The effect of empagliflozin on vascular remodeling related to cardiovascular well-being and sustainable health outcome: A literature review

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Abstract. Cardiovascular disease (CVD) is the most common cause of mortality in patients with diabetes mellitus (DM). The reduction of CVD, which is a non-communicable disease (NCD), serves as a crucial indicator of Sustainable Development Goal (SDG) 3 on Good Health and Well-being. Empagliflozin is an anti-diabetic agent that plays an essential role in reducing the risk of adverse outcomes associated with CVD in addition to lowering the glycaemic effect. Therefore, this study aims to conduct a literature review using data obtained from PubMed and Google Scholar to investigate empagliflozin effects on the progression of vascular remodeling. Sodium-glucose co-transporter 2 inhibitor (SGLT2i) is a class of anti-diabetic agents that has shown positive effects on pathological cardiovascular remodeling. The pathogenesis of vascular disease in DM cannot be dissociated from the engagement of endothelial cells (ECs) and vascular smooth muscle cells (SMCs). An example of SGLT2i known as Empagliflozin is used to enhance the bioavailability of nitric oxide (NO) produced by the endothelium, thereby restoring endothelium-dependent vasodilation in DM patients. Furthermore, it inhibits the inflammatory response by maintaining the structural integrity of endothelial glycocalyx. In SMCs, empagliflozin upregulates the vascular beneficial improvement through reactive oxygen species (ROS). The administration of this drug has been observed to induce the formation of circulating pro-vascular cell subsets in individuals without DM.

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1 Introduction

According to the World Health Organization (WHO), cardiovascular disease (CVD) is the leading cause of mortality, accounting for over 17 million deaths annually. One of the key indicators in Sustainable Development Goal (SDG) 3, which is focused on good health and well-being, is a decrease in the number of non-communicable diseases, one of which is cardiovascular disease. By 2030, this part of the SDG aims to achieve a one-third reduction in premature mortality from NCD through the implementation of effective prevention and treatment strategies [1].

Cardiovascular disease (CVD) is the most common cause of mortality in patients with diabetes mellitus (DM), a chronic metabolic disorder that has rapidly increased all over the world. Patients with DM may be more prone to hospitalization due to complications arising from CVD [2]. The adverse effects of DM influence patient quality of life from a social and mental health perspective. These lead to the high cost of health services demand [3, 4], therefore, many therapeutic agents have been developed to lower the hyperglycemic state of DM. The newest class of anti-diabetic agents, known as sodium-glucose co-transporter 2 inhibitor (SGLT2i), appears to offer considerable promise. SGLT2i has the potential to play a beneficial role in regulating glucose metabolism. Decreasing the reabsorption of glucose in the proximal tubules of the kidney, has been shown to induce glycosuria and contribute to the reduction of fasting and postprandial blood sugar levels in patients diagnosed with DM. This function mechanism is blood glucose level dependent, thereby preventing the fatigue or overstimulation of beta cells and hypoglycemia state [5].

A recent clinical investigation reports that SGLT2i enhances cardiovascular outcomes among DM patients. The role of SGLT2i has shown a positive effect on pathological cardiovascular remodeling in patients with and without DM [8]. Empagliflozin, a selective inhibitor of sodium-glucose co-transporter, received approval for treating type 2 DM from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Additionally, the EMPA REG-OUTCOME trial showed that administering empagliflozin once daily in DM patients would reduce the risks of cardiovascular mortality, hospitalization for heart failure, and death [6]. The reduction of cardiovascular outcomes and mortality with empagliflozin was persistent in further studies investigating these effects across the range of cardiovascular risks [7].

Efforts to foster ground-breaking advancements in the healthcare landscape are important to ensure healthy lives and promote well-being for individuals of all ages. By the previous investigations, empagliflozin is considered a prospective pharmaceutical innovation, offering an optimal therapeutic method for vascular remodeling. Therefore, this study aims to conduct a literature review to identify the mechanisms of empagliflozin in reducing cardiovascular adverse effects that initiate vascular remodeling.

2 Method

This study aimed was to conduct a literature search of relevant publications on empagliflozin and vascular remodeling. The search process was conducted on a number of databases, including PubMed and Google Scholar. In order to identify relevant publications, a process was undertaken which involved the use of keywords such as SGLT2i, empagliflozin, and vascular remodeling. Furthermore, relevant publications about the effect of empagliflozin on vascular progression were screened and reviewed. The studies included in this review encompass a range of methodologies, including in vitro and animal studies, clinical trials, reviews, meta-analyses, and guidelines. Meanwhile, articles that were not originally written in English or did not adhere to the required abstract format were excluded.

3 Result and Discussion

SDG3 which is to "ensure access to affordable, reliable, and sustainable energy for all" can be achieved by prioritizing drug discovery and development [1]. For example, empagliflozin is a drug previously categorized under the class of glycemic-lowering agents for the treatment of type 2 DM. Accumulating evidence has shown that empagliflozin confers benefits beyond glycemic management, thereby prompting a shift in DM and comorbidities management, with a particular focus on the prevention of cardiovascular events [9].

Several investigations reported evidence regarding the role of empagliflozin in reducing the progression of vascular remodeling, which was previously thought to be a one-way process consisting of adaptive or maladaptive changes in blood vessels. Adaptive remodeling occurs when the vessels widen in response to increased blood flow, while maladaptive remodeling includes narrowing or thickening due to disease. A new study suggests that vascular remodeling is a multifaceted process featuring intricate interactions between various cellular and molecular mechanisms [10]. The pathogenesis of vascular disease in diabetes mellitus (DM) is directly linked to the involvement of two key cell types: endothelial cells (EC) and vascular smooth muscle cells (SMC) [11, 12].

A hyperglycemic state may cause cardiovascular remodeling effects in a complex and multidimensional way. Cardiovascular abnormalities due to the hyperglycemic state are defined as alterations in the cardiovascular system occurring at the molecular and cellular levels. These affect the structure and function of tissues along with organs, leading to remodeling. DM is a significant risk factor for the development of microvascular complications, including retinopathy, nephropathy, neuropathy, and macrovascular complications such as ischaemic heart disease, peripheral vascular disease, and cerebrovascular disease [13]. DM microangiopathy is characterized by microvascular changes, which affect extracellular matrix protein synthesis and capillary basement membrane thickening. These changes can result in macrovascular complications, along with advanced glycation end products, oxidative stress, mild inflammation, and neovascularisation [14].

3.1 Role of empagliflozin in ECs function

3.1.1 Empagliflozin preserves endothelium-dependent vasodilation

Numerous clinical studies have investigated the effect of empagliflozin on EC function. The administration of empagliflozin on a single daily occasion to patients with DM and coronary artery disease (CAD) demonstrated an enhancement of endothelial function, as evaluated through the assessment of blood flow-mediated dilatation (FMD). The improvement in FMD observed after 6 months was found to be triggered by a significant reduction in triglyceride plasma levels [15]. Additionally, the administration of empagliflozin increased the controller of vascular tone, known as shear stress, by changing blood viscosity. The elevation of shear stress is responsible for FMD improvement through a physiological mechanism including increased shear, enhanced stimulus, and greater arterial dilation [16].

3.1.2 Empagliflozin increases no bioavailability

ECs line the intima surfaces of blood vessels and provide an essential vascular modulator. These cells release nitric oxide (NO), produced by endothelial NO synthase (eNOS), to maintain vascular tone and permeability as well as regulate inflammation, vascular wall morphology and composition, and thrombosis. A previous study demonstrated that phlorizin,

a sodium-glucose co-transporter 2 inhibitor (SGLT2i), exerts protective effects on the endothelium through the activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/endothelial nitric oxide synthase (eNOS) signaling pathway, as well as by increasing nitric oxide (NO) production through the activation of p- eNOS. These findings suggest that phlorizin has potential for the treatment of heart failure. The study was conducted by inducing palmitic acid (PA) in human umbilical vein endothelial cells [11]. SGLT2i demonstrated pleiothopic effects on arterial and venous endothelial cells stimulated by tumor necrosis factor-alpha (TNFα). These effects include the restoration of NO bioavailability and the inhibition of reactive oxygen species (ROS) by empagliflozin and dapagliflozin [17]. In a different study, the same results demonstrated that empagliflozin exerts beneficial effects on cardiac endothelial cells by reducing mitochondrial oxidative damage and ROS, thus increasing NO bioavailability [18].

3.1.3 Empagliflozin preserves ECs Glycolax

Empagliflozin may diminish inflammatory processes by preserving the structural stability of the glycocalyx in ECs. Glycocalyx consists of proteoglycans, glucosamine, and glycolipids which serve as a protective barrier for ECs from inflammatory cells, restrict the permeability of the vascular system, and function as a sensor of mechanical forces [19]. In DM conditions, disruption of the glycocalyx in endothelial cells is a common occurrence. This can increase vascular membrane permeability [20]. In vitro studies conducted on human abdominal aortic endothelial cells (HAAEC) demonstrated that empagliflozin can restore the integrity of the glycocalyx by restoring the mechanical transduction of ECs with disrupted glycocalyx and promoting the HAAEC phenotype in a pro-inflammatory environment [21].

3.1.4 Empagliflozin effect on Stem and Progenitor cells

Newly developed endothelial stem and progenitor cells may contribute to the progression of pathological remodeling [22]. Several studies have been conducted in manipulating SGLT receptors on stem and progenitor cells. A previous study demonstrated that empagliflozin administration facilitates the restoration of various types of circulating pro-vascular cells in non-diabetic patients. Moreover, cardiovascular advantages of empagliflozin tend to partly arise from reducing the exhaustion of vascular regenerative cells, regardless of DM status. Empagliflozin has been demonstrated to promote regenerative cells by increasing the expression of pro-angiogenic cells, precursors of cell regeneration, and decreasing the expression of pro-inflammatory cells. These effects are monitored over a six-month follow-up period, and empagliflozin has been shown to reduce adverse cardiac effects in patients with cardiovascular disease [6].

3.2 Role of empagliflozin in vascular SMC function

Empagliflozin has been reported to improve the function of SMCs, which consist of many differentiated and mature cell layers in the blood vessels [12]. SMCs are responsible for maintaining the structural integrity of blood vessels and play a role in both physiological and pathological cell remodeling due to their ability to change phenotypes dynamically. The presence of environmental stimuli and signals to these cells can result in alterations to the plasticity of the cells, with a reduction in the synthesis of contractile proteins and an increase in the synthesis of the extracellular matrix, as well as an increase in the proliferation and migration rates of the cells [23]. The development of intimal lesions in DM enhances the proliferation and migration of SMCs [24].

The therapeutic ability of empagliflozin includes enhancing vascular remodeling across different pathological conditions. In addition to its efficacy in controlling glycemia, empagliflozin has been demonstrated to improve cardiovascular injury and remodeling, significantly reduce vascular dysfunction, and mitigate cognitive decline in both obese rats and rats with type 2 diabetes mellitus [25]. In a rat study of a pulmonary hypertension model induced by monocrotaline, empagliflozin has been demonstrated to reduce the vascular remodeling effect of the pulmonary artery, right ventricular hypertrophy, and fibrosis activity, thereby reducing the mortality rate. The administration of empagliflozin resulted in a reduction in muscularization of the pulmonary artery and the thickness of the medial wall artery in animals compared to the control group. These findings were accompanied by an increase in apoptosis and a decrease in proliferation activity within the pulmonary arterial wall [26]. Furthermore, empagliflozin demonstrated efficacy in mitigating pulmonary hypertension due to exercise in obese rats. The mechanism involved a remarkable increase in guanylate cyclase (SGC) enzyme activity in [SMCs] of the pulmonary artery [27].

After empagliflozin treatment in a previous study, a vasoactive peptide apelin identified using RNA (Ribonucleic Acid) sequencing played a role in upregulating SMCs and ECs of DM human coronary arteries. Apelin-dependent regulation of SMC function was found to be mediated through ROS [28]. Additionally, apelin has been shown to induce NO release and promote cell proliferation and vascular healing in ECs [29]. This compound is present in several organs, including the heart and vasculature, and can act as an endogenous ligand for the apelin receptor (APJ) associated with CVD pathogenesis [30].

4 Conclusion

In conclusion, as SGD3 targets to enhance health and prevent premature mortality from NCD, empagliflozin is poised to become the most recent breakthrough in drug development for cardiovascular disorders. This study showed that empagliflozin had beneficial effects on vascular remodeling progression through multiple mechanisms, including the engagement of ECs and SMCs. Despite the absence of clarification regarding the precise mechanism used by empagliflozin and other SGLT2i to reduce pathological vascular remodeling, various essential effects have been reported. Further research is required to provide new insights into the mechanisms of action of SGLT2i in vascular cells, including their specific functional, cellular metabolic, and molecular effects.

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