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THE EFFECTS OF PRECONDITIONING ON DIABETES INDUCED ENDOTHELIAL DYSFUNCTION: A SYSTEMATIC REVIEW

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ABSTRACT

The manipulation of diabetes mellitus on Endothelial Dysfunction is not clearly defined. Ischemic preconditioning (IP) is a powerful mechanism of protection discovered in the several organs such as Heart, Brain and kidney, in which ischemia inconsistently protects the heart cells of myocardium against other ischemic insults. Many factors such as diseases and medications may influence IP expression. Although diabetes poses higher risk, of the stroke in heart & brain, but the physiopathology underlying this condition is uncertain. Moreover, although diabetes causes the endothelial Dysfunction which believed to alter intracellular pathways related to protective mechanisms, by it is still controversial whether diabetes may interfere with ischemic preconditioning and whether this might influence clinical outcomes. This review article looks at published reports with animal models and humans that tried to evaluate the possible influence of diabetes on endothelial as well as ischemic preconditioning of heart.

KEYWORD: Endothelial Dysfunction, Ischemic preconditioning (IP), diabetes mellitus.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic hyperglycemic disease condition attributed to defective insulin secretion or action or both According to World Health Organization (WHO), 1.5 million people died with DM in 2012. Moreover, more than 80% of the total deaths occurred due to DM are from low- and middle-income countries. The prevalence of diabetes is also increasing very rapidly in India. According to International Diabetes Federation (IDF) (2017), 72 million cases of diabetes were reported from India with a prevalence of 8.8%. Most of the cases with DM either have Insulin dependent DM (known as type 1 DM) or non-insulin dependent DM (known as type 2 DM). (Kaur, Kaur, & Singh, 2018). Diabetes promotes cardiac dysfunction. Vascular endothelial dysfunction is thought to be one of the key risk factors. The impact of diabetes on the endothelium involves several alterations, including hyperglycemia, fatty acid oxidation, reduced nitric oxide (NO), oxidative stress, inflammatory activation, and altered barrier function. The current review provides an update on mechanisms that specifically target endothelial dysfunction, which may lead to diabetic cardiomyopathy. Cardiac ischemic preconditioning (IPC), ie, brief repeated periods of nonlethal ischemia, protects the heart from prolonged ischemic insult and reperfusion injury, decreasing infarct size and improving cardiac function. Even though the clinical benefit of ischemic conditioning has been tested in an increasing number of proof-of-concept studies, our knowledge of the underlying molecular mechanisms that mediate these cardioprotective effects is still incomplete.

2. Ischemia-reperfusion injury: A Brief Overviews

Ischemia-reperfusion injury is associated with serious clinical manifestations, including myocardial hibernation, acute heart failure, cerebral dysfunction, gastrointestinal dysfunction, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome. Ischemia-reperfusion injury is a critical medical condition that poses an important therapeutic challenge for physicians. In this review article, we present recent advances focusing on the basic pathophysiology of ischemia-reperfusion injury, especially the involvement of reactive oxygen species and cell death pathways. The involvement of the NADPH oxidase system, nitric oxide synthase system, and xanthine oxidase system are also described. When the blood supply is re-established after prolonged ischemia, local inflammation and ROS production increase, leading to secondary injury. Cell damage induced by prolonged ischemia-reperfusion injury may lead to apoptosis, autophagy, necrosis, and necroptosis.

3. Mechanism of ischemia-reperfusion injury

Several physiological mechanisms promote ischemia and lead to hypoxia and hypo perfusion, including atherosclerosis and acute myocardial infarction. The obstruction of arterial blood flow causes hypoxia and leads to dysfunction of the electron transport chain in

mitochondria. Decreasing ATP production in mitochondria induces anaerobic metabolism, dysfunction of sodium-potassium pumps, and detachment Overview of the mechanism of ischemia-reperfusion injury. The ischemic state induces anaerobic metabolism, leading to a lower level of ATP production and failure of ion-exchange channels. Failure of ionexchange channels leads to cell swelling and impaired enzymatic activity in the cytoplasm. Mitochondrial damage and electrolyte imbalance in the reperfusion state promote oxidative stress from three major systems: the NADPH oxidase system, nitric oxide synthase system, and xanthine oxidase system. ROS retention induces cell damage, leading to cell death via four pathways: autophagy, mitoptosis, necrosis and necroptosis, and apoptosis. (Kaur, Kaur, & Singh, 2018).

4. Diabetes with Vascular dementia

Diabetes has been found to be consistently associated with the risk of VaD and there is the significant association between glucose intolerance and the risks of both VaD and AD Diabetic people had a 1.5 to 4 fold risk for AD as well as VaD. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress. The insulin resistance (i.e., hyperinsulinemia) in people with impaired glucose tolerance has been one of risk factors for cognitive decline. Furthermore, diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic Oxidative stress and vascular endothelial are recognized as important contributing factors in the pathogenesis of AD and dementia of vascular origin Only limited therapeutic interventions are available to reduce the incidence of VaD. (Sharma., etal. 2011).

5. Nitric Oxide Synthesis and Nitric Oxide Synthase Enzyme Isoforms

NO is a highly reactive, readily diffusible gaseous free radical with strong intrinsic oxidant properties. It is synthesized by 3 distinct subtypes of the NO synthase (NOS) enzyme, each with unique expression patterns and functional properties: neuronal NOS (nNOS, NOS1), inducible NOS (iNOS, NOS2), and endothelial NOS (eNOS, NOS3). Broadly, these proteins catalyze the production of NO and L-citrulline from L-arginine and O_2, using electrons donated from dihydronicotinamide-adenine dinucleotide phosphate (NADPH). This process is tightly regulated requiring several key protein–protein interactions and multiple prosthetic groups and cofactors. In monomeric form, the NOS subtypes are incapable of binding to L-arginine, and subsequently can function primarily as weak NADPH oxidases resulting in the production of harmful superoxide radical anion ($O_2^{\bullet-}$). When bound by the calcium signaling protein calmodulin (CaM), the transfer of electrons through a flavin adenine mononucleotide and flavin adenine dinucleotide domain is enhanced. Finally, in the presence of heme and tetrahydrobiopterin (BH_4), NOS monomers form homodimers capable of using the donated NADPH electrons to catalyze the 2-step oxidation of L-arginine to L-citrulline and NO. In the first step, NOS promotes the hydroxylation of L-arginine to Nω-hydroxy-L-arginine, which remains bound by the enzyme. In the second step, NOS catalyzes the oxidation of Nω-hydroxy-L-arginine to L-citrulline, thereby releasing NO (Fig. 1).

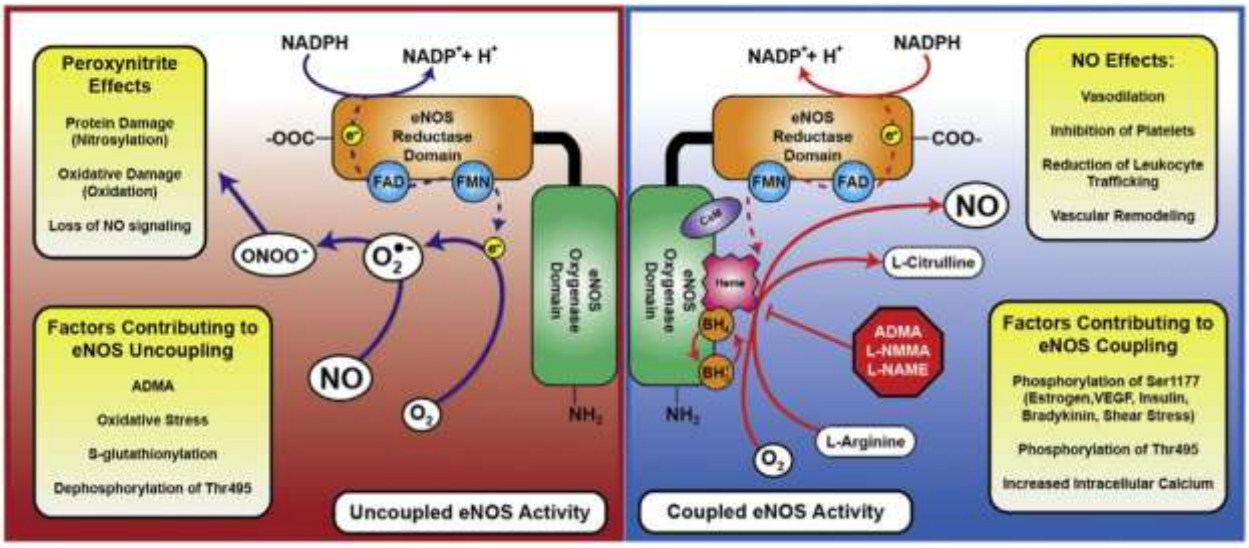

Fig. 1:

eNOS regulation, coupling, and uncoupling. During coupled eNOS activity (*blue side*), in the presence of heme and tetrahydrobiopterin, electrons from NADPH are passed through a core of flavin adenine dinucleotide–flavin adenine mononucleotide in the reductase domain to the Heme prosthetic group on the oxygenase domain. Here, l-arginine and O_2 are consumed to create l-citrulline and NO. In the uncoupled state (*red side*), electrons are passed directly from the flavin adenine dinucleotide (FAD)–flavin adenine mononucleotide (FMN) core of the reductase domain to O_2, generating superoxide ($O_2^{\bullet-}$), which can ultimately combine with

locally produced NO to make peroxynitrite ($ONOO^-$). Several of the effects of $ONOO^-$ and NO are listed here, as well as factors contributing to both coupling and uncoupling of eNOS activity. These are explained in greater detail in the body of the text. VEGF, vascular endothelial growth factor.(Anthony R Cyr., etal 2020).

Table 1: Diabetes Mellitus associated with recent targets of endothelial dysfunction.

Cause	Target	Effect	Risk factor	Ref
Diabetes Milletus	Adiponectin	Endothelial dysfunction	Obesity	(Achari & Jain, 2017)
Diabetes Milletus	nitric oxide (NO) and prostacyclin	Endothelial dysfunction	microvasculature	(Shi & Vanhoutte, 2017)
Glucose-induced	O-GlcNAcylation	Endothelial dysfunction	cardiovascular disease	(Clyne, 2021)
Diabetes Milletus	Thrombocytes & coagulation factor	platelet dysfunction	hemostasis	(Babik, et al., 2018)
Diabetes Milletus	low-density lipoprotein (LDL)	coronary vessels	cardiovascular disease	(Mäkimattila & Yki-Järvinen, 2002)
Diabetes Milletus	angiotensin II, endothelin-1,	endothelial dysfunction	hypertension	(Wong, Wong, Tian, & Huang, 2010)
diabetes	RAS, BMP4, and ROS-dependent COX-2-derived prostanoids	endothelial dysfunction	hypertension	(Wong, Tian, & Huang, 2013)
type 1 diabetes	polyol pathway activation	endothelial dysfunction	macrovascular disease	(Bertoluci, Cé, da Silva, & Puñales, 2008)
diabetes	Endothelial progenitor cells (EPCs)	endothelium. Decreased EPC number	cardiovascular (CVD) risk.	(Desouza, 2013)
diabetes mellitus	Peroxynitrite (ONOO-),	endothelial dysfunction	Macro and microvascular diseases	(Zou, Cohen, & Ullrich, 2004)

Table 1: Diabetes Mellitus associated with recent targets of Ischemic Preconditioning.

Causes	Target	Beneficial Effects On	Improve Functioning In	Ref
Diabetes mellitus	Ketogenic diet (KD)	Cardiac ischemic preconditioning	PCOS=Polycystic ovary syndrome,	(Gupta, Khandelwal, Kalra, Gupta, Dutta, & Aggarwal, 2017)
Diabetes mellitus and in patients	opening of K-ATP channels	myocardial ischemic preconditioning	symptomatic coronary artery disease	(Rezende, et al., 2013)
Genetically modified Diabetes	Male Zucker diabetic fatty (ZDF) rats	Animal Model of Diabetes	Mitochondrial dysfunction	(Hjortbak, et al., 2018)
off-pump coronary artery bypass (OPCAB)	Adenosine	Cardiac ischemic preconditioning	myocardial ischemia.	(Forouzannia, et al., 2013)
GSK3β (glycogen synthase kinase 3 beta)	MG53 phosphorylation at serine 255 (S255)	Cardiac ischemic preconditioning	acute myocardial injury,	(Lv, et al., 2022)
Diabetes mellitus (DM)	liver ischemic preconditioning (RLIPC)	Cardiac ischemic preconditioning	LVESP, LVEDP, dp/dtmax, and - dp/dtmax.	(Hu, Chen, Zhang, Liu, & Abbott, 2017)
Diabetes mellitus (DM)	insulin/poly(ethylene glycol)-carboxymethyl chitosan (PEG-CMCS)	heart ischemia/reperfusion injury (HI/RI)	creatine kinase (CK), lactic dehydrogenase (LDH), putrescine (Pu), myocardial infarct size, and NF-κB and spermidine/spermine N'-acetyltransferase (SSAT)	(Tong, Liu, Yan, Li, Ruan, & Yang, 2018)
Diabetes mellitus (DM)	isoflurane	isoflurane-induced preconditioning.	mitochondrial ATP-regulated K(+) channels.	(Tanaka, et al., 2002)
Diabetic Kidney Disease	Transcriptome	Human Adipose-Derived Mesenchymal Stromal Cells	Immunomodulatory and Paracrine Activities	(Hickson, et al., 2021)

6. Vascular Endothelium

Atherosclerosis is the process of vascular wall thickening and hardening, and it is the primary cause of coronary heart disease, ischemic stroke, and peripheral arterial disease Numerous epidemiological studies suggest that adiponectin deficiency (hypoadiponectinemia) is associated with coronary artery disease and hypertension left ventricular hypertrophy and a greater risk of myocardial infarction Experimental studies with cell cultures and animal models have shown cardioprotective action of adiponectin in cell types, including: vascular endothelial cells, smooth muscle cells, and cardiac myocytes and adiponectin-deficient mice The vasculoprotective and angiogenic properties of adiponectin have demonstrated in adiponectin-deficient mice in which adiponectin improves revascularization of ischemic limbs and rescues from cerebral ischemia-reperfusion (Achari & Jain, 2017).

7. DISCUSSION

Main findings

This systematic review of 40 studies demonstrated that preconditioning effectively improves cardiac function and reduces clinical, serologic, and histologic markers associated with myocardial pathogenesis and progression while promoting repair in diabetic animals. Subgroup analyses compared the effects of varying cell types, tissue and host sources, doses, preconditioning methods, and delivery routes in ischemia reperfusion injury in heart, however diabetes cause the endothelial dysfunction by uncoupling the mechanism of Nitric oxide pathway. Diabetes is associated with the origin of various disease mention in the table 1 it indicate the recent target are the precursor metabolites used in the different pathway of the cardiovascular disease target Adiponectin is the most abundant peptide secreted by adipocytes, whose reduction plays a central role in obesity-related diseases, including insulin resistance/type 2 diabetes and cardiovascular disease. (Achari & Jain, 2017). O-linked-N acetyl glucosaminylation (O-GlcNAcylation) is a type of glycosylation that occurs when a monosaccharide, O-GlcNAc, is added onto serine or threonine residues of nuclear or cytoplasmic proteins by O-GlcNAc transferase (OGT) and which can be reversibly removed by O-GlcNAcase (OGA). O-GlcNAcylation couples the processes of nutrient sensing, metabolism, signal transduction and transcription, and plays important roles in development, normal physiology and physiopathology. Cumulative studies have indicated that O-GlcNAcylation affects the functions of protein substrates in a number of ways, including protein cellular localization, protein stability and protein/protein interaction. Particularly, O-GlcNAcylation has been shown to have nitric oxide (NO) and prostacyclin (Crisafulli, et al., 2020), There is a particular need for an increased awareness of diabetic patients in cardiovascular units, where the incidence of this disease reaches as high as 30-40%. The main hallmarks of the pathologic metabolic milieu of diabetes are hyperglycaemia, insulin resistance and pathologic lipid metabolism. The biochemical, cellular and organ-level pathophysiological changes lead to endothelial dysfunction including a low-grade prothrombotic balance, inflammatory state and, as a consequence, impaired micro- and macrocirculation. Diabetes is also followed by platelet dysfunction resulting from intracellular hyperglycaemia, because thrombocytes have insulin-independent glucose transporters in their cell membrane. The levels of the coagulation factors of the plasma are increased, and these factors are also modified by oxidation and glycation. Diabetes mellitus is a prothrombotic condition resulting from direct and indirect tendencies of the endothelial platelet and the plasma coagulation factors. (Babik, et al., 2018) Endothelial dysfunction frequently coexists with features of insulin resistance, such as the presence of small dense low-density lipoprotein (LDL) particles even in nondiabetic individuals. This association is independent of obesity and other causes of endothelial dysfunction, such as LDL cholesterol, hypertension, and smoking. In patients with type 1 diabetes, endothelial dysfunction has been found in approximately half of the studies. In some but not all studies, endothelial dysfunction has been especially severe in patients with poor glycemic control. Reversal or amelioration of endothelial dysfunction has been documented by many commonly used therapeutic agents such as successful insulin therapy, fibrates, and angiotensin-converting enzyme inhibitors, but also with some but not all agents that act as antioxidants. Long-term studies addressing the prognostic significance of endothelial dysfunction and its reversal are urgently needed to determine whether measurement of endothelial function could be used to identify individuals at risk better than can be done at present using classic risk factor assessment among patients with type 2 diabetes especially. (Mäkimattila & Yki-Järvinen, 2002), Endothelial progenitor cells (EPCs) are vital for the maintenance and repair of the endothelium. Decreased EPC number and function have been associated with increased cardiovascular (CVD) risk. Patients with diabetes have decreased number of circulating EPCs and decreased EPC function. This may account for some of the increased CVD risk seen in patients with diabetes that is not explained by traditional risk factors such as glycemic control, dyslipidemia and hypertension. Recent studies seem to indicate that drugs commonly used in diabetes patients such as metformin, thiazolidinediones, GLP-1 agonists, DPP-4 inhibitors, insulin, statins and ACE inhibitors may increase EPC number and improve EPC function (Desouza, 2013)., enos effective in improving cardiac function. Table 2 mainly focused the target used for the preconditioning of the vital organ such as heart kidnay and brain collectively, these findings may inform design of future experiments in animals and optimize therapeutic strategies for translation to clinical trials for ischemia reperfusion injury.

CONCLUSION

In conclusion, this systematic review provides insurmountable evidence for the efficacy of in

experimental animal models of ischemia reperfusion injury. Endothelial improved functional and structural outcomes inherent in pathogenesis and progression of myocardium for which treatment-related factors further modified this effect. These quantitatively summarized preclinical findings can help guide therapy selection and delivery strategies to aid in successful translation of findings to clinical trials.

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Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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