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An Analysis of the Connection between Type 2 Diabetes and Heart Failure

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Abstract. Type 2 diabetes (T2D) and heart failure (HF) are two of the most prevalent chronic conditions worldwide, both of which contribute significantly to global morbidity and mortality rates. Individuals with T2D are at a 2-5 times higher risk of developing HF. At the same time, a substantial proportion of patients with HF also suffer from diabetes, introducing complex clinical challenges that complicate the management of both conditions. This article explores the links between T2D and HF, with a particular focus on shared pathophysiological mechanisms, risk factors, and clinical implications. Through a systematic literature review of peer-reviewed studies, this research identifies and critically evaluates the common pathways that contribute to the development and progression of both conditions, such as insulin resistance, chronic inflammation, and obesity-induced lipotoxicity. Additionally, the study discusses the impact of these mechanisms on the heart. It explores the potential for integrated therapeutic strategies aimed at simultaneously managing the metabolic and cardiovascular risks associated with T2D and HF. The findings underscore the importance of a holistic approach to patient care, emphasizing the need for early intervention and targeted treatments that address the dual burden of these interrelated conditions.

Keywords: Type 2 diabetes, Heart failure, Obesity, Diabetic cardiomyopathy, Atherosclerosis, Hyperglycemia.

1. Introduction

T2D and HF are two of the most prevalent and interrelated chronic conditions globally, posing significant challenges for healthcare systems and contributing to high morbidity and mortality rates. Individuals with diabetes are 2-5 times as likely to develop heart failure compared to those without the condition. Although diabetes affects approximately 10% to 15% of the general population, recent research indicates that 44% of patients who received medical treatments for heart failure have diabetes. The presence of these comorbidities introduces distinctive clinical challenges that complicate patient management [1]. The pathophysiological connection between these conditions is complex and multifaceted, involving shared mechanisms. Understanding these connections is crucial for improving patient outcomes, as the coexistence of T2D and HF not only worsens prognosis but also complicates the management of both conditions [2]. Most current studies have focused on the mechanisms and treatment options for diabetes, heart failure, and diabetic cardiomyopathy, respectively, but very few studies have summarised the co-morbidities of diabetes and heart failure. For example, Kenny and Abel analyse the two perspectives of therapies to treat diabetes against heart failure and therapies to treat heart failure

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for diabetes; the pathomechanisms it discusses still see diabetes as the cause of heart failure, and the paper argues that the effects caused by both are reciprocal [1]. This essay will explore the intricate links between T2D and HF, focussing on the shared pathophysiological mechanisms, risk factors, and clinical implications, to enhance therapeutic strategies and promote more effective management of these interrelated conditions.

2. Method

This study investigates the shared risk factors and pathophysiological mechanisms between type 2 diabetes and heart failure. It was conducted as a systematic literature review whereby selected studies were critically reviewed to address the research problem. Search for scientific databases such as PubMed, Web of Science, and Google Scholar to identify peer-reviewed primary journal articles on health-related problems, including type 2 diabetes, heart failure, atherosclerosis, and cardiomyopathy. The significance of this research lies in its potential to inform and enhance clinical practice. By elucidating the common pathways that link T2DM and HF, healthcare professionals can better identify patients at risk, implement early interventions, and tailor treatment strategies that address both conditions simultaneously. Only studies published in the English language were considered for review to minimize errors associated with translation. The key population of focus was obese individuals who have or have the risk of diabetes and heart failure. Studies based on other populations and conditions are excluded. The main body of this essay organizes the extracted data from peer-reviewed articles into thematic categories based on shared risk factors, pathophysiological mechanisms, and treatment modalities, and provides a descriptive summary of the findings. Evaluate the effectiveness and safety of different treatment modalities, considering their impact on both type 2 diabetes and heart failure.

3. Mechanism of type2 diabetes and heart failure

T2DM is marked by both a decrease in insulin sensitivity and a relative shortage of insulin. This condition arises when body cells become increasingly resistant to the hormone insulin, which plays a key role in allowing glucose to enter cells from the bloodstream. As a compensatory response, the pancreas increases insulin production to keep blood sugar levels stable, leading to hyperinsulinemia. However, as insulin resistance progressively worsens, pancreatic β-cells are unable to meet the heightened demand for insulin, causing blood glucose to rise, a state known as hyperglycemia [3].

Heart failure (HF), on the other hand, is characterized by the heart's inability to pump sufficient blood to fulfil the body's needs, often leading to symptoms like breathlessness, fatigue, and fluid buildup. This condition is frequently the result of underlying issues such as ischemic heart disease, high blood pressure, or diabetes, which can harm the heart muscle.

The epidemiological link between T2D and HF is well-established, with diabetes significantly increasing the risk of HF development because they share similar risk factors and pathophysiological mechanisms.

The interaction between T2D and HF necessitates approaches to management as the presence of comorbidities presents unique clinical challenges, such as the need for careful balancing of glucose control with cardiovascular therapies. Thus, understanding the interactions between T2D and HF underscores the importance of integrated care strategies aimed at addressing both metabolic and cardiovascular risks simultaneously.

4. Shared risk factors and corresponding pathophysiological mechanisms

4.1. Insulin Resistance and Hyperglycemia

Several mechanisms contribute to insulin resistance, including increased levels of free fatty acids (FFAs), inflammation, and mitochondrial dysfunction. High levels of circulating FFAs, often start due to a combination of genetic predisposition and lifestyle factors such as obesity, sedentary behavior, and poor diet. These factors contribute to excessive nutrient intake, particularly high levels of refined carbohydrates and fats, interfere with insulin signalling pathways in muscle and liver tissues. With

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disrupted insulin signalling, tissues become less responsive to insulin. In the liver, this leads to unchecked gluconeogenesis, while in muscle and adipose tissue, glucose uptake is impaired. This leads to a reduction in glucose uptake by muscles and increased glucose production by the liver, resulting in hyperglycemia, hyperinsulinemia (as the pancreas compensates by producing more insulin), and dyslipidaemia (high levels of circulating triglycerides and FFAs). The condition directly impacts myocardial energy metabolism.

Chronic hyperglycemia in T2DM leads to various complications through multiple pathways, such as the formation of advanced glycation end products (AGEs). The Maillard reaction, a non-enzymatic glycation process, creates AGEs when reducing sugars come into contact with free amino groups found in proteins, lipids, or nucleic acids. Schiff bases and Amadori products are formed as a result of this reaction, and these eventually go through more intricate rearrangements to generate AGEs [4].

AGEs can bind to specific receptors, such as the receptor for AGEs (RAGE), triggering oxidative stress and inflammation. In individuals with diabetes, chronic hyperglycemia increases the availability of glucose to interact with proteins and lipids, leading to excessive formation of AGEs. This excessive formation is detrimental because AGEs accumulate in tissues, altering normal protein function, and contribute to various complications associated with diabetes, such as cardiovascular diseases, neuropathy, and retinopathy.

Insulin resistance is also associated with increased levels of reactive oxygen species (ROS). ROS are primarily generated in the mitochondria during oxidative phosphorylation. In diabetes, high glucose levels cause an overproduction of ROS by increasing the flux of electrons through the mitochondrial electron transport chain. Normally, around 0.2% to 2% of electrons leak from the respiratory chain, reacting with oxygen to form superoxide anion (O_2^-) [5].

Hyperglycemia makes the mitochondria's production of ROS worse. Increased input into metabolic pathways such as the polyol pathway and AGE formation — both of which contribute to further production of ROS — is a result of elevated glucose levels. Mitochondrial overproduction of superoxide radicals inhibits the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), leading to the activation of the polyol pathway, increased AGE formation, and hexosamine pathway flux. Each of these pathways further contributes to oxidative stress, perpetuating a cycle of increased ROS production and cellular damage.

The heart is particularly susceptible to oxidative damage because of its high metabolic activity and density of mitochondria. Persistent oxidative stress leads to pathological changes, including cardiomyocyte hypertrophy, fibrosis, inflammation, and apoptosis. These changes contribute to impaired cardiac function, such as reduced diastolic and systolic function, and can progress to heart failure. The overproduction of ROS activates stress-sensitive pathways, including the activation of protein kinase C, NF-κB, and JNKs, which further contribute to inflammation, cause damage to blood vessels and tissues such as the endothelium [3,5].

The endothelium, the thin layer of cells lining blood vessels, plays a crucial role in vascular health by regulating vasodilation, inflammation, and clotting. Insulin normally promotes endothelial nitric oxide (NO) production, leading to vasodilation and anti-inflammatory effects. However, impaired insulin signalling decreases the availability of NO, leading to endothelial dysfunction, and the oxidative stress caused by hyperglycemia and lipid abnormalities further damages the endothelial cells by increasing the production of superoxide radicals. This not only reduces NO bioavailability but also promotes endothelial cell death, and reduces the vasodilatory capacity of blood vessels [6].

The damaged endothelium expresses more adhesion molecules (e.g., VCAM-1, ICAM-1) that attract circulating immune cells like monocytes. These cells penetrate the endothelial layer and differentiate into macrophages, which ingest lipids and become foam cells. Foam cells accumulate and form fatty streaks, the early stage of atherosclerosis. As the inflammation persists, smooth muscle cells migrate to the intima (the innermost layer of the artery), proliferate, and secrete extracellular matrix, contributing to the development of a fibrous cap over the lipid core. Then the persistent inflammation can weaken the fibrous cap, making it prone to rupture. Plaque rupture exposes the thrombogenic core, leading to the formation of a blood clot, which can obstruct blood flow [6]. Over time, atherosclerosis can lead to

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significant narrowing of the coronary arteries, the vessels that supply blood to the heart muscle. This can result in chronic ischemic conditions, such as angina, or acute events, such as myocardial infarction (heart attack), where a coronary artery becomes completely blocked.

4.2. Hypertension

The generation of ROS by the mitochondria is exacerbated by hyperglycemia. Elevated glucose levels lead to increased input into metabolic pathways like the polyol pathway and AGE formation, both of which contribute to greater ROS production. The development of a chain of metabolic disturbances set off by insulin resistance leads to hyperglycemia, hyperinsulinemia, and dyslipidemia, and causes damage to the endothelium, leading to the formation of atherosclerotic plaques. Over time, this vascular damage can cause coronary artery disease, increasing the risk of heart failure through mechanisms such as myocardial infarction, ischemic cardiomyopathy, and increased cardiac workload due to hypertension.

4.3. Chronic Inflammation

Chronic low-grade inflammation, commonly linked to metabolic syndrome and obesity, serves as a mutual underlying mechanism in both T2D and HF. In both conditions, inflammatory markers such as C-reactive protein (CRP) are elevated, which worsens cardiovascular dysfunction and promotes insulin resistance. Elevated glucose levels activate inflammatory pathways, leading to persistent inflammation and the release of cytokines like TNF-α and IL-6, which further impair insulin sensitivity and endothelial function. This cascade accelerates the development of atherosclerosis and heart failure.

Inflammation plays a critical role, as cytokines such as TNF-α and IL-6 disrupt insulin signalling, fostering resistance to insulin. Mitochondrial dysfunction within insulin-responsive tissues reduces glucose utilization while increasing fatty acid oxidation, further contributing to insulin resistance [3]. Additionally, Wang and Zhao found that in diabetic individuals, secondary hypertension is strongly linked to changes in pro-inflammatory (IL-6, TNF-α) and anti-inflammatory (IL-10) cytokines [7]. Higher levels of these cytokines in the serum indicate a heightened risk for hypertension. Shared risk factors between diabetes and heart failure also facilitate the progression of one another.

4.4. Obesity—free fatty acid(FFA)

Obesity is a significant risk factor for both type 2 diabetes and heart failure, playing a pivotal role in the onset and progression of these conditions through intricate metabolic and molecular processes. Central mechanisms linking the two include lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, inflammation, and mitochondrial dysfunction. Excess fatty acids (FA) from adipose tissue and circulating lipoproteins are absorbed by non-adipose tissues, causing lipid accumulation and subsequent lipotoxicity in cardiomyocytes. This process involves the buildup of long-chain nonesterified fatty acids (NEFA), such as acylcarnitines, ceramides, and diacylglycerol, in organs like the liver and skeletal muscles, which can result in myocardial lipotoxicity, contributing to cell death and cardiac dysfunction [8]. Lipid accumulation disrupts normal cellular function, impairing insulin signaling and promoting insulin resistance. In insulin-resistant states, glucose metabolism and triacylglycerol synthesis are hindered, preventing the re-esterification of free fatty acids (FFA), which leads to elevated FFA levels [9].

Lipid overload and insulin resistance reinforce each other. Additionally, NEFA accumulation in insulin-sensitive tissues further impairs insulin signaling by activating protein kinase C (PKC) isoforms, which disrupt the insulin receptor's function. This activation leads to the phosphorylation of serine residues in insulin receptor substrates (IRS), hindering the proper transmission of insulin signals and inhibiting glucose uptake [10]. This phenomenon is central to obesity-induced insulin resistance, which contributes to hyperglycemia and, ultimately, the development of type 2 diabetes.

In acquired cardiomyopathies, as described by Weinberg, glucose substitutes fatty acids as the primary fuel for oxidative metabolism, leading to the accumulation of non-esterified fatty acids (NEFA) and triglycerides. Functional mutations in enzymes responsible for fatty acid metabolism cause NEFA

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to build up in myocytes, resulting in elevated levels of myocyte triglycerides, ceramides, and nitric oxide synthase. This, in turn, contributes to myocardial contractile dysfunction, as observed in the rats used in the study. These rats exhibited notable abdominal obesity, elevated triglyceride and NEFA levels in the bloodstream, and multi-organ lipotoxicity, including insulin resistance in the liver and heart muscle cells [8].

4.5. Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a disorder of the heart muscle in people with diabetes, if there is no other coronary artery disease to explain the heart muscle disorder. Non-diabetic heart failure is still controversial since it depends on animal pathology, fatty acids can be converted into ketone bodies along with an overall loss of mitochondrial respiratory capacity. However, it is much less controversial in diabetic cardiomyopathy, from glucose to fatty acids, which also represents a loss of metabolic flexibility. It will cause changes in the heart structurally and metabolically.

For the structural changes, obesity and hyperinsulinemia lead to left ventricular hypertrophy through the production of adipokines like leptin and resistin. These inflammatory cytokines have been implicated in obesity-associated heart failure, as mentioned above [1]. Increased collagen deposition in the myocardium and around blood vessels, is linked to diastolic dysfunction which is characterized by impaired relaxation and increased stiffness of the LV. Systolic dysfunction develops after diastolic dysfunction, it impairs the contractility due to altered myocardial structure and metabolism, as well as increased oxidative stress and lipid accumulation [1]. As the glucose uptake is impaired, The diabetic heart predominantly relies on free fatty acids (FFA) for energy. FA oxidation is less efficient than glucose oxidation, increasing myocardial oxygen consumption and weakening the heart.

5. Conclusion

In conclusion, diabetes and heart failure can be considered co-morbidities. They often occur together, and the presence of diabetes can exacerbate heart failure. The shared risk factors, such as insulin resistance, chronic inflammation, and obesity, along with the common pathophysiological mechanisms, including endothelial dysfunction, oxidative stress, and lipotoxicity, create a complex landscape that complicates the management of both conditions. Understanding these connections is vital for developing effective therapeutic strategies that address the metabolic and cardiovascular risks simultaneously, improving patient outcomes. While this study examines the relationship between diabetes and heart failure, its explanation of some of these mechanisms is unclear, and more recent relevant literature needs to be consulted to bring clarity to the specific mechanisms involved. In the future, these specific mechanisms could be used to develop targeted therapeutic options.

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