antioxidant defences, oxidative stress occurs. This elevates ROS levels, which have many harmful effects on the cardiovascular system, including oxidative damage to cells, disruption of vascular hemostasis due to interference with glycogen synthases kinase 3b, and inflammation.

- **Metalloproteinases Matrix**

Matrix metalloproteinases (MMPs) and their related tissue inhibitors, the TIMPs (Nakamura et al. 1994; Shankland et al. 1996; Gomez et al. 1997), are a family of enzymes involved for extracellular matrix (ECM) destruction and remodelling (Death et al. Among metalloproteinases, MMP-2 and MMP-9 are involved in the pathogenesis of a variety of cardiovascular disorders (Janssens and Lijnen, 2006; Mohammad and kowluru, 2011). These conditions include cardiac fibrosis, atherosclerosis, congestive heart failure, myocardial infarction, and cardiomyopathy.

Renin, angiotensin, and aldosterone system (RAAS).

Increased oxidative damage, apoptosis, or necrosis of cardiomyocytes and endothelial cells in diabetic hearts, all of which lead to increased interstitial fibrosis, have been linked to RAAS activation during diabetes mellitus (Frustaci et al., 2000). Direct signalling through the angiotensin-1 receptors leads to increased NADPH oxidase activity and elevation of ROS, resulting in oxidative damage to cardiomyocytes and endothelial cell death (Murdoch et al., 2006). The exact mechanism by which this dysfunction arises is unclear. Activation of the

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RAAS is known to have a significant role in the onset of diabetic cardiomyopathy. Under normal settings, mitochondria are the primary source of intracellular ROS production; but, in disease situations, a wide variety of additional cellular components contribute to ROS generation (Thannickal&Fanburg, 2000).

- **PKC Activation**

Calcium handling in myocytes is disrupted because protein kinase C phosphorylates many proteins directly engaged in the cardiac excitation-contraction coupling. Hyperglycemia increases AGE production, which may cause protein structural changes and disease the stiffening of the heart muscle (Goh and Cooper, 2008). There is some evidence that diacylglycerol (DAG) up-regulates protein kinase C in response to hyperglycemia (Noh and King, 2007). The contraction proteins Troponin-T, Troponin-I, and the Troponin-tropomyosin complex are inhibited by PKC. Induction of the immediate early gene program and subsequent stimulation of late genes that increase production of angiotensin converting enzyme (ACE), a-MHC, and skeletal a-actin occur as a result of elevated PKC activity via the mitogen-activated protein kinase (MAPK) cascade. The defects that lead to the onset of diabetic cardiomyopathy may have their origins in ACE (Kim and Iwao, 2000). This provides support for the hypothesis that diabetic capillary changes contribute to cardiac cell damage, interstitial fibrosis, and, eventually, diabetic cardiomyopathy.

- **Endothelial dysfunction's potential role**

Diabetic patients often have endothelial dysfunction in the coronary vasculature, which may result in impaired blood flow regulation. Avogaro et al. (2011) postulate that high glucose induces protein Kinase C activity, which may contribute to endothelial dysfunction in diabetes and the progression of diabetic cardiomyopathy. Epicardial coronary artery endothelium-dependent dilatation is diminished in diabetics despite a low risk of atherosclerosis. Vasoconstriction is increased because the endothelium produces more vasoconstrictor prostanoids in diabetes individuals.

The connection between oxidative stress and chronic diseases like diabetes and cardiovascular disease

Current research points to oxidative stress as a possible mechanism underlying both diabetes and its consequences. Research on nitric oxide's impact on diabetes mellitus is ongoing. Thiobarbituric acid reactive substances (TBARS) are consistently elevated when streptozotocin (STZ) or alloxan induce diabetes in rats from increased generation of free radicals (Gutierrez et al., 2011). Normal cellular metabolism produces oxidants in mitochondria and peroxisomes, as well as from a number of enzyme systems in the cytoplasm. In addition, reactive oxygen species (ROS) generation may be triggered by a variety of environmental factors. Increased generation of free radicals, particularly reactive oxygen species (ROS), is a hallmark of diabetes due to prolonged hyperglycemia. In addition, it has been shown that hyperglycemia stimulates lipid peroxidation of low density lipoprotein (LDL) through a superoxide-dependent mechanism, leading to the production of free radicals (Maritim et al., 2003).

Hydroperoxides are hazardous to cells both in their original form and after being degraded into even more dangerous hydroxyl radicals. In diabetes, advanced glycation end products (AGEs) and the amadori product they produce are a source of free radicals (Basta et al., 2008). The development of diabetes problems has been linked to oxidative stress and

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alterations in nitric oxide production. The development of late diabetes problems has been related, however, to increased oxidative stress and the consequent activation of the transcription factor NF-ţB. Nitric oxide is thought to mediate beta-cell damage, and NF-ţB increases its synthesis (Song et al., 2009). Reactive peroxyl nitrite radicals may be formed when nitric oxide reacts with superoxide anion radicals.

CONCLUSION

The exploration of the concept and development of Diabetes Mellitus (DM) and Diabetic Cardiomyopathy (DCM) underscores the intricate relationship between metabolic health and cardiovascular well-being. Diabetes Mellitus, a chronic metabolic disorder with various classifications, serves as a precursor to diverse complications, among which Diabetic Cardiomyopathy stands out as a distinct entity.

Diabetic Cardiomyopathy's development is a multifaceted process, driven by a combination of factors including hyperglycemia-induced oxidative stress, inflammation, and alterations in myocardial energetics. These mechanisms collectively culminate in structural and functional changes within the heart, leading to the increased risk of heart failure and other cardiovascular complications in diabetic individuals.

Understanding the mechanisms linking DM and DCM is crucial for effective clinical management and prevention strategies. Advanced diagnostic techniques enable early identification of cardiac dysfunction, facilitating timely interventions and personalized treatment plans. The significance of holistic approaches, ranging from lifestyle modifications to pharmacological therapies, is highlighted as key to reducing the impact of DM on cardiovascular health.

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