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Medical Bulletin

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ORAL ANTIDIABETIC DRUGS IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION

The liver has an important role in carbohydrate metabolism and is responsible for glucose homeostasis by means of glycogenolysis and neoglucogenesis. The metabolic homeostasis of glucose is impaired in the presence of chronic liver disease (CLD) resulting in insulin resistance (IR), glucose intolerance and diabetes.

Prevalence of non-alcoholic fatty liver disease (NAFLD), a major cause of CLD worldwide is estimated at ~33% of the global population and 55% in those with type 2 diabetes mellitus (T2DM). T2DM has been reported to accelerate the progression of NAFLD to more severe stages of non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC), while the presence of NAFLD increases the risk of T2DM and makes achieving optimal glycemic control more difficult.

Management of diabetes in patients with CLD is challenging as liver is the major site of metabolism for most of the oral antidiabetic drugs (OADs). Moreover, CLD is associated with complications such as impaired renal function, hypoalbuminemia, lactic acidosis, and hypoglycemia. Hence, there is acceleration of CLD progression in the setting of poor glycemic control if not managed with appropriate glucose lowering agents.

✤ Classification of Liver Impairment

The Child-Pugh score consists of 5 characteristics of liver disease: degree of ascites, serum concentrations of bilirubin and albumin, prothrombin time or international normalized ratio (INR) and degree of encephalopathy. Each measure is scored from 1 to 3, with 3 indicating most severe derangement. A total score of 5 to 6 is Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise) and 10 to 15 is class C (decompensated disease).

Parameters	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL	2 to 3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8 to 3.5 g/dL	<2.8 g/dL
Prothrombin time (seconds over control) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

✤ Antidiabetic Treatment

Below is a summary of existing data and recommendations for the use of OADs in T2DM patients with CLD.

I. Biguanides (Metformin):

Metformin is unmetabolized by the liver and undergoes renal elimination. However, metformin might cause lactic acidosis in predisposed patients (with heart, renal and liver failure). Metformin shifts intracellular oxidation-reduction potential toward anaerobic metabolism augmenting lactate production. It also suppresses conversion of glucose from lactate in liver and hence decreases lactate clearance. Therefore, there may be an enhanced risk of developing lactic acidosis in the clinical setting of impaired liver function. It is estimated that incidence of lactic acidosis is only 0.03-0.5 cases/1000 patient-years in metformin-treated population. Systematic review of 194 trials revealed no cases of fatal or nonfatal lactic acidosis in metformin group compared to non-users. Hence, there is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis.

However, Metformin has not been studied in patients with liver disease to date. All available information about liver dysfunction predisposing to metformin-associated lactic acidosis is drawn from case reports and postulated mechanisms. Most of those patients had cirrhosis, with some degree of renal impairment. Therefore below are the recommendations for its use;

- Metformin can be used in patients with mild hepatic impairment
- To be use with caution in patients with moderate chronic liver disease
- It should be avoided in severe hepatic dysfunction

II. Sulphonylureas:

Sulfonylureas (SUs) are metabolized into active and inactive metabolites in the liver. Protein binding of SUs may be reduced due to hypoalbuminemia which enhances free drug plasma concentrations resulting into frequent hypoglycemia. In severe impairment, there may be diminished gluconeogenic capacity. Moreover, SUs may also exhibit additive hypoglycemia in case of decompensated liver cirrhosis characterized by peripheral hyperinsulinism, resulting from reduced insulin hepatic clearance and higher insulin secretion rate. CLD patients who are malnourished are at higher risk of hypoglycemia. Alcohol-induced enzyme degradation of SUs in patients with alcoholic liver disease may manifest decreased clinical effectiveness of SUs. ADA and EASD states that in severe hepatic disease, insulin secretagogues should be avoided due to the risk of hypoglycemia. Therefore, it is recommended that SUs should be avoided in patients with CLD due to greater risk of hypoglycemia.

III. Meglitinides:

Glinides (Nateglinide and Repaglinide) have shorter half-lives than SUs and they do not have significant renal excretion. They are extensively bound to serum albumin protein and are metabolized by oxidative biotransformation (CYP 450) and conjugation with glucuronic acid in the liver. Repaglinide's metabolism is mainly affected by the presence of CLD while this is not the case for Nateglinide. One possible explanation for this discrepancy is that Repaglinide is metabolized by CYP isoform 2C8 and Nateglinide by CYP isoform 2C9.

Repaglinide clearance is significantly reduced in patients with hepatic impairment (HI) and should be used with caution, while in T2DM with severe HI the drug is contraindicated. On the other hand, Nateglinide pharmacokinetics (PK) is not affected in patients with HI and therefore, no adjustment of its dosage is needed in patients with mild to moderate HI. There are no data available in patients with severe impairment.

IV. Alpha-glucosidase inhibitors (AGI):

Voglibose, an AGI, acts locally within the gastrointestinal tract by inhibiting enzymes (glycoside hydrolases) needed to digest carbohydrates. The metabolism of voglibose in liver is negligible. The renal excretion is negligible & plasma concentrations after oral dose have been undetectable. However negligible is the metabolism of voglibose in liver, it should be used with caution in liver diseases. Hepatotoxicity may occur in some patients. Rise in liver enzymes has been observed in upto 20% of patients during therapy. Cases of hepatitis with severe cholestasis attributed to voglibose hypersensitivity, have been reported.

V. Thiazolidinediones (TZD):

Pioglitazone is the only drug of this class available for clinical use in India. It is extensively metabolized by hydroxylation and oxidation. It is excreted primarily as metabolites and their conjugates in bile and feces.

Hepatic safety of pioglitazone in more than 20,000 patients with T2DM reported no case of hepatic impairment and no alanine aminotransferase (ALT) abnormalities. In a study, where the hepatic safety profile of Pioglitazone was examined, there was no case of hepatocellular injury with pioglitazone use. Several clinical trials found that TZD treatment can prevent subsequent events, such as increase in oxidative stress, lipid peroxidation, and pro-inflammatory cytokines that contribute to the development of NAFLD to NASH. According to the position statement of the ADA in case of chirrosis or serum ALT level exceeding 2.5 times of upper normal limit (ULN), pioglitazone should be avoided. However, ADA highlighted importance of TZDs in the treatment of NASH. On the basis of available evidence, it is recommended that Pioglitazone should be used with caution in CLD patients. It should be avoided in patients whose liver enzymes are >3 times ULN range. Pioglitazone may be used in Child-Pugh Class A patients. However, it should be avoided in Class B and C patients.

VI. Dipeptidyl-peptidase-4 inhibitors (DDP-4i):

Hepatic metabolism is a minor pathway for Sitagliptin and Vildagliptin and major part of the drug is either excreted unchanged by renal pathway or through hydrolysis. Metabolism also is a minor pathway for Linagliptin and ~80% of the dose is eliminated through enterohepatic recycling. Saxagliptin is primarily metabolized by hepatic CYP3A4/5 and eliminated through renal and hepatic routes.

For Sitagliptin, a few cases of drug-induced hepatic injury and of elevated hepatic enzymes have been reported. Pooled data from 38 studies, found greater proportion of vildagliptin recipients to have mild elevations in liver enzymes. Vildagliptin was also not associated with an increased risk of hepatic adverse events. Only two patients experienced severe elevations in liver enzymes attributable to vildagliptin treatment. Both cases were asymptomatic & resolved upon discontinuation of treatment. Sitagliptin PK is not affected by moderate HI. Similarly, vildagliptin PK is not affected in patients with mild, moderate or severe HI. Studies have reported no liver safety issues for saxagliptin. Its PK is affected only in a small degree of patients with HI. A meta-analysis of 8 placebo-controlled trials confirmed the hepatic safety of Linagliptin.

Therefore, it is recommended that except for Vildagliptin, DPP-4 inhibitors can be used with caution without dose modification. More specifically, DPP-4 inhibitors may be used in Child-Pugh Class A patients while their use requires caution in Class B patients. Administration of DPP-4 inhibitors is not preferred in Class C patients.

VII. Sodium glucose co-transporter 2 inhibitors (SGLT-2i):

Canagliflozin, Dapagliflozin, and Empagliflozin are agents currently available in India. SGLT-2i share similar PK characteristics. They undergo hepatic metabolism through glucuronidation and small proportions of the parent drug are eliminated through renal route. The safety of Empagliflozin in patients with HI has been confirmed in a study investigating the effect of various degrees of HI on the PK of Empagliflozin. In patients with HI, Empagliflozin PK was affected in a very small degree. The same pattern was found for Canagliflozin. A study on the PK and safety profile of Dapagliflozin in patients with HI showed that systemic exposure to Dapagliflozin correlated with the degree of HI. Therefore, Dapagliflozin should be used with caution in these patients. Thus, SGLT-2i can be used with caution and lower doses should be considered during initiation of therapy in CLD patients. These agents are contra-indicated in severe liver dysfunction. The risk of dehydration and hypotension is associated with the use SGLT-2i hence, caution is required. Precisely, SGLT-2i are safe in Child-Pugh Class A patients, however, they should be used with caution in Class B patients. Agents of this class should better be avoided in Class C patients.

VIII. Glucagon-like peptide-1 receptor agonists (GLP-1 RA):

Hepatic metabolism is not the main pathway for the elimination of GLP-1RAs. Exenatide is primarily eliminated by kidney. Liraglutide and Dulaglutide are endogenously metabolized into their component

amino acids by general protein catabolism pathways. There is limited information available about the safety and efficacy of GLP-1RAs in HI patients, hence caution is advised on their use in this patient population. Drugs of this class can be administered to Child-Pugh Class A patients. However, due to paucity of data in HI patients, GLP-1RAs should be avoided in Class B and C patients.

In conclusion, careful and judicial selection of an antidiabetic agent is important in patients with associated CLD.

Source: *Arvanitakis K, et al. Diabetes Metab Syndr. 2024; 18(1): 102935, World J Meta Anal. 2019; 7(8): 380-388, Indian J Endocrinol Metab. 2017 Mar-Apr; 21(2): 341–354.*

SGLT2 INHIBITORS COULD REDUCE RISK OF NEPHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

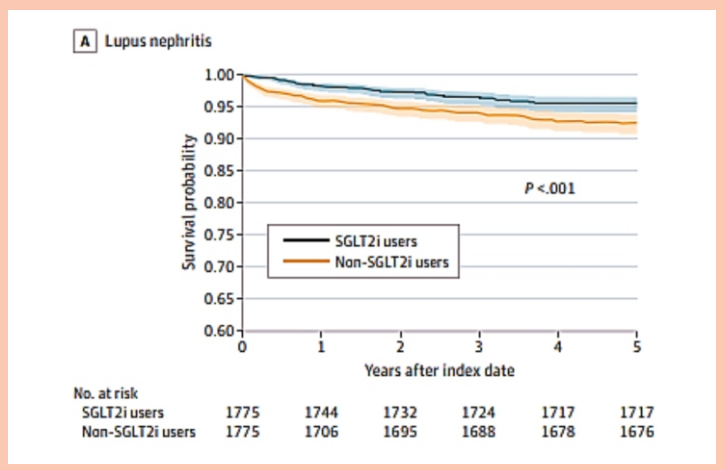
Systemic lupus erythematosus (SLE) is a relapsing and life-threatening autoimmune disease that occurs when the body's immune system has lost tolerance to its nuclear antigens. It is associated with approximately 2.2-times higher mortality rates than individuals without SLE. ***Lupus nephritis*** is the most common and severe complication of SLE affecting approximately 40% to 60% of patients. Despite significant advances in the understanding and treatment of lupus nephritis in recent years, treatment outcomes remain unsatisfactory and it remains a major cause of morbidity and mortality in patients with SLE.

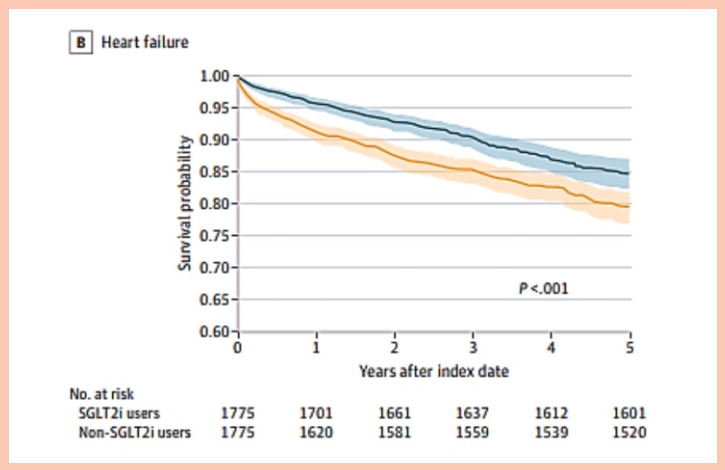
While SLE and type 2 diabetes (T2D) often do not coexist, but their combined presence may increase the risk of poor outcomes due to their association with kidney and cardiovascular disease (CVD).

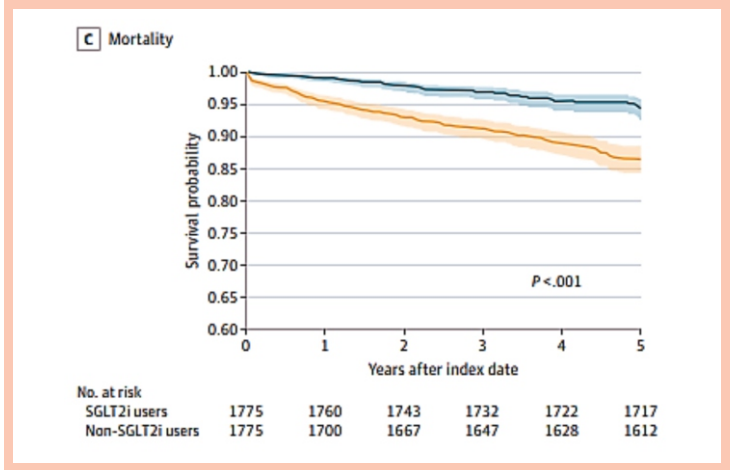
A phase I/II study found increased glucose metabolism within immune cells of individuals with SLE. Metabolic modulation to control this hyperactive immune response has emerged as a viable treatment option for SLE. Sodium-glucose cotransporter 2(SGLT2) inhibitor (SGLT2i) class is known to possess cardio-renal benefits beyond glycemic control in people with T2D. SGLT2is may reduce the risk of diabetic kidney disease by increasing glycosuria and improving glomerular hyperfiltration and a meta-analysis found it to be associated with cardio-renal protective effects mediated by reducing intraglomerular pressure. Since the development of lupus nephritis is also associated with increased intraglomerular pressure, SGLT2is may reduce the risk of lupus nephritis in patients with SLE.

Yen FS, et al (2024) recently conducted a study to examine the relationship between SGLT2i use and reduced adverse outcomes in patients with SLE and T2D. The study's findings supported the use of SGLT2is;

- Study consisted of 1775 matched pairs of SGLT2i users and nonusers with SLE and T2D.
- Use of SGLT2is was associated with significantly reduced risk of lupus nephritis, dialysis, kidney transplant, heart failure, and all-cause mortality compared with no SGLT2i use.
- The results remained consistent over a 1- to 5-year follow-up period.







✤ Possible mechanisms for SGLT2i use and lower risk of lupus nephritis

1. SGLT2is can increase natriuresis, which triggers the tubuloglomerular feedback mechanism. This results in vasoconstriction of the afferent arterioles, which attenuates intraglomerular hypertension, decreases glomerular shear stress and reduces protein levels in urine. It also reduces tubular workload, oxygen demand and injury.

2. SGLT2is may exert immunomodulatory effects by reducing DNA autoantibodies (highly specific marker of SLE), decreasing immune complex deposition in kidney tissues, attenuating kidney dysfunction and development of lupus nephritis.

3. It has been reported that SGLT2is could block lipopolysaccharide-induced and NLRP3-mediated inflammatory responses and regulate macrophage polarisation via interplay with mammalian target of rapamycin (mTOR) and AMP-activated protein kinase pathways; thereby, SGLT2is might further contribute to reducing inflammation, modulating endothelial dysfunction and decelerating atherosclerosis, which are all relevant to the pathophysiology of SLE.

4. SGLT2is can inhibit apoptosis and the production of reactive oxygen species and attenuate glomerular atrophy, kidney fibrosis, and kidney dysfunction.

In the study by Yen FS, et al, some patients had CKD and SGLT2is protective association was found to remain consistent in patients with HbA1c levels of 7% or higher, creatinine levels < 1.5 mg/dL and eGFR < 60 mL/min/1.73 m^2.

With the beneficial properties of SGLT2is, they have become appealing candidates for treating patients with SLE, especially those with lupus nephritis.

In conclusion, SGLT2is may provide multiple benefits beyond glycemic control, including nephroprotection and cardioprotection in patients with both SLE and T2D.

Source: *Yen FS, et al. JAMA Network open. 2024; 7(6):e2416578, Wang H, et al. RMD Open 2022; 8: e002686, Lancet 2022; 400: 1788–801*

Dr. Prabhu Kasture (MD, DPH)
Director Medical Services & Pharmacovigilance
Phone No.: 022-66638043
Email: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt Ltd., Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013.
Website: http://www.bluecrosslabs.com