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ROLE OF ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

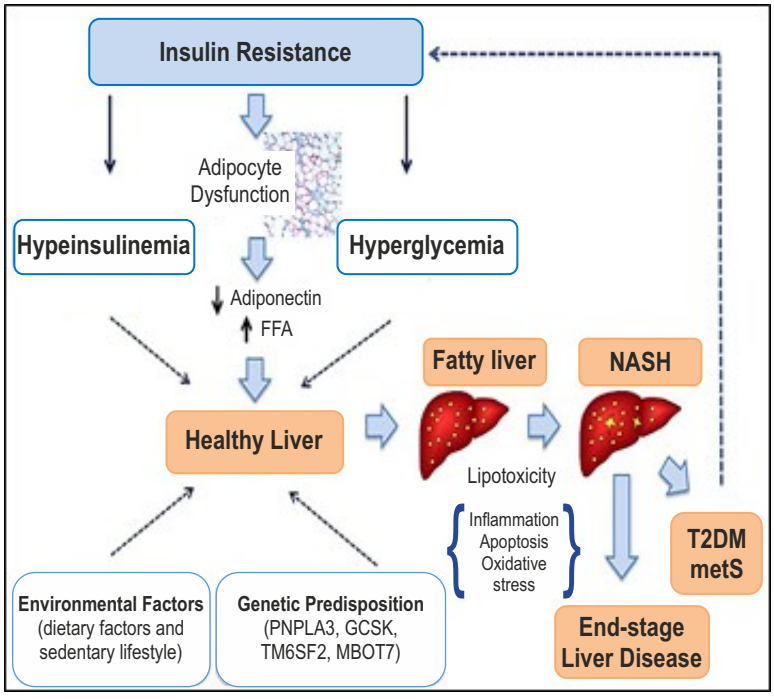
Introduction

Diet and lifestyle changes have led to a worldwide increase in the prevalence of metabolic syndrome (MetS). Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by insulin resistance (IR) & hepatic steatosis in the absence of significant alcohol use, hepatotoxicity, and/or other known liver diseases.

The condition begins from simple steatosis to non-alcoholic steatohepatitis (NASH), which can lead to life-threatening hepatic cirrhosis and hepatocellular carcinoma. NAFLD is currently the most common liver disorder, with a prediction to be the most frequent indication for liver transplantation by 2030. The global estimated prevalence of NAFLD ranges from 6.3 to 33% in the general population.

NAFLD Pathogenesis and Insulin Resistance

IR, with or without fully developed MetS, is the central mechanism of hepatic steatosis in patients with NAFLD, which develops in the setting of an inappropriate diet, sedentary lifestyle, obesity, and advancing age. In addition, imbalances in pro- and anti-oxidant processes as well as pro- and anti-inflammatory cytokines play a significant role in the pathogenesis of NAFLD.



The basic defect in the development of hepatic steatosis is the fat imbalance between import and export to and from the liver, secondary to IR. IR and subsequent hyperinsulinemia seem to be the major factors behind the alterations in the hepatic pathways of uptake, synthesis, degradation, and secretion of free fatty acids (FFAs), which ultimately leads to the accumulation of lipids in the hepatocytes. Elevated plasma concentrations of insulin, glucose, and fatty acids promote hepatic fatty acid and triglyceride uptake, de-novo lipid synthesis and impaired β-oxidation of fatty acids by negative feedback. As a result FFAs are inappropriately transferred to the liver along with inflammatory cytokines and specific adipokines linked to mitochondrial dysfunction, starts a vicious cycle that contributes to impaired insulin signaling and hepatic IR.

*Recently, the **renin-angiotensin-aldosterone system (RAAS)** was reported to be associated with inflammation and fibrosis in NAFLD. Angiotensin receptor blockers (ARBs), which are inhibitors of RAAS may be a multivalent therapeutic agent as they target not only hypertension but also the*

mechanisms of IR and of stellate cell activation via angiotensin as prominent pathways of hepatic damage in this disease.

RAAS and NAFLD

There is an increasing body of evidence showing the RAAS involvement in metabolic regulation, playing an important role in lipid and glucose metabolism. Recent studies have also implicated the importance of local balance between the angiotensin converting enzyme (ACE)/Angiotensin II (Ang-II)/ Ang II receptor type 1 (AT1R) and ACE2/Ang-(1–7)–Mas arms to avoid liver metabolic diseases.

It is likely that the mechanisms by which RAAS could interfere with IR and steatohepatitis might include: 1) interactions with insulin receptors and intracellular signaling pathways; 2) effects on adipogenesis; 3) influences on cytokine and adipokine production; 4) interference with pancreatic β-cell insulin secretion; 5) local hepatic effects interfering with hepatocellular regulatory mechanisms.

NAFLD and RAAS Blocking by ARBs

The mechanisms of ARBs in the treatment of NAFLD mainly include the following three aspects:

(1) Improving insulin sensitivity by restoring impaired intracellular insulin signaling and encouraging the transfer of excess fat from ectopic locations to mature adipocytes.

(2) Improving oxidative stress by upregulating the transcription of ACE2 mRNA. At the same time, it can improve local tissue perfusion & oxygenation by reducing Ang II-mediated vasoconstriction, reduce the increase of reactive oxygen species caused by fatty acid accumulation, & inhibit nuclear factor kB.

(3) ARBs can be activated as selective peroxisome proliferators to play a protective role in the liver. At the same time, lipid metabolism can be further improved through the activation & enhancement of adiponectin. It can also inhibit the uptake of lipids by liver cells, reduce hepatocyte steatosis and improve IR.

Clinical Evidences

Numerous clinical studies have demonstrated the beneficial effects of ARBs in improving the liver function of NAFLD patients. Losartan has been tested in both human and animal studies with overall positive results. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are indicators of the degree of hepatocyte damage. A few studies have observed that Losartan may play a role in reducing transaminase in NAFLD population. A meta-analysis (6 studies) corroborated the same and showed that Losartan 50 mg once daily could reduce increased liver enzyme levels of the NAFLD patients and improved their liver function.

Studies on treatment with Telmisartan have also resulted in similar outcomes & showed a significant insulin-sensitizing effect. In hypertension-associated NASH patients, Telmisartan (20 mg/day)-improved steatosis, necroinflammation, fibrosis, insulin resistance, and the lipid profile. Enjoji et al. evaluated the therapeutic efficacy of Telmisartan (40 mg/day) and Olmesartan (20 mg/day) in NAFLD patients and concluded that both drugs significantly improved IR and liver injury.

Another randomized trial in which Telmisartan and Losartan were administered were found to be comparable in improving the liver enzyme levels.

Thus, ARBs are a promising new strategy for treating NAFLD and its consequences.

Source: Georgescu EF. Adv Ther. 2008; 25(11):1141-1174; Meng C, et al. Open Life Sci. 2023; 18(1): 20220583; Borem L, et al. Hypertens Res. 2018; 41(6): 394–405.

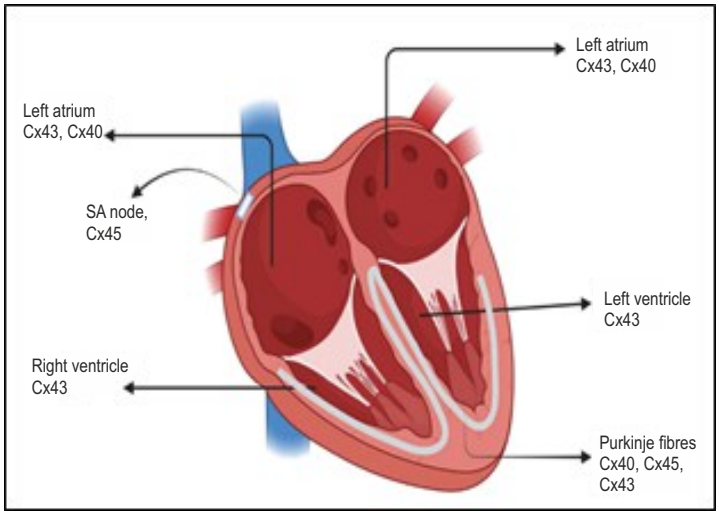
PROTECTIVE EFFECT OF DIABIZ (DAPAGLIFLOZIN) ON CARDIOMYOCYTES: MODULATION OF CONNEXIN PROTEINS

Heart failure (HF) is emerging as an important health problem in countries like India which has been contributed to by the surging prevalence of non-communicable diseases like diabetes mellitus and coronary artery disease. In India, it has been estimated that HF is responsible for about 1.8 million hospitalizations, the age of the patients with HF being lower among Indians (53 years) as compared to the western countries (70 years).

HF is a progressive disorder that is initiated after an index event like myocardial infarction, sustained hypertension, severe arrhythmias, viral infections, stressed environment or genetic disease. This index event damages the cardiomyocytes resulting in the loss of function or collapses in the pumping of the heart. During HF, the progressive cardiomyocyte loss may contribute to cardiac dysfunction and left ventricular remodeling through necrotic, apoptotic or autophagic cell death pathways.

Dapagliflozin exhibits a variety of mechanisms to protect the cardiomyocytes like inhibiting the oxidative stress mediated by NADPH oxidase, improving the biochemical indexes related to cardiac function, its effect on proinflammatory mediators and mainly improving the myocardial hypertrophy by reducing the blood glucose levels. One such protective action of dapagliflozin on the cardiomyocytes is via connexin.

Connexins are emerging as therapeutic targets for HF. They are responsible for maintaining electrical conduction by facilitating the rapid propagation of action potentials, leading to synchronous contractions.



In the heart, the Cx43 is the most abundantly expressed isoform and is localized in the ventricular and atrial cardiomyocytes and also in the endothelial cells, smooth muscle cells and fibroblasts. Cx43 is the most important transmembrane aqueous channel connexin that forms an ion channel between the cardiomyocytes and maintains conduction of electrical signals between the cardiomyocytes.

It has been observed that the Cx43 mRNA and the protein are significantly down regulated in the left ventricle in patients with HF caused by ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. Overall, congestive HF is associated with a significant decrease in the Cx43 levels, leading to enhancement of arrhythmias and systolic dysfunction.

Effect of Dapagliflozin on Cx43

Dapagliflozin has been shown to preserve the CX43 amount and function by the AMP activated protein kinase (AMPK) mediated antioxidative action.

Hence, the activation of AMPK signaling pathway by dapagliflozin reduced production of ROS and attenuated reduction of Cx43 expression and may have the potency to be used as a therapeutic tool in HF.

Source: Ren M et al. Biomed Res Int 2022; 2022: 9687345; Singh A et al. J of Public Health 2021; 29: 585-595; Himelman E et al. The J of Clin Investigation 2020; 130(4): 1713-1727; Lahnwong S et al. Cardiovasc Diabetol 2020; 19(91): 1-13.

ORAL BLUMOX-CA (AMOXICILLIN/CLAVULANATE) FOR THE PREVENTION OF BACTEREMIA FOLLOWING DENTAL EXTRACTIONS

Dental infections are commonly presented by symptoms of pain and swelling in the oral area. These infections should be treated as soon as possible since they cause serious and irreversible complications such as osteomyelitis, brain abscess, airway blockage, carotid infection, sinusitis, septicemia, meningitis, cavernous sinus thrombosis, orbital abscess, and vision loss.

Antibiotics are generally used in dental procedures to treat odontogenic infections, non-odontogenic infections, local infection, focal infection, and prophylaxis.

Antibiotic prophylaxis is prescribed for patients with immunosuppressed conditions, infective endocarditis, metabolic disorders, and patients with prosthetic joints.

Rationale for Amoxicillin/Clavulanate as a place in therapy for dental infections

- According to clinical evidence, Amoxicillin/Clavulanate is the most commonly administered empirical antibiotic in dental practice.
- Gram-positive cocci are responsible for around 65% of orofacial infections, while gram-negative bacilli are seen in 25% of patients. Because Amoxicillin has a broad spectrum of activity against both gram-positive and gram-negative bacteria, it is well suited to treat dental infections.
- The hydroxyl group that distinguishes Amoxicillin from Ampicillin makes the former more lipid-soluble with enhanced bioavailability, duration of action, and better bactericidal activity.
- An in vitro study have shown the efficacy of Amoxicillin against Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis, proving its significance in treating gingival and periodontal infections.

Clinical evidences[6-8]

1. A review literature have demonstrated that taking 2 gm Amoxicillin/1875-125mg Amoxicillin/Clavulanate orally 1-2 hour before surgery lowered dental implant failure considerably. This has been corroborated in a meta-analysis (15 randomized clinical trials).
2. A review on antibiotic prophylaxis in dental practice have stated that,

- Since bacteremia and subsequent infective endocarditis is a common complication following a tooth extraction, the practice of advocating a standard regimen of 2 gm of oral Amoxicillin/1875-125mg Amoxicillin/Clavulanate orally for adults before the start of the dental procedure is widely accepted and followed by dentists.

Thus, proper antibiotic therapy administered at the appropriate time and dose, can help alleviate dental infections related discomfort while reducing the risk of systemic spread.

Oral AMX-CL could be an excellent option for preventing bacteremia secondary to dental procedures in patients at risk.

Source: Diniz F et.al; Oral Diseases. 2023;29:2272–2276

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