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REVIEW ARTICLE

Pathophysiological Pathways Linking Diabetes to Cardiac Hypertrophy: From Insulin Resistance to Personalised Cardioprotection

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Abstract

Diabetes and cardiac hypertrophy are closely interconnected, sharing overlapping metabolic and cardiovascular pathways. This review aimed to investigate the underlying mechanisms that drive this relationship and to evaluate current diagnostic and therapeutic strategies with the goal of improving clinical outcomes. An extensive review of recent literature was undertaken to explore how factors such as insulin resistance, hyperglycaemia, inflammation, oxidative stress and lipotoxicity contribute to cardiac remodelling and functional decline. Developments in diagnostic modalities, including advanced imaging techniques and emerging biomarkers, were examined alongside both lifestyle interventions and pharmacological treatments. Diabetes is a significant contributor to the progression of cardiac hypertrophy, primarily through metabolic dysregulation and persistent low-grade inflammation. The importance of early detection—using sophisticated imaging tools and biomarker profiling—has become increasingly evident for timely and effective intervention. Therapeutic agents such as metformin, sodium glucose cotransporter-2 inhibitors (SGLT2) and glucagon like peptide-1 receptor agonist (GLP-1) have demonstrated beneficial effects in reducing cardiovascular complications in individuals with diabetes. Moreover, novel approaches, including chronotherapy and personalised medicine, are gaining traction as potential means to enhance treatment efficacy and patient outcomes. The robust association between diabetes and cardiac hypertrophy underscores the necessity for a more integrated and nuanced approach to diagnosis and management. Combining early detection with targeted pharmacotherapy and personalised care strategies offers a promising route to addressing this complex clinical challenge. Continued research is essential to refine these approaches and to optimise long-term outcomes for affected patients.

Key words: Diabetes mellitus; Cardiac hypertrophy; Lipotoxicity; Pharmacology, chrono; Sodium-glucose transporter 2 inhibitors.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia), resulting from the body's inability to produce, secrete, or effectively utilise adequate amounts of insulin.[1] However, hyperglycaemia is not the sole concern linked to diabetes; individuals with the condition also face a significantly increased risk of developing cardiovascular complications, including heart failure, stroke and coronary artery disease. Morbidity and mortality in this population are greatly increased by these complications. Numerous studies have shown that people with diabetes are about twice as likely to develop cardiovascular disease as people without the disease.[2] Cardiac hypertrophy or enlargement/ thickening of myocardium/ cardiac muscles referred to a condition that may happen as a way for the body to adapt to more load on the cardiac system, which can happen because of either pathological or physiological stimuli. Several medical conditions are linked to cardiac hypertrophy, the most important of which is high blood pressure, which raises cortisol levels and makes atherosclerotic coronary artery disease worse. These changes in the heart's structure and function make congestive heart failure worse and raise the risk of death from heart disease. So, finding and evaluating cardiac hypertrophy early on is important for making a diagnosis and taking steps to lower morbidity and mortality.[3]

Cardiovascular diseases (CVDs) still pose a threat, to health and longevity among those with diabetes.[4] Diabetic patients with complications like heart attacks or strokes face a significantly higher risk of mortality. These conditions can reduce life expectancy by up to 12 years and nearly double the mortality rate compared to individuals without such health issues.[5] There is a clear and strong connection between diabetes and cardiovascular disease. Individuals with diabetes in this group are at a greater risk of developing conditions that are among the leading causes of mortality.[6] Diabetes impacts both men and women differently when it comes to CVD, which is a major risk factor for mortality in diabetic individuals. While men with diabetes have a 1 to 3 times higher risk of CVD-related death compared to non-diabetic men, the disparity is even greater for women. Diabetic women are three times more likely to die from CVD than their non-diabetic counterparts, making their risk significantly higher.[7]

Becoming more and more widespread and a burden to control the illness of diabetes, the disease brings out the importance of proper management and treatment. The relation that metabolic disturbances produced after the onset of diabetes plus the subsequent cardiac hypertrophy resembles the complexity of cardiovascular health issues. Research indicates that multiple signalling pathways, including the PI3K/Akt pathway, along with oxidative stress and inflammation, play a crucial role in the development of cardiac hypertrophy in diabetic patients. Moreover, the presence of diabetic complications leads to even more severe cardiac inefficiency, which in turn causes challenges in treatment.[8] Regarding treatment, targeting these channels could help regulate the side effects of diabetic cardiomyopathy. Current management strategies, including polymedication, lifestyle modifications and exercise, have proven to be highly effective in controlling blood sugar levels. DM, DM type 2 diabetes especially, is known to cause other diseases like cardiac hypertrophy. Diabetes is a primary contributor

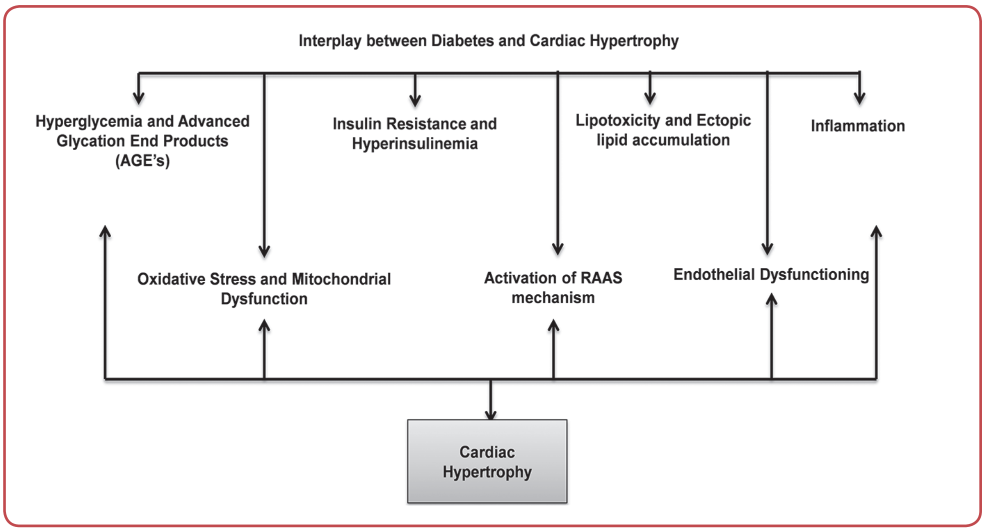

Figure 1: Interlink between diabetes and cardiac hypertrophy
RAAS: Renin-angiotensin-aldosterone system

to heart muscle hypertrophy in individuals with DM, often progressing to severe complications such as high-risk heart attacks and ischaemic heart disease (Figure 1).[9] This rise in diabetes is correct so we see an increase in diabetic cardiomyopathy, which is a heart disease that is caused by cardiac hypertrophy. Many studies have come out and shown that people with diabetes are two to four times more likely to get heart failure than those without diabetes.[10, 11]

Pathophysiology of DM

Diabetes, a condition with diverse causes and symptoms, does not always fit neatly into a single category, yet its classification remains valuable. The categorisation of diabetes largely depends on the patient's health and the diagnosis at the time. Currently, classification is based on the underlying causes and progression of the disease, aiding in accurate diagnosis and timely treatment (Figure 2).[12]
Type 1 diabetes mellitus (T1DM): T1DM, also known as insulin-dependent diabetes (IDDM), is an immune-mediated disease in which the immune system attacks the insulin-producing β-cells in the pancreas. In this condition, T cells destroy these β-cells, reducing insulin production and causing an increase in blood sugar levels.[13] T1DM patients have distinct humoral markers including autoregulation bodies. With the help of specific autoantibodies, the immune system is able to attack and counteract the unusual cells as an autoimmune response (Figure 3). A minimum of one of these autoantibodies is normally observed as part of the clinical diagnosis, whereas 85-90 % of the newly diagnosed T1DM patients show more than one immune marker.[14]

Type 2 diabetes mellitus (T2DM): T2DM, also called non-insulin-dependent diabetes, is marked by two key issues: the body's cells develop resistance to insulin and the pancreatic β-cells responsible for insulin production fail to function effectively.[15] Insulin (a hormone) acts as a key for the body's cells to enter the bloodstream and store power in the form of glycogen. In T2DM, reduced insulin sensitivity leads to impaired insulin secretion. Notably, the body's β-cells must release a sufficient amount of insulin to enable proper absorption by the liver, which helps regulate high blood sugar levels. However, in T2DM, pancreatic β-cells fail to produce enough insulin when normal levels are inadequate to meet the body's demands (Figure 4). The abiding insulin excess could be neutralised by diminishing insulin secretion and mitigating hyperinsulinemia. Such as a consequence, the delivery of decreasing levels of resistance insulin, which is the body's only way of self-regulation against high sugar levels, would contribute to the change as well. In general, diabetic ketoacidosis (DKA) can be minimised as still enough insulin is produced even with

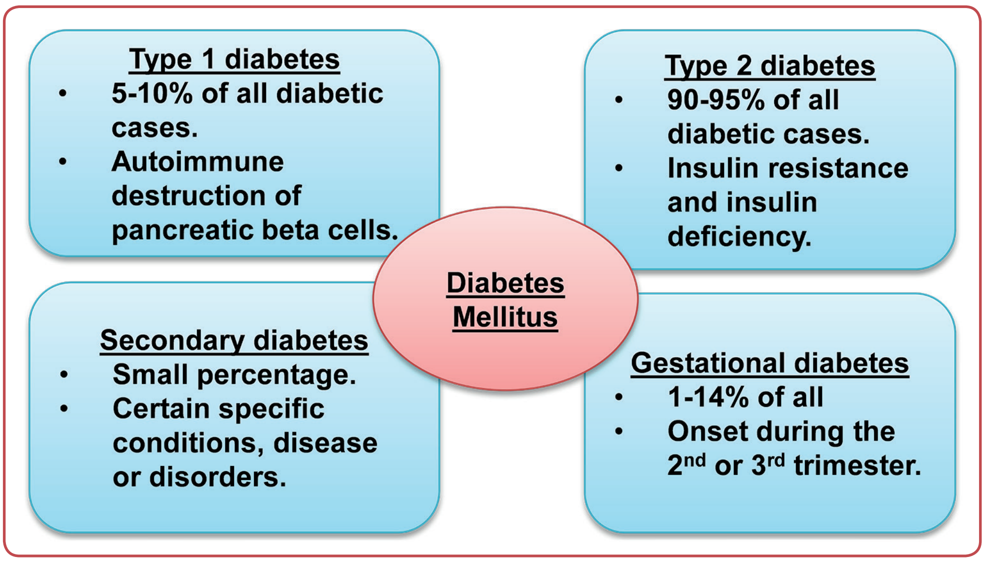

Figure 2: Types of diabetes mellitus

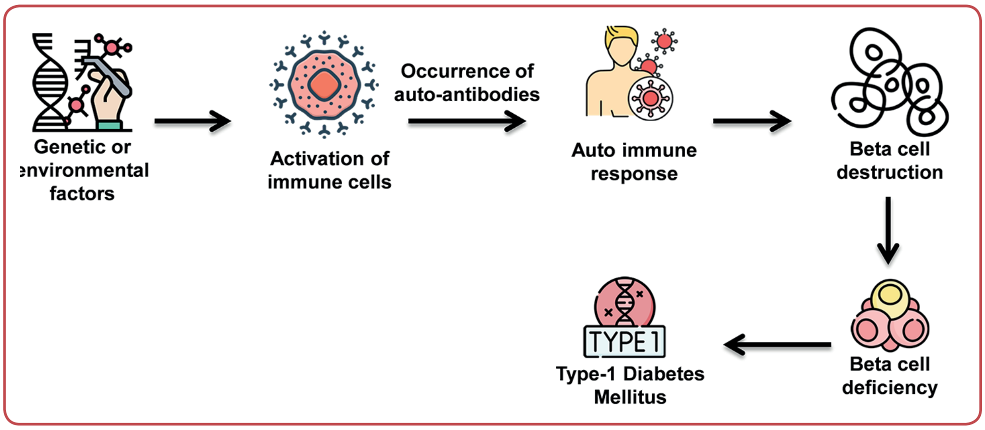

Figure 3: Pathophysiology of type 1 diabetes mellitus (T1DM)

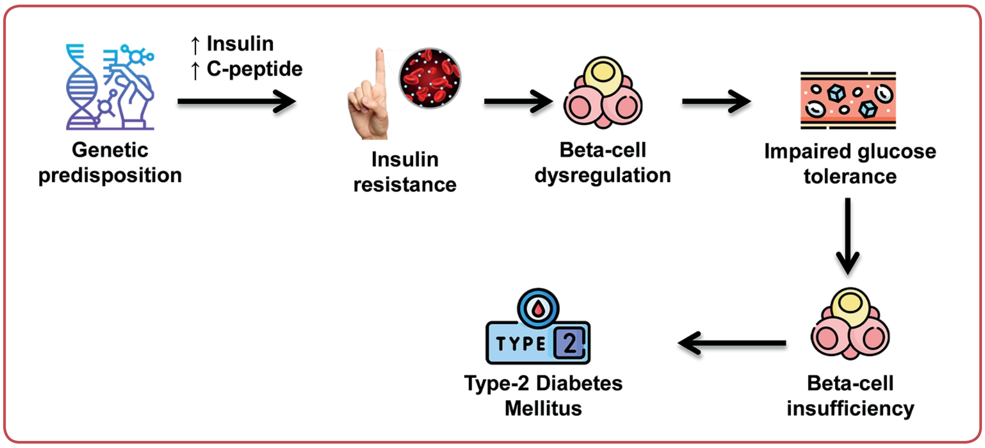

Figure 4: Pathophysiology of type 2 diabetes mellitus (T2DM)

decreased insulin levels.[16] However, DKA might appear under conditions of extreme stress, for example from infections or other medical emergencies. Another normal DKA cause by drugs is corticosteroids and atypical antipsychotics.[17]

Gestational diabetes mellitus (GDM): GDM, also known as pregnancy-associated hyperglycaemia, is a condition characterised by glucose intolerance or the onset of diabetes for the first time during the second or third trimester of pregnancy. Some cases may represent previously undiagnosed type 2 diabetes (T2DM) that began before pregnancy. Unlike pre-existing diabetes, which may persist, GDM typically resolves within 2–3 months postpartum.[18] Individuals who have experienced GDM have a higher risk of developing T2DM later in life compared to those without GDM. Regular medical check-ups to monitor glucose levels are crucial for the early detection of T2DM, making consistent doctor visits essential.[19]

Secondary DM: Aside from T1DM, T2DM and GDM, diabetes can be closely entwined with specific illnesses and ailments. They include endocrine diseases, which extend to affecting the pancreas in such a way that the creation of enzymes is influenced, which is a diabetes that comes from some kind of genetic defect, thus affecting the function of the β-cells, defects that modify insulin working and certain other specific conditions. These forms differ among other types of diabetes whose incidence is indisputable.[20]

Pathophysiology of cardiac hypertrophy

The pathophysiology of cardiac hypertrophy is characterised by a complex interaction of mechanical, neurohormonal and biochemical factors, which result in alterations to the heart's structure and function (Figure 5).[21] The primary mechanisms can be broadly categorised into he-

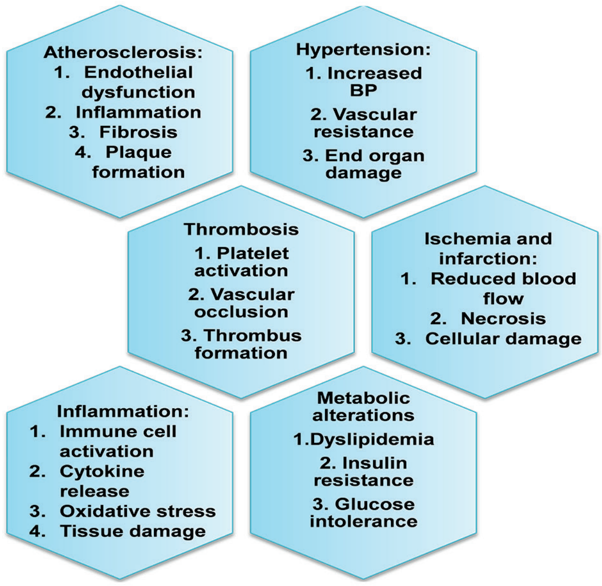

Figure 5: Pathophysiology of cardiac hypertrophy
BP: blood pressure;

modynamic overload, neurohormonal activation and cellular signalling pathways.

Haemodynamics overload: In many instances, cardiac hypertrophy occurs as a response to an increased workload on the heart. This can be caused by:

Pressure overload: Conditions like hypertension result in higher systemic pressure, prompting the heart to adapt by thickening its walls to pump blood more effectively.

Volume overload: Conditions such as valvular heart disease led to increased blood volume in the heart chambers, causing dilation and hypertrophy of the myocytes to accommodate the extra volume.[22]

Neurohormonal activation: The neurohormonal system is crucial in the development of cardiac hypertrophy. Activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) leads to increased levels of hormones like angiotensin II and norepinephrine.[23] These substances promote:

Myocyte hypertrophy: Through growth factors like transforming growth factor-beta (TGF-β) and endothelin-1, which signal pathways that influence cell growth and remodelling.

Fibrosis: Progressive fibrosis contributes to stiffness and reduces cardiac compliance, leading to diastolic dysfunction and worsening heart function.[24]

Cellular signalling pathways: Within the cardiac myocytes, several signalling pathways are activated during hypertrophy:

PI3K/Akt pathway: This pathway promotes cellular survival and growth, allowing myocytes to adapt to increased stress.

MAPK pathway: The mitogen-activated protein kinase pathway promotes cellular proliferation and hypertrophy, playing a key role in the overall increase in cell size.[25]

Pathophysiological links between diabetes and cardiac hypertrophy

The pathophysiological relationship between diabetes and cardiac hypertrophy is intricate and multifactorial, involving a mix of metabolic disturbances, hemodynamic alterations and neurohormonal activation. Understanding these connections is vital in addressing the increased cardiovascular risk faced by individuals with diabetes.[26]

Insulin resistance and hyperglycaemia: Insulin resistance, a hallmark of T2DM, leads to elevated blood sugar levels that trigger damaging metabolic effects in the heart muscle. The measures taken by heart muscles in the presence of high blood sugar since the hyperglycaemia becomes chronic are mainly aimed at enhancing glucose uptake. However, hyperglycaemia that is persistent and, therefore, high glucose levels prove to be the main factor that leads to the creation of harmful metabolites, which are, for instance, advanced glycation end-products (AGEs). AGEs, in turn, provoke oxidative stress and therefore inflammation, which are the principal elements of myocardial injury. Diabetes also disrupts the use of myocardial substrates, shifting the main consumed substrates from fat oxidation into glycolysis and the production of lactate. Lasting these metabolic changes can cause thickening of the vessel walls, the body's reaction to the higher blood pressure, which can promote structural idealism and successful adaptation of the myofibrils in the heart and, in turn, prove to be beneficial for weak heart function but the diminished ability of the ventricle to fill properly might still occur.[27]

Inflammation and oxidative stress: Diabetes promotes oxidative stress through several mechanisms, including (a) impaired regulation of the mitochondrial electron transport chain, which is a primary source of oxidative stress, (b) increased activity of the RAAS and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and (c) elevated oxidative stress caused by the interaction between AGEs and their receptor, leading to the production of reactive oxygen species.[28] The activation of the NLRP3 - nucleotide-binding oligomerisation domain-like receptor family, pyrin domain-containing inflammasome in diabetes plays a role in chronic inflammation, which subsequently exacerbates the development of diabetic cardiomyopathy at its onset.[29] The interaction between oxidative stress and inflammation is a key factor in increasing the production of reactive oxygen species and the release of inflammatory molecules. This process leads to changes and accumulation in heart failure, along with its remodelling, which further exacerbates the condition.[30]

Lipotoxicity: Lipotoxicity that is caused by elevated free fatty acid (FFA) levels in obesity and insulin resistance is detrimental to the heart. Therefore, myocyte dysfunction due to lipotoxicity is particularly important. What happens is that the excess FFAs are accumulated inside the heart cells causing various cell functions to be broken and they will also induce oxidative stress which in turn can lead to apoptosis or the cell death mechanism, necrosis.[31] Cellular injury prompts compensatory hypertrophic responses while preserving cardiac contractile function, ultimately contributing to pathological cardiac remodelling. Additionally, lipotoxicity is closely linked to increased levels of inflammatory cytokines, which

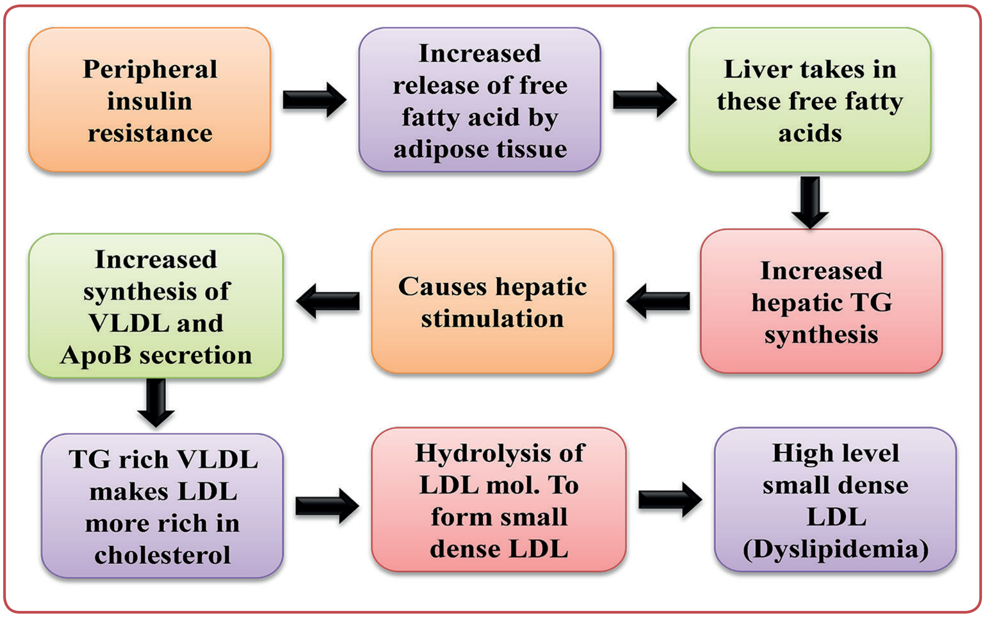

Figure 6: Dyslipidaemia mechanism in diabetic patients
TG: triglycerides; VLDL: very-low-density lipoprotein; LDL: low-density lipoprotein; ApoB: apolipoprotein B;

worsen endothelial dysfunction, promote fibrosis and accelerate the process of cardiac hypertrophy, thereby increasing the risk of heart failure and cardiovascular events (Figure 6).[32]

Mitochondrial damage: Insulin resistance causes impaired glucose metabolism and decreased oxidative capacity, leading to an imbalance in uptake and oxidation of fatty acids. Eventually, this leads to dysfunction in the mitochondria.[33] Insulin resistance and diabetes and their complications, are directly related to subcellular level of mitochondrial dysfunction.[34] Accumulation of lipid and enhanced production of reactive oxygen species caused by the reduction of mitochondrial function in myocardial cells deteriorates diabetic cardiomyopathy and worsens cardiac function.[35] The pathway of mitophagy is the elimination of defective mitochondria by a kind of autophagy, which is the crucially maintaining the quality of mitochondria. In the diabetic cardiomyopathy model, mitophagy acts a stabilising role by targeting dysfunctional mitochondria to eliminate them and therefore prevents oxidative stress and reduces myocardial apoptosis.[33] The electron transport chain of the mitochondria has two sites that generate reactive oxygen species and it has been reported that increased glucose metabolism in diabetes also promotes reactive oxygen species generation.[34]

Activated leukocyte: Insulin resistance and diabetes seem to result in an excessive activation of the inflammatory response. Inflammation is the main driver of leukocytes and the latter contribute to the oxidative stress associated with diabetes. Reactive oxygen species are also generated by activated leukocytes besides the mitochondria.[36]

Diagnostic approaches

Screening for cardiovascular risk in diabetic patients: The diagnostic processes for cardiac hypertrophy in T2DM also comprise multi-modality assessment strategy, including clinical evaluation, imaging and laboratory assessment. Early diagnosis of cardiac hypertrophy is very important in the regulation of T2DM, as it can help to slow down the development of more advanced cardiac morbidities.

Blood pressure (BP) measurement: Patients with stable coronary artery disease (CAD) and T2DM may find a target of 140/90 mm Hg reasonable, or they may opt for higher blood pressure targets. For individuals at a greater risk of stroke and microvascular complications, lower blood pressure targets (< 130/80 mm Hg) can be advised.[37] If the T2DM patient blood pressure measure is greater than 120/80 mm Hg, lifestyle intervention should be considered. In pregnant women suffering from diabetes and chronic high blood pressure, a BP of 110–135/85 mm Hg should be sought to prevent the risk of developing gestational hypertension.[38]

Lipid profile: Patients having diabetes have more likely a chance of developing dyslipidaemia. An important characteristic of dyslipidaemia is an increased level of low-density lipoproteins, or ApoB shown in Table 1.[39]

Microalbuminuria testing: Macroalbuminuria implies greater damage to the kidneys than normal and has been correlated with cardiovascular disease. Patients with macroalbuminuria, due to elevated levels of low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C), face a tenfold higher risk of cardiovascular disease compared to those without the condition.[40] These add fur-

Table 1: Lipid profile in diabetic patient

Type of diabetes	Cholesterol panel
Type 1 diabetes mellitus	Resembling to those of individuals without DM.[40]
Type 2 diabetes mellitus	An increase in apoB levels, as well as cholesterol ester depletion in LDL.[41]
Poor diabetes management	HDL and LDL cholesterol levels decrease, while IDL, VLDL and triglycerides increase.[42]

TG: triglycerides; HDL: high-density lipoprotein; VLDL: very-low-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate-density lipoprotein; ApoB: apolipoprotein B;

ther risk to cardiovascular disease and mortality. Better regulation and control of glucose lead to decreased incidence of microalbuminuria.[43] The presence of albumin in the urine signals early kidney damage and is linked to a higher risk of cardiovascular disease.

HbA_1c testing: Maintaining an HbA_1c level below 7 % in individuals with T2DM lowers the risk of microvascular complications and cardiovascular diseases. Furthermore, patients with a limited life span, critical issues in small and large blood vessels, substantial additional health problems, or enduring T2DM may have a reduced HbA_1c target, potentially below 8.0 %, customised for their particular circumstances.[44]

Assessment of lifestyle factor: Reducing heart attack and stroke fatalities and mitigating their economic effects can be improved by targeting at-risk demographics. Preventing or delaying cardiac hypertrophy can be achieved by managing blood sugar, blood pressure and cholesterol, alongside lifestyle modifications such as smoking cessation, maintaining a healthy diet and engaging in regular physical activity.

Biomarkers and imaging techniques

Echocardiography: Individuals with diabetes have an increased incidence of heart failure, a condition that cannot be solely explained by the presence of obstructive CAD and other conventional risk factors.[45] Sometimes, tiny blood vessels get hurt, leading to changes and making it tough for the heart to pump and relax properly.[46] Multitude of studies indicates that there is an association between DM with mass and wall thickness of left ventricle along with impaired left ventricular systolic function.[47, 48] Regression analysis indicated that the degree of ischaemia and left ventricular dysfunction while at rest were independent predictors of death.[49]

Cardiac magnetic resonance imaging (MRI): MR, an effective method for evaluating anatomical and physiological features of the myocardial tissue. Studies utilising steady-state free precession sequences have shown significant variations in left ventricular muscle mass, volume and function among patients with insulin resistance, T2DM and T1DM.[50, 51] A relatively new technique called T1 mapping measures the effect of the increased concentration of gadolinium in the extracellular space on T1 relaxation times. This enables the assessment of myocardial interstitial fibrosis: the extracellular volume fraction.[52] MR spectroscopy, while still being investigated, has offered valuable understanding of pathophysiology of heart muscle dysfunction due to diabetes.

Radionuclide imaging: One study has differed, showing that the characteristics became detectable using radionuclide imaging in the case of individuals with DM. Positron-emission tomography, non-invasive assessment of myocardial blood flow reserve is another well-established method-cardiac effect of particular lesions, diffused disease and coronary microvasculature function are integrated into it.[53]

Coronary intima media thickness (CIMT): CIMT evaluated for its use as a substitute indication of atherosclerosis and has been proven to have a connection with the development of coronary heart disease.[54, 55] CIMT was formerly considered valid for assessing the earlier European Society of Cardiology (ESC) guidelines regarding significant cardiovascular risk in relatively low-risk, asymptomatic adults. However, subsequent studies were consolidated under the aegis of the 2013 the American College of Cardiology and American Heart Association (ACC/AHA) guidelines and showed that this risk cannot predict CHD reliably.[56]

Lifestyle modification

Preventing cardiac hypertrophy in high-risk individuals can significantly lower mortality rates and reduce the financial strain of heart failure and other cardiac complications. Effective metabolic control through blood glucose, blood pressure and cholesterol management, combined with a healthy diet, smoking cessation and increased physical activity, can help prevent or delay the onset of cardiac hypertrophy. Secondary prevention is the direct management of the possible contributing factors for diabetic patients already diagnosed with cardiac hypertrophy. In 1999, the AHA endorsed a comprehensive medical intervention as a secondary prevention measure for diabetic patients who had clinically established cardiac hypertrophy, thereby emphasising aggressive management in reducing disease progression and improving patient's outcome.[57]

Lifestyle interventions, like exercise and dietary changes, seem to decrease the amount of visceral adipose tissue and ectopic fat, subsequently improving the cardiac profile.[58–60] Adopting lifestyle changes and managing habits can significantly lower blood pressure and effectively control hypertension. It is equally important to exercise regularly, quit smoking and limit your time spent being sedentary as an effective method of blood pressure control.[61]

It has been found that changes in lifestyle can provide a means to lower BP, enhance metabolic processes and improve the circulatory system in collaboration with antihypertensive medications. Regular consumption of peanuts, tree nuts and grain is useful for lowering cholesterol and BP due to their rich contents of unsaturated fat. Patients with 5 % body weight loss may then expect an improvement in lipid profile, glycaemic control and insulin resistance. An improvement in high BP, triglyceride concentration and HDL-C levels can be seen from weight loss.[61–63]

Pharmacological interventions

Anti-diabetic agents

Metformin: Multiple observational studies have shown that metformin offers a much more acceptable safety profile in patients with heart failure than do insulin or sulfonylureas.[64] Metformin acts as a catalyst by activating AMP-activated protein kinase, regulating metabolism through multiple mechanisms in organs such as the heart, liver and muscles. In mice with ishaemic heart failure, metformin enhanced left ventricular function and improved survival rates.[65] Metformin is considered one of the effective methods for reducing the risk of cardiac hypertrophy in patients with T2DM who do not have overt heart disease.[66]

Sodium glucose cotransporter-2 inhibitors (SGLT2): These impair and improve, heart failure via two additional ways, which are believed to be metabolic and haemodynamic. Metabolic mechanisms include lowering glucose, safeguarding from lipotoxicity, promoting weight reduction, increasing ketone levels of blood glucose and addressing insulin resistance. While the other is generally evident in being diuretic and lowering blood pressure, a more kinetic one is not clear yet. By the way, SGLT2 inhibitors can also hinder lipid aggregation in visceral fat and promote fat burning against lipotoxicity, yet their specific action on the myocardium isn't yet established. More studies are required to clarify this property.[67]

Glucagon like peptide-1 receptor agonist (GLP-1): GLP-1 receptor agonists, shows a beneficial effect on cardiac hypertrophy, heart failure and renal health and have been shown to reduce weight gain, blood pressure, glycosylated haemoglobin and low-density lipoprotein levels. Therefore, GLP-1 agonists should be considered for use in the context of secondary prevention concerning T2DM and cardiac hypertrophy.[68]

Sulfonylureas: Properly designed studies have observed a significantly higher risk for heart failure in sulfonylureas. A comparison was made of various antidiabetic drugs in a retrospective study assessing their risk for MI, overall mortality and for HF.[69] Reported findings indicate that the use of sulfonylureas alone led to a 24-61 % increase in total mortality and an 18-30 % increase in heart failure compared to metformin monotherapy.

Thiazolidine derivatives: Among the thiazolidinediones, pioglitazone has been linked to a higher risk of heart failure and is not recommended for patients with existing heart failure.[69] Pioglitazone does not impact heart function directly. Instead, it works on the collecting duct by activating sodium transporters in the proximal tubule and epithelial sodium channels, leading to increased Na^+ reabsorption and fluid retention. To avoid the development of heart failure caused by retaining fluids, it is preferable to consider using pioglitazone along with thiazide diuretics or mineralocorticoid receptor antagonist.[26]

Antiplatelet therapy

In the management of cardiac hypertrophy in the diabetic populations, use of antiplatelet therapy remains crucial. Patients with T2DM has shown an increase in the expression of platelet P2Y12, which contributes to enhanced platelet activation and this amplifies the state of hypercoagulation, predisposing to cardiac hypertrophy.[70] Aspirin, a widely used antiplatelet drug, lowers the occurrence of cardiovascular events by preventing platelet aggregation. A meta-analysis revealed that aspirin decreased the risk of vascular events in patients with a history of vascular conditions by approximately 25 %.[71] Researchers have found that discontinuing aspirin early in patients with acute coronary syndrome or undergoing percutaneous coronary intervention (PCI) reduces bleeding events without adversely affecting cardiovascular outcomes.[72]

Chrono pharmacology and diabetes treatment

DM treatment and management are heavily influenced by chrono pharmacological aspects. Specifically, the time of drug administration and individual activity have a great impact on blood glucose levels.[73] Circadian rhythm regulates the release of insulin and counterregulatory hormones such as glucagon, cortisol, growth hormone and epinephrine, helping to control blood insulin levels based on the body's needs. At night, there is the increased hormone production of growth hormone, followed by cortisol leading to increased glucose production by the liver. In nondiabetics, the pancreas produces increased insulin to compensate against a fast rise in glucose, stabilising the levels. Nondiabetics with diabetes (Type I or Type II) may show higher glucose levels at night to significantly change morning levels. Between 4 am and 8 am, there is an increase in blood glucose, which is referred to as the "dawn phenomenon." Circadian disruption has been found to elevate insulin resistance and impair pancreatic function.[74]

Emerging research and future prospective

Glycaemic control: Maintaining one's blood glucose levels, glycaemic control, will have great implications in the patient's health. Glycaemic control and cardiovascular outcomes are interwoven with many variables, varying from broad vascular complications to narrow vascular complications. The microvasculature does not simply impose those myriad health conditions due to their ability to damage all small blood vessels throughout the body. These complications see glycaemic control related to other conditions such as diabetic retinopathy, nephropathy and neuropathy, with DCCT one of the more notable studies on this subject.[75, 76]

Personalised medication: Management of diabetes wants personalised attention toward the attainment of optimal glycaemic control, which is an extremely important matter. The establishment of glycaemic goals should be based on age, presence of coexisting medical conditions, life expectancy and risk for hypoglycaemia.[77]

Smart insulin pen: Affordable smart pens have proven methodically useful for people using metered dose inhaler therapy. Demonstrating dosage with reminders, calculating insulin boluses and proper interval injections determine how these aids in diabetes management from CGM data. A mobile application can accompany these smart pens, which can be programmed either by the patient or by the healthcare provider. Presently, there is only one smart pen that has received FDA approval: the InPen from *Medtronic* in Northridge, CA.[78, 79]

Inhaled insulin (*Afreeza*): Inhaled insulin rapidly mimics the insulin response of healthy individuals. Technosphere insulin (TI), marketed under the brand name *Afreeza* by *Mankind Corporation*, is the only available pulmonary insulin in the United States. Studies indicate that TI acts more quickly but has a shorter duration of action compared to traditional rapid-acting insulins like *Aspart, Lispro* or *Glulisine*.[80–82]

Future research scopes

Ongoing research is focused on developing new treatments for diabetic patients with cardiac hypertrophy. These investigational therapies aim to target inflammation, lipid metabolism and other related pathways. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) assessed the effectiveness of canakinumab, an anti-inflammatory drug, in reducing cardiovascular events.[83] The prospect of transforming diabetes and cardiac hypertrophy management is immense, with the addition of digital health solutions. Some applications even allow for remote interaction with healthcare professionals. Real-time data from wearables-CGMs and fitness trackers-enable individuals to easily supervise and maintain their health better. The collection and sharing of health information raise issues regarding patient privacy and data security. Some individuals may face limitations in accessing digital health solutions as a result of lack of smartphones, computers and stable internet connections, hindering their effectiveness.[84]

Multidisciplinary approach: As part of the management of cardiac hypertrophy in high-risk populations, especially among such populations as diabetes, it is crucial to recognise the significance of team-based management. Sophisticated procedures, considering cardiovascular complications, imply that one specialist cannot fulfil all the roles. All specialists function as a team whereby each specialist plays their role based on established histories of the patient, current health status, lifestyle, preferences and goals of the patient. This will provide direction to possibly all risk factors and satisfactory treatment of the patients.[84]

Conclusion

The complex interaction between diabetes and cardiac hypertrophy stresses the urgent requirement for an integrated approach to the management of cardiovascular complications in diabetic patients. The current modalities of treatment consist of glucose, lipid and blood pressure control as all of these factors are associated with the hypertrophic remodelling of the heart. Future studies should explain the precise roles of inflammation, oxidative stress and metabolic dysregulation in facilitating cardiac hypertrophy. Investigating novel therapeutic targets, such as modulation of inflammatory pathways (eg IL-1β inhibitors like canakinumab) and mitochondrial function, holds promise toward furthering greater therapeutic opportunities. Personalised medicine taking into account genetic, metabolic and lifestyle parameters might also improve treatment outcomes. Furthermore, extensive clinical trials are necessary to assess the efficacy and safety of emerging treatments like GLP-1 receptor agonists and SGLT2 inhibitors in preventing or reversing cardiac hypertrophy in diabetic patients. The integration of digital health solutions and multi-disciplinary care approaches will also be crucial in improving patient medication adherence, monitoring and cardiovascular health in general.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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