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Research Article

Tackling Two Titans: Diabetes Treatment Strategies and their Influence on Cardiomyopathies

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Abstract

In individuals with diabetes, the occurrence of heart failure varies from 9% to 22%, marking a fourfold rise compared to the general population. This heightened prevalence is particularly pronounced in diabetic patients aged 60 years or older. Recent studies highlight a rapid increase in mortalities related to cardiomyopathies, attributed to the alarming surge in cases of type 2 diabetes mellitus. Global epidemics like diabetes and heart failure (HF) often referred to as the "deadly duo," pose a significant burden on society due to heightened hospitalization costs and a grim prognosis. Therefore, it is necessary to implement new strategies for improving the diagnosis and treatment of diabetes and heart failure. Early diagnosis of diabetes and heart failure may have results in keeping patients healthy and it helps in reducing the risk factors of such serious complications. Currently, the application of artificial intelligence (AI) and Machine Learning (ML) in the field of diabetes has increased which may help improve the classification system and may have the possibility to solve this problem at an early stage. In this article, our aim is to examine the multifaceted relationship between diabetes and heart failure using (AI/ML). The application of AI and ML in diabetes and heart failure research has been widely explored in basic biomedical research. Therefore, in this review, we highlighted the impactful use of AI/ML in underlying mechanisms of diabetic cardiomyopathy by using various therapeutic drugs to explore the risk factors and consider their implications on patient response. By unraveling this intricate relationship, we can strive to enhance our knowledge to pave the way for improved preventive measures, early detection, and more effective management of these intertwined titans.

Keywords: Diabetes Mellitus, Cardiomyopathy, Treatment options, drugs, Genes, Inhibitors, glycaemic control, myocardial infarction, Machine Learning, Artificial Intelligence.

Introduction

Diabetes mellitus (DM) and heart failure (HF) are two prevalent health conditions that continue to pose significant challenges to global public health. In 2021, the International Diabetes Federation estimates that there were approximately 537 million people aged 20-79 with diabetes worldwide and it is expected that this number will reach 784 million by 2045 [1]. While they are distinct conditions, research has increasingly uncovered a compelling link between diabetes and heart failure emphasizing the intricate relationship between these two diseases [2]. The obvious significance of this effect unveils the connection between diabetes mellitus leading to myocardial infarction or heart failure and was reported to be bad for patients with diabetes, as compared to non-diabetics. Understanding the complex interplay between diabetes and heart failure is of paramount importance, as it can have far-reaching implications for clinical management, patient outcomes, and public health strategies [3].

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Rivellese et al. underscored the elevated risk of heart failure in the diabetic population, reporting a range of 1 to 3 times higher in males and 2 to 5 times higher in females compared to non-diabetics. This highlights the imperative for targeted diabetes management strategies to mitigate the economic impact of the disease [4]. Muscle weakness of the heart due to challenges posed by therapeutic drugs for DM changes the structural and functional features of the heart ultimately leading to heart collapse a typical feature of Diabetic cardiomyopathy. The underlying events of these processes are poorly understood but can be attributed to energy metabolism, lipid peroxidation, calcium signaling, reduced glucose uptake, and other factors [5]. The economic burden of DM may be mostly ascribed to both macrovascular and microvascular complications such as myocardial infarction, hypertension, peripheral vascular disease, end-stage renal disease, nephropathy, retinopathy, neuropathy, and heart failure [6]. Several mechanisms have been involved in the pathogenesis of diabetic cardiomyopathy (DCM), such as alterations in myocardial energy metabolism and calcium signaling. Metabolic disturbances during diabetic cardiomyopathy are characterized by increased lipid oxidation, intramyocardial triglyceride accumulation, and reduced glucose utilization. These changes result in enhanced oxidative stress, mitochondrial dysfunction, and apoptosis of the cardiomyocytes figure-1 [6, 7]. While diabetes and hypertension commonly co-occur due to shared metabolic pathways, there is evidence suggesting that prolonged use of glycaemic control therapies may induce myocardial infarction. However, experimental studies are scarce on this topic, and the available data are primarily derived from meta-analyses.

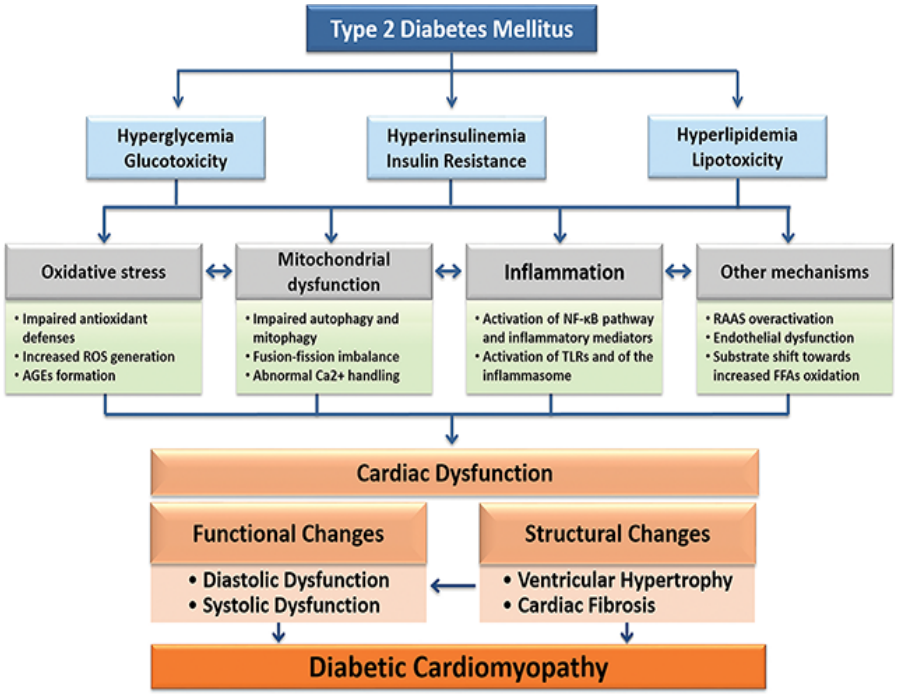

Figure 1. *Source: google images - Showing pathogenesis of Diabetic Cardiomyopathy.*

In diabetes mellitus, the metabolic abnormalities are considered the main induction for the cellular and molecular pathways associated with structural and functional changes due to oxidative stress, mitochondrial dysfunction, and myocardial inflammation results in DCM, Adopted from [9].

Given the familiarity of this concept, we aim to emphasize the role of AI in elucidating how drugs used in Type 2 Diabetes Mellitus (T2DM) can lead to Myocardial Infarction or Cardiomyopathies, and explore the correlation between specific medications and the progression of heart failure in individuals with T2DM, with a primary focus on leveraging AI for comprehensive understanding. While harnessing the unique advantages and confronting inherent limitations, Machine Learning (ML) and Artificial Intelligence (AI) methodologies conver the development of robust automatic Diabetes Mellitus detection systems.

AI and Mechanisms Underlying the Connection

Currently, digital health technologies (DHTs) are transforming medical and health practices especially due the application of artificial intelligence and Machine Learning [8]. These technologies incorporate the use of computational algorithms that stimulate and perform tasks that traditionally require human intelligence such as problem-solving and learning. AI promises to unfold several interconnected mechanisms that contribute to the link between T2DM and cardiomyopathies including metabolic disturbances [9]. In recent times, there has been a growing focus on the application of artificial intelligence, specifically in the realms of Machine Learning and deep learning (DL), within the field of medical research figure-2. This heightened interest is primarily attributed to the remarkable capacity of AI to scrutinize extensive biomedical datasets, encompassing electronic health records (EHRs), medical imaging, multi-omics data, behavioral/wellness information, and environmental data.

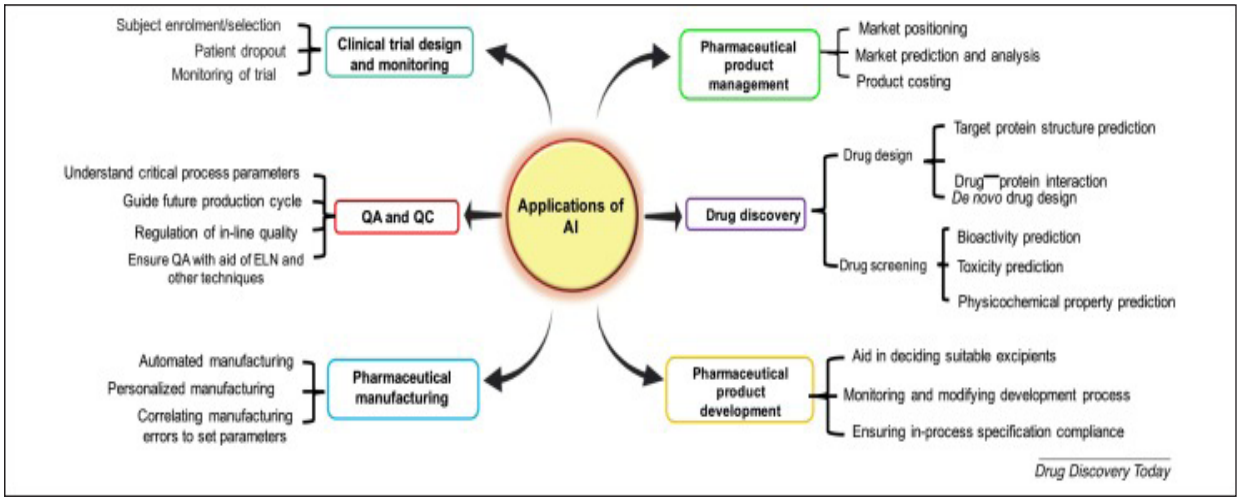

Figure 2. *Source: google images - Application of artificial intelligence and Machine Learning (AI/ML).*

Schematic representation of different applications of AI/ML design to assist and analyze patients' medical information and implement in drug discovery and development, adopted from[10]

AI/ML-driven models have emerged as promising tools for the development of predictive models for T2DM. These models leverage the analytical power of AI to sift through intricate and multidimensional datasets, identifying individuals at high risk of T2DM, unveiling associated risk factors and biomarkers tied to T2DM development, and providing insights for personalized interventions aimed at disease prevention [10, 11, 12]. Insulin resistance and hyperglycemia, hallmarks of T2DM, have direct and indirect effects on the heart muscle. They lead to oxidative stress, inflammation, and abnormal energy utilization within cardiomyocytes, thereby impairing their structure and function. T2DM is also associated with microvascular abnormalities that impact the blood supply to various tissues, including the heart. This compromised blood flow can contribute to myocardial fibrosis, impaired contractility, and overall cardiac dysfunction. Further, elevated blood sugar levels in T2DM lead to the formation of Advanced Glycation End Products (AGEs), which accumulate in various tissues, including the heart. AGEs promote inflammation and fibrosis within the myocardium, contributing to the development of cardiomyopathies[13].

Exploratory ideas for leveraging AI in this phenomenon rest on mitochondrial dysfunction. Mitochondria are crucial for providing energy to cardiomyocytes. T2DM can disrupt mitochondrial function, leading to energy depletion and oxidative stress, which are implicated in the pathogenesis of cardiomyopathies. It is anticipated that AI and ML have offered an overview and given useful guidance in diagnosing and understanding DM (13, 14)

Commonly used Drugs and their Implications

Management of cardiovascular disease (CVD) in patients with long-standing diabetes often involves the use of multiple classes of medications. A comprehensive, multidisciplinary approach is the key in managing these patients [15]. The following two tables' present information on the commonly used drugs [7, 16] by diabetic patients, and upon their admission to Intensive care units, the drugs for CVD were considered [17].

Table 1. *showing the list of drugs commonly used by the diabetic patients*

Medication Class	Examples/ references	Mechanism of Action	Common Use
Metformin	Metformin [18, 19]	Improves insulin sensitivity and reduces glucose production by the liver.	Type 2 diabetes
Sulfonylureas	Gliclazide, Glimepiride, Glipizide [20]	Stimulate the pancreas to release more insulin. Often used in combination with other medications.	Type 2 diabetes
Meglitinides	Repaglinide, Nateglinide [21]	Stimulate insulin secretion from the pancreas, with shorter-lived action compared to sulfonylureas.	Type 2 diabetes
Thiazolidinediones (TZDs)	Rosiglitazone, Pioglitazone [22]	Improve insulin sensitivity in peripheral tissues. Less commonly used due to concerns about side effects.	Type 2 diabetes
DPP-4 Inhibitors (Gliptins)	Sitagliptin, Saxagliptin [23]	Enhance the action of incretin hormones, increasing insulin release and reducing glucagon secretion.	Type 2 diabetes
GLP-1 Receptor Agonists	Liraglutide, Exenatide, Dulaglutide /[24,25]	Mimic the action of GLP-1, an incretin hormone, to increase insulin secretion, suppress glucagon release, and slow gastric emptying.	Type 2 diabetes
SGLT2 Inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin [26]	Reduce glucose reabsorption in the kidneys, leading to increased glucose excretion in urine.	Type 2 diabetes
Insulin	Various types with different durations (Rapid acting, Short-acting, Intermediate-acting, Long-acting [27,28]	Essential for type 1 and advanced type 2 diabetes. Regulates blood glucose levels.	Type 1 and advanced type 2 diabetes
Combination Medications	Various combinations [29,30,31]	Combine different classes of drugs to provide multiple mechanisms of action in one tablet. For example, metformin can be combined with a sulfonylurea or a DPP-4 inhibitor.	Type 2 diabetes
Insulin Analogues	Insulin lispro, Insulin aspart, Insulin glargine[32]	Modified versions of human insulin designed to have more predictable effects.	Type 1 and type 2 diabetes

The mechanisms of action can vary for different medications within each class and their crosstalk may be additional factors involved in their effects on the cardiovascular system [33]. Hence there is a need to clarify the variables with respect to the population and the specific heart effects. For instance, Individuals diagnosed with Type 2 diabetes may have an increased susceptibility to cardiovascular myopathies [34]. Moreover, relevant statistics or research findings support this hypothesis.

Management of cardiovascular disease (CVD) and myocardial infarction (MI) in patients with T2DM involves a combination of lifestyle modifications, glycemic control, and the use of medications. The choice of drugs depends on individual patient characteristics and risk factors. Commonly used drugs for CVD and MI in patients with T2DM are presented in the table-2 below:

Table 2. *Showing the drugs for diabetic patients who visited the hospital – ICU dept. with chest pain and probable CVD*

Medication Class	Examples	Indication/Use	
Statins	Atorvastatin, Rosuvastatin	Lipid-lowering, prevention of atherosclerosis, reducing cardiovascular events	type 2 diabetes
Antiplatelet Agents	Aspirin, Clopidogrel, Ticagrelor	Prevention of blood clot formation, reducing the risk of cardiovascular events	type 2 diabetes
ACE Inhibitors	Enalapril, Lisinopril	Management of hypertension, cardiovascular protection, renal protection	type 2 diabetes
ARBs (Angiotensin II Receptor Blockers)	Losartan, Valsartan	Management of hypertension, cardiovascular protection, renal protection	type 2 diabetes
Beta-Blockers	Metoprolol, Carvedilol, Bisoprolol	Management of hypertension, reducing heart workload, improving outcomes after a heart attack	Heart attack
SGLT-2 Inhibitors	Empagliflozin, Canagliflozin, Dapagliflozin	Cardiovascular benefits, heart failure prevention, glycemic control	type 2 diabetes
GLP-1 Receptor Agonists	Liraglutide, Dulaglutide, Semaglutide	Cardiovascular benefits, reducing cardiovascular events, glycemic control	type 2 diabetes
Aldosterone Antagonists	Spironolactone, Eplerenone	Considered in heart failure with reduced ejection fraction	type 2 diabetes

The above list is not exhaustive, but these drugs are commonly used to manage diabetes and its associated cardiovascular risks. Regarding Insulin long-term use of insulin itself is generally considered safe when used as prescribed for managing diabetes, but diabetes itself is a risk factor for cardiovascular disease. Poorly controlled blood sugar levels over the long term can contribute to cardiovascular complications. Further, individual patient factors, such as age, comorbidities, and contraindications, play a crucial role in determining the most appropriate treatment plan. The selection of medications can be personalized based on the specific needs and characteristics of each patient, and it is essential for to regularly monitor and adjust the treatment plan [35].

Implications of a Few of the Widely Used Drugs

Thiazolidinediones (TZDs), Pioglitazone and Rosiglitazone

The ramifications of combining certain drugs can be perplexing, as individual responses may vary significantly. Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone have been identified for their ability to enhance insulin sensitivity and regulate blood sugar levels. However, their usage is not without concerns, particularly cardiovascular effects, including fluid retention and an elevated risk of heart failure. This has led to the restriction of rosiglitazone in some countries, while pioglitazone remains a viable option with careful consideration and selective patient application [36]. These medications function by targeting peroxisome proliferator-activated receptors (PPARs), specifically PPAR-gamma, situated in adipose tissue, skeletal muscle, and the liver. The activation of PPAR-gamma improves insulin sensitivity, resulting in heightened glucose uptake and utilization in peripheral tissues, along with reduced glucose production in the liver. Despite their beneficial effects, TZDs also possess the potential to induce fluid retention and edema, factors that may contribute to the development of heart failure.

Sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibitors: Empagliflozin and Dapagliflozin

SGLT2 inhibitors, such as empagliflozin and dapagliflozin, belong to a class of medications designed to lower blood glucose levels by impeding the reabsorption of glucose in the kidneys. Recent clinical trials have unveiled their notable cardiovascular benefits. It was previously

hypothesized that these inhibitors might be linked to an elevated risk of heart failure upon initiation. The mechanism underlying the action of SGLT2 co-transporters lies in their ability to reabsorb glucose from the renal tubules into the bloodstream. Blocking these transporters with SGLT2 inhibitors results in increased urinary glucose excretion which consequences in leading to reduced blood glucose levels [37].

While the cardiovascular advantages of SGLT2 inhibitors encompass diminished cardiovascular mortality and fewer heart failure hospitalizations, it is noteworthy that their initiation may induce transient fluid shifts, potentially heightening the risk of heart failure. Nevertheless, the long-term cardiovascular benefits generally outweigh the initial risks, particularly in patients grappling with both type 2 diabetes and cardiovascular disease.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: Sitagliptin, Saxagliptin, and Linagliptin

The Dipeptidyl peptidase-4 (DPP-4) inhibitors including sitagliptin, saxagliptin, and linagliptin function by elevating incretin hormone levels to regulate blood sugar. Notably, these medications have demonstrated a neutral cardiovascular profile, indicating that they do not substantially elevate or reduce the likelihood of cardiovascular events [38].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as commonly used over-the-counter medications like ibuprofen and naproxen, have been associated with an elevated risk of heart failure in susceptible individuals. NSAIDs belong to a class of medications widely employed to alleviate pain, diminish inflammation, and reduce fever. Their mechanism of action involves the inhibition of prostaglandin production, which serves as a chemical messenger in the inflammatory response. While this inhibition is beneficial in managing pain and inflammation, it also disrupts the production of prostaglandins crucial for maintaining normal kidney function and regulating blood flow in the cardiovascular system. Consequently, NSAIDs can induce fluid retention, elevate blood pressure, and potentially strain the heart, thereby increasing the likelihood of heart failure in susceptible individuals [38, 39]. Caution is advised when using these medications, particularly in higher doses or for prolonged durations.

The mechanisms of action can exhibit variations among different medications within each class, and there might be additional factors influencing their impact on the cardiovascular system [39]. Therefore, it is imperative to elucidate the variables concerning both the population and the specific cardiac effects. For instance, those individuals diagnosed with Type 2 diabetes may demonstrate an elevated vulnerability to cardiovascular myopathies The drugs that are of the highest risk for heart failure and must be avoided in heart failure include; Ibuprofen, naproxen, and selective COX-2 inhibitors such as diclofenac, celecoxib, and meloxicam [40]. Furthermore, pertinent statistics or research findings substantiate this hypothesis.

Bidirectional Interplay between the "Deadly Deo"

The intricate link between cardiomyopathies and T2DM underscores the importance of understanding their complex interplay for better management and prevention strategies.

Type 2 diabetes is a chronic metabolic disorder characterized by insulin resistance and elevated blood sugar levels. It affects millions of individuals worldwide and is associated with a wide range of complications, including cardiovascular diseases. Cardiomyopathies, on the other hand, refer to structural and functional abnormalities of the heart muscle that often lead to heart failure, arrhythmias, and sudden cardiac death.

Research has shown a bidirectional relationship between T2DM and cardiomyopathies [41]. Individuals with T2DM are at an increased risk of developing various forms of cardiomyopathies, including dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy. Conversely, patients with certain types of cardiomyopathies may also be at an elevated risk of developing T2DM, highlighting the complex interplay between these conditions.Despite our extensive knowledge, the pathophysiology of Diabetic-cardiac myopathies development and progression remains shrouded in mystery, casting a daunting shadow over the quest for effective therapies to combat this diabetic complication [42, 43].

The intricate link between cardiomyopathies and Type 2 diabetes underscores the need for comprehensive approaches to prevention, diagnosis, and management.

As the prevalence of both conditions continues to rise globally, understanding the complex mechanisms driving their association is crucial for developing effective therapeutic strategies and improving the quality of life for individuals affected by these conditions [44]. Ongoing research efforts hold promise for unravelling the intricacies of this connection and devising innovative treatments that address both T2DM and cardiomyopathies simultaneously. Previous researchers have beautifully shown the vicious circle of how the "deadly deo" could manage to destroy the normal functioning of the heart to cause sudden heart failure as shown in figure-3.

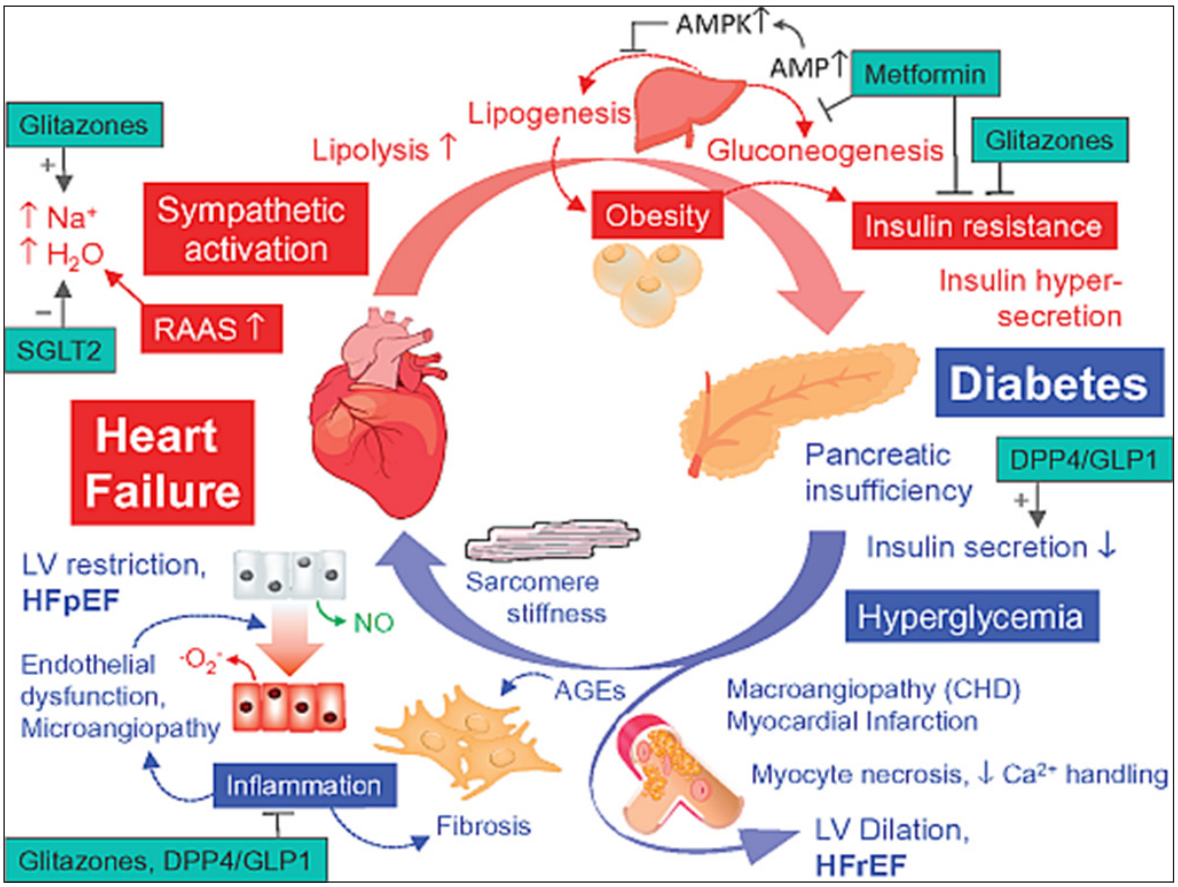

Figure 3. *Schematic representation of Diabetic, Heart Failure and Renal Dysfunction. Adopted from [45]*

Conclusion based on AI on Cardiomyopathy Links in Type 2 Diabetes

In conclusion, the exploration of AI's applications in understanding the intricate links between cardiomyopathy and Type 2 Diabetes holds great promise for advancing our understanding and management of these complex diseases [46]. The multifaceted nature of both conditions demands a comprehensive approach that combines medical expertise with cutting-edge technological tools. AI-driven analyses have demonstrated the ability to uncover subtle patterns, predict outcomes, and guide personalized treatment strategies, enhancing the precision and efficacy of interventions.

Through the integration of various data sources, including genomic, proteomic, and clinical data, AI algorithms have the potential to identify novel biomarkers, elucidate underlying mechanisms, and ultimately contribute to early detection and intervention. Machine Learning techniques, such as deep learning and predictive modelling, empower healthcare professionals to identify high-risk patients, tailor treatment regimens, and optimize patient outcomes.

Nonetheless, it's crucial to acknowledge the challenges associated with AI implementation in this context [47]. Ethical considerations, data privacy, and the need for rigorous validation of AI-driven insights remain significant hurdles. Collaboration between medical experts, data

scientists, and regulatory bodies is essential to ensure the responsible and effective use of AI technologies [48].

As the field of AI continues to evolve, ongoing research and clinical trials will be instrumental in harnessing its full potential for addressing the intricate links between cardiomyopathy and Type 2 Diabetes. By fostering a synergy between human expertise and machine intelligence, we can pave the way for more precise diagnoses, targeted therapies, and improved patient outcomes. As we navigate this transformative journey, a multidisciplinary approach that places patients at the centre will be a key to realizing the full benefits of AI in advancing our understanding of these interconnected health challenges.

Declarations

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Conflict of Interest

None Declared

Financial Disclosure

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Ethical Issues

None

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