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A Study Of Therapeutic Potential Of RAAS Blocker Mediated Correction Of SGLT Activity In Diabetic Patient

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Abstract

Diabetes mellitus is a group of chronic metabolic conditions which result from defective insulin secretion, insulin action or both.In the type 1 and type 2 diabetes mellitus cardio-renal injury development are frequent.However,in diabetes pathology, inhibition of SGLT1 results in an increase glucose homeostasis by decreasing dietary glucose absorption in the intestines.The rise plasma renin function, median arterial pressure and renal vascular resistance, circulatory and local (intrarenal) activation of RAAS, was linked to short-term mild hyperglycemia without glycosuria in early phases.The nicotinamide adenine dinucleotide phosphate (NADPH) mediated generation of ROS via activation of Angiotensin II as a deleterious effect of RAAS in the event of cardio-renal injury. Diabetes-related cardiovascular (CV) and renal complications can be attenuated by antihypertensive renin angiotensin aldosterone system inhibitors (RAAS), especially by inhibitors of the angiotensin converting enzyme (ACE), angiotensin receptor blockers (ARBs, etc.).An optimized concepts system for diabetes kidney pathogenesis and its relationship with cardiovascular diseases would allow surveillance and pharmacotherapeutics to be developed to reduce the likelihood of serious clinical cases and early deaths. Therefore, the aim of the study to explore the exact molecular insight of RAAS blocker specifically ARBs in the prevention of diabetes and its cardio-renal injury.

Key words:RAAS blockers, SGLT, Bilirubin, Diabetes, Cardio-renal injury

1. Introduction

Diabetes mellitus is a group of chronic metabolic conditions which result from defective insulin secretion, insulin action or both. The importance of insulin, as an anabolic hormone, results in metabolic abnormalities in carbohydrates, lipids and proteins. Low insulin levels at the insulin-receptor level, signal transduction mechanism, or effector enzymes or genes are triggered by these metabolic abnormalities,

in order to meet sufficient response and/or insulin resistance of tissues of target, mostly of skeletal muscles, adiposal and to a lesser degree of liver.The classical diabetes classification introduced in 1997 by the ADA as Type 1, Type 2, Other Type and gestational diabetes mellitus (GDM) remains the best accepted and adopted classification(1).Diabetes type 1 accounts for 5%-10% of individuals experiencing diabetes disease andin children and young people Type 1 diabetes accounts for 80 -90% of diabetes(2, 3). Type 1 diabetes is caused by the loss of β pancreas cells due to autoimmune activation including T-cell mediated inflammatory response (insulitis) as well as a humoral (B cell) response(4-6).Autoantibodies against the cells of pancreatic islets are the hallmark of type 1 diabetes, although their function in disease pathogenesis is not apparent. These autoantibodies include islet-cell autoantibodies, insulin autoantibodies (IAAs), decarboxylase glutamic acid (GAD, GAD65), tyrosine phosphatases (IA2 and IA2β) proteins, and zinc transporters protein (ZnT8A)(7).

According to a 2013 IDF survey, a global prevalence of diabetes in adults (20-79), with 14 million men over women (198 million men vs 184 million women), a majority between 40-59 year olds, was 8.3% (382 million people), with an estimated increase in numbers above 592 million by 2035 with a global prevalence of 10.1%(8). Over 90%-95% of patients with diabetes belong to this type and most of them are adults. Insulin resistance in type 2 patients with diabetes raises insulin requirements in tissues targeted by insulin. In addition to resistance to insulin, the elevated insulin demand of pancreatic β cells could not be fulfilled due to defects in cells' function(9). Type 2 diabetes mellitus(T2DM) is a strong and classic risk factor for CKD and AKI and offers a good model to research the association between cardiovascular and renal diseases. AKI episodes have an increased risk for CKD, cardiovascular complications and overall death(10-16). In addition, Pinier et al.(17)highlighted a complex connection between AKI and CKD and acute, chronic cardiovascular events and mortality in patients with type 2 diabetes. In T2DM patients, the mortality rates are about double those without T2DM(18) and their risk for cardio-renal damage can be largely increased(19, 20).In T2DMpatients, those with hypertension, and those who developed CKD, cardiovascular accident rates and related mortality were higher. Up to 18% of patients were developed with CKD after 4 years, but surprisingly, short-term (1 year) but non-long-term (4 years) AKI episodes were found to have an effect on CKD development or mortality and emphasize the importance of classical risk factors such as diabetes mellitus(21). The main aetiologic factor responsible for the progression of diabetic kidney disease is hyperglycemia. Multiple pathophysiologic disorders (including high blood pressure, changed tubuloglomerular response, renal hypoxia, lipotoxicity, podocyte damage, inflammation, mitochondrial impairment, compromised autophagy and increased sodium hydrogen exchange activities) lead to progressionary glomerular sclerosis and the decline to glomerular filtration rate after hyperglycaemia has been identified(22).The quantitative contribution of these anomalies and their function in type 1 and type 2 diabetes mellitus to the development of cardio-renal injury remains.

Diabetes-related cardiovascular (CV) and renal complications can be attenuated by antihypertensive renin angiotensin aldosterone system inhibitors (RAAS), especially by inhibitors of the angiotensin converting enzyme (ACE), angiotensin receptor blockers (ARBs, etc.), and probably direct renin inhibitors (DRIs).The rise plasma renin function, median arterial pressure and renal vascular resistance, circulatory and local (intrarenal) activation of RAAS, was linked to short-term mild hyperglycemia without glycosuria in early phases(23).A prospective research emphasize higher FPG and insulin resistance at the baseline in multi-ethnic individuals with type 2 diabetes mellitus, higher aldosterone and PRA and higher risk for

type 2 diabetes mellitus incidents over 10.5 years(24).For instance, the Miller study(25) showed significantly higher arterial pressure during hyperglycemia than euglycemic conditions, and that the arterial pressure was well susceptible to losartan potassium therapy, while the losartan therapy response during euglycemia was minimal.In addition, Osei and his colleagues(26) demonstrated promising responsiveness to captopril and eprosartan during hyperglycemia, indicating that hyperglycemia contributes to a rise in the renal vascular tone induced by Ang II.An optimized concepts system for diabetes kidney pathogenesis and its relationship with cardiovascular diseases would allow surveillance and pharmacotherapeutics to be developed to reduce the likelihood of serious clinical cases and early deaths. Therefore, the aim of the study to elucidate the exact molecular explanation of RAAS blocker specifically ARBs in the prevention of diabetes and its cardio-renal consequences.

2. Selection of literature review

Articles have been accessed by searching for the literature in Proquest,ScienceDirect, Cochrane, Pub Med, Science Web, Embase, Mendeley and Springer, by filtering the related reference lists by hand. While multiple keywords were used in addition to the literature review such as "Renin angiotensin aldosterone system," "Epidemiology of diabetes", “Types and pathophysiology in of diabetes", "Involvement of sodium glucose transporter in diabetes", "Bilirubin role in diabetes" “Biological activity of RAAS”, “Potential of RAAS blockers on SGLT mediated glucose absorption”, This article is for publications in English. Reference lists are also scanned for articles not included on the initial quest.

3. Overview of Renin angiotensin aldosterone system

Interrelated hemodynamic and neurohormonal pathways including the sympathetic nervous system (SNS), RAAS, and the induction of endotheline and arginine vasopressin systems have been involved in cardiorenal syndrome(27).Cardio-renal damage progress through renal perfusion downregulation that induces renin secretion, which in turn enables RAAS followed by SNS activation(28). Over-activation of RAAS can cause metabolic changes which impact both BP and insulin resistance, by raising vasoconstriction, increasing sodium in the kidney and stimulating the secretion of the aldosterone hormone(29) andIncreased aldosterone levels are linked to resistance to insulin and type 2 diabetes mellitus event.RAAS initiation take place by releasing the pro-renin, is distinguished as a prohormone that that convert into active renin, the rates limiting enzyme that controls the homeostasis of the kidneys(30).Prorenin is formed in response to many factors, including decreased kidney perfusion, activation of the sympathetic nervous system, and reduced sodium distribution in the macula densa(31).The cascade of the enzyme initiates the synthesis from circulating, mostly hepatic angiotensinogen of the very inactive decapeptide angiotensin I (32).The non-specific enzyme angiotensin-converting (ACE) is then processed to Angiotensin II by angiotensin I(33).Although the circulating RAS is essential for the systemic control of cardiovascular tissue, activation of this tissue altered local functions with the synthesis of Ang II, and may therefore directly affect endothelium and smooth muscle cells independently of the endocrine effects of this tissue on systemic hemodynamics. The effects of angiotensin II, primarily by angiotensin type 1 receptors, include vascular inflammation and oxidative damage(34). The intense sodium avidity and ventricular reshaping of RAAS are malfunctioning responses to altered haemodynamics, sympathetic signals and progressive renal dysfunction(35). The nicotinamide adenine dinucleotide phosphate (NADPH) mediated generation of ROS via activation of Angiotensin II as a deleterious effect of RAAS in the event of cardio-renal

injury(36).Angiotensin II is theoretically involved in vascular inflammation through a pathway of a nuclear factor kappa B (NF-kB), which causes the formation of adhesion molecules(37, 38) (Figure 1).

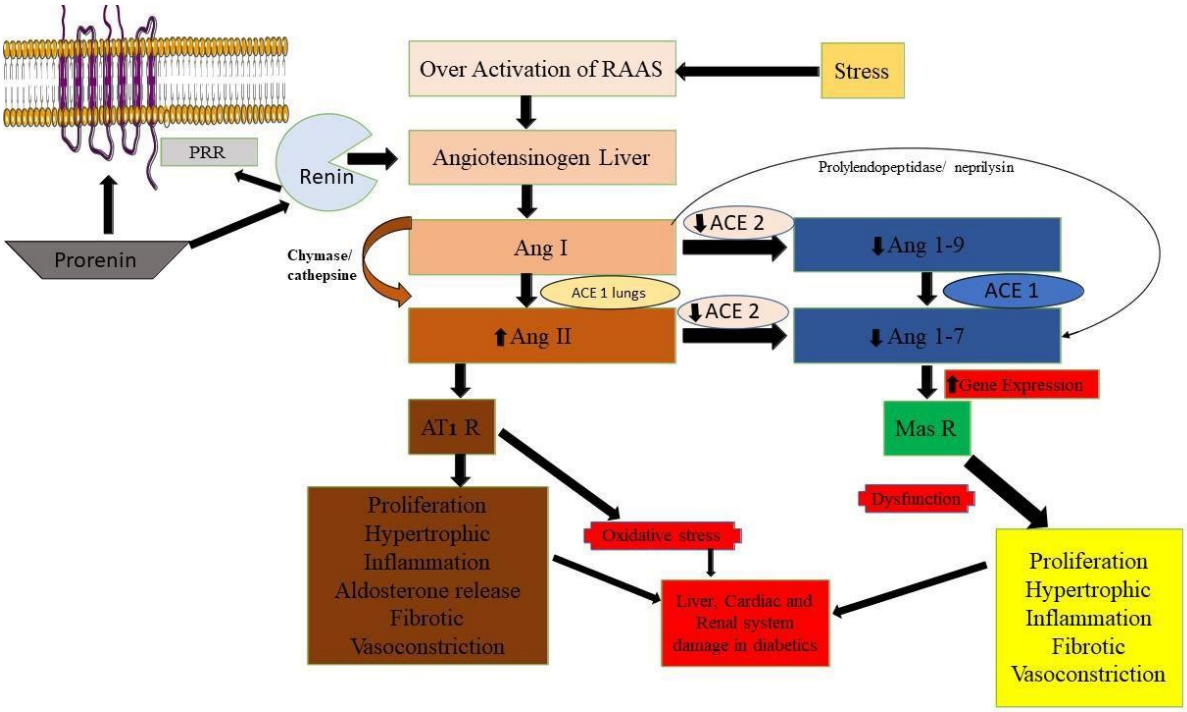

Figure1: Pathophysiological disturbance of RAAS in diabetes mediated liver cardiac and renal injury

4. Involvement of SGLT in diabetics

12 members were found in the SLC5A gene family. Sodium-glucose cotransporter 1 (SGLT1), first detected in intestinal epithelial cells, reveals the workings of the cotransporters (SLC5A1)(39).Expression of SGLT1 mRNA in different human tissues including the kidney, muscles of the skeleton, liver, lung, cardiac cell, trachea, uterus cervix, stomach, mesenteric adipose tissue, pancreas alpha cells and brain is observed by RT-PCR(40-43).SGLT1 is also confirmed in cholangiocytes(44) where glucose reabsorption from bile is facilitated.In myocardial ischemia, SGLT1 is also increased by 2 to 3(45). Furthermore, elevation of the blood glucose after meals has an elevated chance of diabetes complications(46).The risk of cardiovascular disease is linked with post-prandial hyperglycemia; measures to avoid glucose transportation in diabetics are also used in cardiac disease therapies. The small intestine is the main place for absorption of the dietary glucose mainly by SGLT1 on the boundary membranes of the brush(47, 48).Diabetes has not fully known the impact on intestinal SGLT1 expression. Some studies have shown that expression of gastrointestinal SGLT1 and transport of glucose are enhanced due to T1DM caused by streptozotocine in rodents(49-51).

LIK066 (licogliflozin) is an agent for dual SGLT1/2 that shows beneficial aspects in metabolic hormone profiles with increased GLP-1, PYY and glucagon levels and decreased levels of GIP, insulin, and blood glucose(52, 53).A number of compounds have been developed regarding selective SGLT1 inhibition. The most selective inhibitor of the SGLT1is, actually, ~300times selective, Mizagliflozin (also known as DSP-3235 or KGA-3235) over SGLT2.Inhibition of SGLT1 results in an increase glucose homeostasis by decreasing dietary glucose absorption in the intestines and increasing the release of incretin like

glucagon-like peptide-1(54, 55). Inhibition SGLT1 inhibition is of limited glucosuric influence in the normal kidney and increased in diabetes and during SGLT2 inhibition, which deliver more glucose to SGLT1 in late proximal tubule.It was interesting, in a recent randomized T2DM patient study, that canagliflozin, a selective inhibitor for SGLT2, was administered in advance of meals and improved plasma GLP-1 levels. While canagliflozin is approximately 260 times more targeted to SGLT2 than to SGLT1, intestinal glucose absorption was stated to have been inhibited by the concentration of intestinal lumen 10 times as high as the IC50 of SGLT1(53, 56).

5. Potential of renin angiotensin aldosterone system blocker mediated correction of SGLT activity

A new analysis of the rodents revealed the defensive role of bilirubin against DN through reduction of oxidative stress through deregulating renal NADPH Oxidase. Bilirubin is believed to be a powerful endogenous antioxidant(57, 58).However, the function of high concentrations of bilirubin in diabetes is uncertain.The authors found during a significant 2016 study that a marginally raised bilirubin concentration has a protection effect on a number of disorders, including cardiovascular disease and diabetes, correlated with enhanced oxidative stress, approaching altered bilirubin metabolism may be considered a possible biomedical strategy to ameliorate a variety of symptoms.The relationship between the amount of bilirubin and the prevalence, development and prognosis of the disease has been studied.In various disorders, including antherosclerosis, cancer and diabetes nephropathy, bilirubin has been shown to inhibit oxidative stress(59, 60).Although increased concentrations of bilirubin decreased pancreas β-cells damage caused by streptozotocin by reducing oxidative stress(61)or increased rodent sensitivity towards insulin(62). A number of studies have previously strengthened the correlation between the bilirubin concentration and diabetes complication incidence; multiple tests have shown that the elevated bilirubin concentration has a beneficial effect on diabetic complications(63). High levels of TBil were found to guard against the development of diabetes in Korean men in another four years' retrospect study (n = 5960)(64).According to laboratory trials, previous laboratory studies demonstrated that elevated bilirubin has a 26 to 31% decrease in human diabetes risk(65, 66).Diabetic patients with Gilbert syndrome(moderate hyperbilirubinemia exists in 5-10%) have demonstrated reduced oxidative stress markers and lower diabetic nephropathy and CVD risk(67-69).As a standard index of diabetes control, DBil, IBil and TBil have different therapeutic effects.Additionally, IBil in plasma is transported to the hepatocytes through albumin, which converts IBil to DBil by the UDP-glucuronyl transferase 1A1 enzyme(70). Higher DBil can indicate hepatocellular damage while TBil is within the standard(71).In addition, hepatic insulin resistance in healthy subjects is linked to enhanced liver enzymes. TBil and IBil were found by several experiments to be more effective than DBil to prevent multiple diseases, including stroke, metabolic syndrome and type 2 diabetes risk(72-74).Notably, the AGTR1 angiotensin receptor blocker losartane, is biotransformed through UDP-glucuronyl transferase 1A1 enzyme that leads to reduce the efficacy of RAAS blockers (75). Thus, modulation of bilirubin levels (e.g., clinical strategies that inhibithepatic UGT1A1, is a key enzyme in bilirubin conjugation and control that leads to rise in IBil levels) may have protection from the risk of T2D may be expected to occur(76-78).The RAAS-blocker induced stabilization of billirubin was observed in the historical prospective research of the RENAAL trial, and the experiment further reveals an independent inverse correlation between the amount of bilirubin and nephropathy in Type 2 patients(74). Moreover, bilirubin binds to PPR-alpha leads to regulate the expression of UGT1A1 in late

small intestine and other beneficial effect including reduction in body wight, increase insulin sensitivity, reduces inflammation and cardiovascular consequences(79-82).On the other hand, RAAS blockers induces angiotensin II mediated inhibition of aldosterone and overexpression of SGLT1 that leads to inhibit and delayed intestinal glucose absorption along with sodium salt in diabetes(83).SGLT1/2 inhibition may be beneficial because of the limited efficacy demonstrated by SGLT2 inhibitors in diabetic patients with moderate to severe renal impairment(84). However, The UGT1A1 activation through high glucose in the late part of small intestine decreased serum conjugated bilirubin levels due to processed by the gut microbiome to urobilinoids and stercobilin dramatically in neonatal hUGT1 mice while it did not affect the expression of UGT1A1 in the liver thereby hyperbilirubinemia does not occur in diabetes(85-87).Similarly, a study considers low fasting concentrations of serum bilirubin (<8.53 µM) as an independent indicator of significant cardiovascular adverse effects, including ischemia - revascularization of the target vessel(88). The serum bilirubin levels in adipose tissue are negatively linked to abdominal obesity and hypertriglyceridemia(89) (Figure 2).

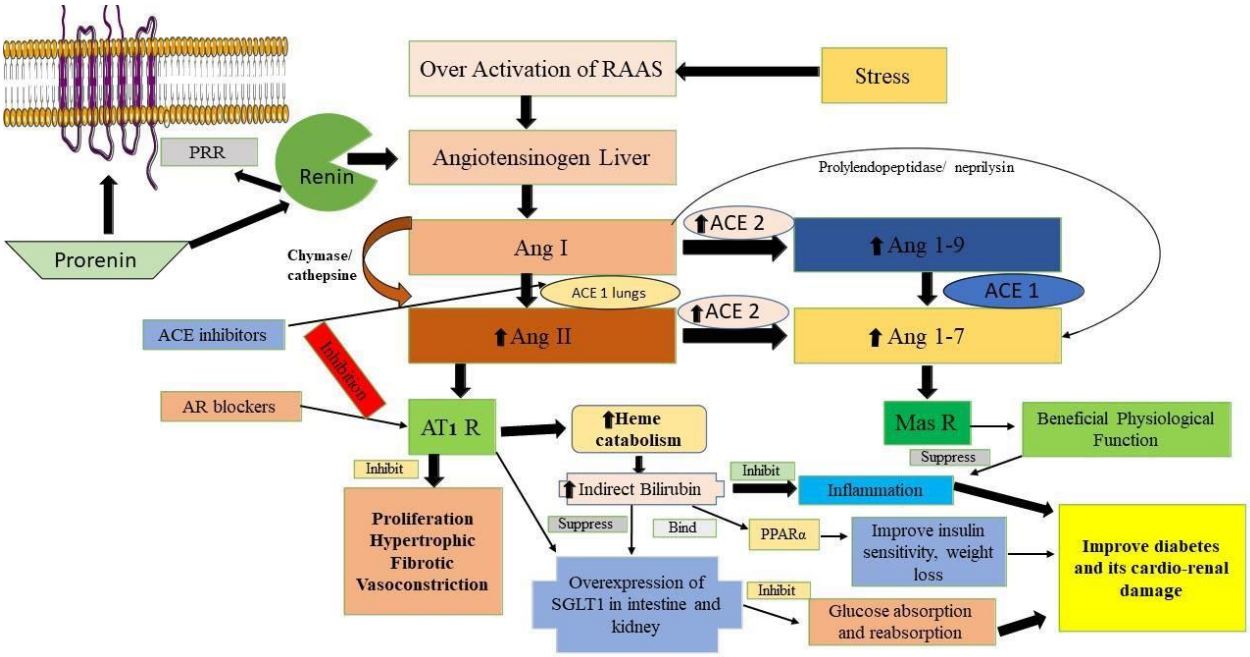

Figure 2: Potential of RAAS blockers mediated correction of SGLT activity in diabetic patient

6. Conclusion

Bilirubin, like many hormones, travels in circulatory system and enters the target in cells, binds mostly PPARα, to produce gene response.This defensive line offered by Bilirubin is evidence that the danger fully low levels of this key hormone can potentiate adverse clinical effects, which could contribute to cardio-renal injury, for the patients with endocrine, nutritional and metabolic diseases. In various studies found that, despite initial decreases in hemoglobin levels, therapy with losartan or irbesartan ARBs did not lead to reduced concentrations of bilirubin. SGLT-1, a cotransporter to control of bile glucose absorption. Moreover, RAAS blockers induces angiotensin II mediated inhibition of aldosterone and overexpression of SGLT1 that leads to inhibit and delayed intestinal glucose absorption along with

sodium salt in diabetes.On the other hand, bilirubin binds to PPR-alpha beneficial effect including reduction in body wight, increase insulin sensitivity, reduces inflammation and cardio-renal injury. To fully understand the therapeutic capability of RAAS Blocker mediated activation of different biomolecule, future investigations on bilirubin and its correction of SGLT1 functionality are required.

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