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Review Article

Antidiabetic drugs and liver function – An update

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ABSTRACT

In a developing country like India, Type 2 Diabetes Mellitus is on the increase and this has been attributed to life style modification. Use of antidiabetic drugs are the treatment of choice to control this disease. Many brand of pharmaceutical drugs are being used depending upon its efficacy in controlling glucose, but each drug has its effect not only controlling glucose level but altering other organ functions notably liver. Six different oral hypoglycemic agents are being prescribed for Type 2 Diabetes Mellitus patients. viz, sulphonylureas, biguanides, alpha-glucosidase inhibitors, glinides, thiozolidinediones and dipeptidyl peptidase-4 inhibitors. The aim of this review article is to analyse the merits and demerits of these drugs and its effect on liver function during long time use.

Key words: Type 2 DM, Antidiabetic drugs, CLD, NAFLD, Metformin

INTRODUCTION

Drugs used in treating diabetes function by stabilizing and controlling blood glucose levels. Available data on the effectiveness of the mechanisms of actions of the antidiabetic drugs are few. Many pharmaceutical companies focus on manufacturing new brands of antidiabetic drugs.[1] Six different brands of oral hypoglycemic drugs viz., sulfonylureas, biguanides, alpha-glucosidase inhibitors, glinides, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors are being used by majority of Type 2 Diabetes Mellitus patients. This article describes the mechanism of action, side effects and clinical use in practice. Every drug therapy should be supported by lifestyle changes and the agents to be used should be selected after consideration of patient's patho-physiological state of diabetes, the presence of any complications, age, functional disorders of the liver, kidney, heart, lung and the risk for hypoglycemia.[2]

The presence of chronic liver diseases (CLD) may drastically limit the use of anti-diabetic drugs. CLD increase insulin resistance, and in some risk groups promote the development of diabetes. Therefore, antidiabetic treatment should be adapted to the severity of liver disease. However, diabetes, notably when associated with obesity and dyslipidemia, participates in the development of nonalcoholic fatty liver disease (NAFLD) and to steato-hepatitis that may progress to cirrhosis and hepatocellular carcinoma [3]. Numerous factors could favor drug-induced mitochondrial and metabolic toxicity, such as the structure of the parent molecule, genetic predispositions (in particular those involving mitochondrial enzymes), alcohol intoxication, hepatitis C virus infection, and obesity. In obese and diabetic patients, some drugs may induce acute liver injury more frequently while others may worsen the pre-existent steatosis (or steatohepatitis) [4].

Availability of the rodent diabetic models offers a unique opportunity to uncover mechanisms of clinical interest in averting human diabetic sensitivity to drug-induced hepatotoxicities. While the rat diabetic models appear to be suitable, the diabetic mouse models might not be suitable in preclinical testing for potential hepatotoxic effects of drugs or toxicants, because regardless of Type 1 or Type2 Diabetes Mellitus(Type 1 or Type 2 DM), mice are resistant to acute drug-or toxicant-induced toxicities [5].In recent years, treatment strategies have focused on the development of novel therapeutic options that affect many of the defects contributing to Type 2 DM and that provide durable glucose control through a blunting of disease progression. Optimal

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management of Type 2 DM should include early initiation of therapy using multiple drugs, with different mechanisms of action, in combination [6]. Overall, available data suggest that metformin has beneficial effects on body weight reduction and metabolic parameters, with uncertain effects on liver histology, while pioglitazone may improve liver histology. Few data, mostly preclinical, are available on DPP-4 inhibitors and Glucagon-like peptide-1(GLP-1) analogues. The heterogeneity of these studies about treatment guidelines, and further randomized, controlled studies are needed [7].

In a mouse model of intrahepatic cholestasis, metformin treatment induced Farnesoid X Receptor (FXR) phosphorylation, perturbed bile acid homeostasis, and worsened liver injury, indicating that Adenosine Mono Phosphate Kinase (AMPK) directly phosphorylates and regulates FXR transcriptional activity to precipitate liver injury under conditions favoring cholestasis [8].Metformin might be of benefit in the treatment of NAFLD, also in non-diabetic patients, when associated to hypocaloric diet and weight control. However, the heterogeneity of these studies still prevents us from reaching firm conclusions about treatment guidelines. Moreover, metformin could have beneficial tissue-specific effects in NAFLD patients irrespective of its effects as insulin sensitizer [9]. Metformin treatment was associated with significant decrease in Aortic Pulse Wave Velocity (APWV) and also apoAI in NAFLD patients. This beneficial vascular effect was accompanied by an improvement in glucose and lipid metabolism as well as liver enzymes [10].

Metformin is, if not contraindicated and if tolerated, usually preferred over other antidiabetic drugs for the first line treatment of Type2 DM. The particular decision on which antidiabetic agent to use is based on variables such as efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia, risk, and patient preferences. However, there is no guidance how to consider these in the selection of antidiabetic drug treatment. There are clear contraindications for some drugs in those with impaired renal and liver function and precautions in those with heart failure for the use of metformin and glitazones. On the other hand, GLP-1 analogs, DPP-4 inhibitors and acarbose are generally less critical and can be used in the majority of patients [11]. The combination of metformin plus a sulfonylurea is associated with a greater risk of hypoglycemia and mortality than the combination of metformin and a thiazolidinedione (ie, glitazone). Thiazolidinediones are contraindicated in patients with severe heart failure or liver disease. Newer drug classes target incretin, the hormone that stimulates food-dependent insulin secretion. The incretin mimetic exenatide, a high-cost injectable drug, is similar to metformin for reduction of HbA1c and body mass index. Incretin-enhancing dipeptidyl-peptidase 4 inhibitors (ie, gliptins) are inferior to metformin for lowering HbA1c and body mass index; little is known about their effect on all-cause mortality. Fixed combination products might improve ease of use and adherence; they might also reduce cost and risk of adverse effects [12].

Activities of hepatic and renal superoxide dismutase (SOD) and catalase (CAT), serum alkaline phosphatase, lactate dehydrogenase and alanine aminotransferase were not significantly affected in metformin and Ginkgo Biloba (GB) treated rats, whereas testicular SOD, CAT, glutathione, serum aspartate aminotransferase and conjugated bilirubin were markedly affected by metformin treatment. Histopathological results showed marked necrosis, degeneration of seminiferous tubules and defoliation of spermatocytes in testis of metformin -treated rats. Taken together, metformin and GB induced lipid peroxidation, affected seminal qualities and decreased antioxidant status. These drugs may interfere with normal biochemical processes in testis and liver of the rats [13]. Metformin decreases Protein Kinase A (PKA) activity, leading to decreased pAMPK(Ser173) and increased pAMPK(Thr172), suggesting a novel mechanism involving PKA-dependent AMPK phosphorylation that provides new insight into how glucagon and metformin modulate hepatic insulin resistance [14].

In mouse hepatocytes, metformin leads to the accumulation of AMP and related nucleotides, which inhibit adenylatecyclase, reduce levels of cyclic AMP and PKA activity, abrogate phosphorylation of critical protein targets of PKA, and block glucagon-dependent glucose output from hepatocytes. These data support a mechanism of action for metformin involving antagonism of glucagon, and suggest an approach for the development of antidiabetic drugs [15]. AMPK is dispensable for the effects of metformin on hepatic glucose output in primary hepatocytes and available data suggest that the antidiabetic effects of metformin in the liver are mediated directly by reducing energy charge [16]. Metformin-induced inhibition of glucose production was preserved under forced expression of gluconeogenic genes through Peroxisome Proliferator Activated Receptor-γ (PPAR-γ)coactivator 1alpha (PGC-1alpha) overexpression, indicating that metformin suppresses gluconeogenesis via a transcription-independent process, suggesting that metformin

inhibits hepatic gluconeogenesis in an LKB1- and AMPK-independent manner via a decrease in hepatic energy state[17].Recent data support a novel mechanism of action for metformin involving antagonism of glucagon signaling pathways by inducing the accumulation of AMP, which inhibits adenylatecyclase and reduced levels of cAMP [18].

Metformin has been reported to restore ovarian function in polycystic ovary syndrome (PCOS), reduced fatty liver, and to lower microvascular and macrovascular complications associated with Type 2DM. Its use has also recently been suggested as an adjuvant treatment for cancer or gestational diabetes and for the prevention in pre-diabetic populations. These emerging new therapeutic areas for metformin needs review together with recent findings from pharmacogenetic studies linking genetic variations to drug response, a promising new step towards personalized medicine in the treatment of Type 2DM [19].Obese, hyperglycemic mice display hepatic insulin resistance, but metformin is still effective in treating the hyperglycemia of these mice since it stimulates CREB Binding Protein (CBP) phosphorylation by bypassing the block in insulin signaling, suggesting that CBP phosphorylation at Ser436 by metformin as critical for its therapeutic effect, and as a potential target for pharmaceutical intervention [20].

Metformin, one of the most widely prescribed Type 2 DM therapeutics, requires Liver Kinase B1 (LKB1) in the liver to lower blood glucose levels [21]. As for stable liver disease, metformin and thiazolenediones have shown mixed results, with some showing them to be effective in improving liver transaminases in addition to histological improvement in steatosis and inflammation. α-glucosidase inhibitors may be helpful in decreasing hepatic encephalopathy. Upregulation of DPP-4 has been suggested as a possible pathogenetic mechanism for HCV-related insulin resistance, and treatment with DPP-4 inhibitors could improve insulin sensitivity in diabetic patients with liver disease. Patients with impaired liver function with associated insulin resistance may need increased insulin requirements. On the other hand, patients with altered liver metabolism might need decreased insulin requirements [22].

As Type 2 DM progresses in older persons, polypharmacy intensification is usually required to reach adequate glycaemic control, with the risk of adverse effects. In particular, clinical evidence shows that the use of sulfonylureas is associated with a greater risk of hypoglycaemica, whereas metformin and alpha-glucosidase inhibitors are associated with an increased risk of adverse gastrointestinal effects. The adverse effects of the recently introduced DPP-4 inhibitors are nasopharyngitis and/or upper respiratory tract infections. The literature suggests that oral antidiabetic agents are suitable for older persons; however, underappreciated risk factors, such as cognitive decline in frail individuals, have an important impact on oral antidiabetic treatment options [23].

Metformin is a promising therapeutic agent for the elimination of tumor-initiating HCC cells and suggest as-yet-unknown functions other than its inhibitory effect on the AMPK/mTOR pathway [24]. Metformin suppresses Signal Transducers and Activators Transcription (STAT3) activation via LKB1-AMPK-mTOR-independent but reactive oxygen species-related and autocrine IL-6 production-related pathways. Thus, metformin helps to overcome tumor drug resistance by targeting STAT3 [25]. Preliminary data suggested that incretin-based therapies may be beneficial in patients with CLD, more particularly in the presence of NAFLD. Nevertheless, caution should be recommended, especially in patients with advanced cirrhosis, because of a lack of clinical experience with incretin-based therapies in these vulnerable patients [26]. Specifically, safety, glycemic control, and weight were compared in patients treated with exenatide once weekly [ExQW] versus exenatide BID (ExBID), sitagliptin, pioglitazone, or insulin glargine. Moreover, measures of β-cell function, cardiovascular risk, inflammation, and hepatic health were investigated. During ExQW clinical development, consistent clinical efficacy (glycosylated hemoglobin, -1.5% to -1.9%; weight, -2 kg to -4 kg) and safety data were observed in patients with T2DM treated with ExQW [27].

The insulin-sensitizing drugs, which were biguanides (metformin) and thiazolidinediones (pioglitazone) have been shown to correct not only insulin resistance but also steatosis and inflammation in the liver. Metformin and pioglitazone might be useful drugs against non-alcoholic steatohepatitis (NASH), however further investigations were needed [28]. The thiazolidinediones are associated with an increase in body weight, although this can be avoided with careful lifestyle management. Thiazolidinediones may also lead to oedema and are associated with a low incidence of hepatocellular injury. Thiazolidinediones are contraindicated in patients with underlying heart disease who are at risk of congestive heart failure and in patients who have abnormal hepatic function. The desired blood

glucose-lowering effect and adverse event profiles of these agents should be considered when recommending these agents to diabetic patients. The potential for metformin or the thiazolidinediones to impact long-term cardiovascular outcomes remains under investigation [29]. Combination of the fixed dose of glibenclamide and simvastatin might be efficacious in patients with diabetic dyslipidemia and increased oxidative stress. Furthermore, this combination therapy offers dosage convenience to the patients and by virtue of its dual mode of action might be a useful addition to the therapeutic armamentarium for patients with diabetic dyslipidemia and oxidative stress [30].

Type 2 DM is a complex and progressive disease that is showing an apparently unstoppable increase worldwide. Although there is general agreement on the first-line use of metformin in most patients with Type 2 DM, the ideal drug sequence after metformin failure is an area of increasing uncertainty. In clinical studies, DPP-4 inhibitors were generally safe and well tolerated. However, there are limited data on their tolerability, due to their relatively recent marketing approval. Alogliptin will be used most when avoidance of hypoglycemic events is paramount, such as in patients with congestive heart failure, renal failure, and liver disease, and in the elderly [31].

A thiazolidinedione compound, pioglitazone (Actos) has been used for Type 2 DM. It ameliorates the insulin resistance of Type 2 DM and improves hyperglycemia, resulting in the decrease of HbA1c. Pioglitazone activates the nuclear peroxisome PPAR- γ which leads to increased transcription of various proteins, all of which enhance insulin action [32]. Compounds 5c and 5e were most effective in lowering the blood glucose level comparable to standard drug pioglitazone. Compound 5e exhibited potent PPAR-γ transactivation of 48.72% in comparison to pioglitazone (62.48%). All the molecules showed good glide score against the PPAR-γ target in molecular docking study. PPAR-γ gene expression was significantly increased by compound 5e (2.56-fold) in comparison to standard drug pioglitazone. Compounds 5e and 5c did not cause any damage to the liver and may be considered as promising candidates for the development of new antidiabetic agents [33]. Liver GST and G6PDH activities decreased significantly in five-week diabetic rats compared to controls and glyburide therapy restored these activities for GST and G6PDH. Elevations of hepatic antioxidant enzymes with glyburide administration suggest that glyburide may directly alter hepatic enzyme activities [34].

The beneficial pharmacology exhibited by oral insulin MSDC-0602 on insulin sensitivity suggests that PPAR-γ sparing Thiazolidinediones (TZDs)are effective for treatment of Type 2 DM with reduced risk of PPARγ-mediated side effects [35]. The activity of human and baboon hepatic microsomes in metabolizing glyburide was similar, but the activity of human and baboon placental microsomes was 7% and 0.3% of their respective hepatic microsomes. The data obtained suggest that more than 1 CYP isozyme is responsible for catalyzing the hydroxylation of glyburide [36]. Pharmacologic inhibition of DPP-4 may provide a new therapeutic option for slowing the progression of NAFLD. Future research is expected to support the efficacy and tolerability of DPP-4 modulation in early liver steatosis [37]. The anti-diabetic foot ulcer Formula 1 contains ingredients active in modifying tissue glucose homeostasis in vitro but these biological activities could not be associated with improved glycaemic control of diabetes in vivo [38].

All effects of glibenclamide are probably due to decreases in oxidative phosphorylation. Stimulation of glucose release is the opposite of what should be expected for a hypoglycemic drug and it also contrasts with some reports of diminishing effects in the presence of glucagon plus insulin. This means that the stimulatory action on glycogenolysis that was seen as a net effect could be counterbalancing inhibitory effects in vivo. This combination of events could eventually diminish the effectiveness of the drug as a hypoglycemic agent in the fed state [39]. Pioglitazone may improve insulin sensitivity both by affecting serum adipokine concentrations and by reducing the intracellular triglyceride content of liver and skeletal muscle in individuals with Type 2 DM [40].

The oral antidiabetic drugs glibenclamide, glimepiride and nateglinide inhibited the transport of the model substrate bromosulfophthalein, particularly the Organic Anion Transport Protein 2B1 (OATP2B1)-mediated uptake. The OATP-mediated atorvastatin uptake was inhibited in a similar manner. For glibenclamide, inhibitory constants (Ki values) of 13.6 μM, 8.1 μM and 0.5 μM for OATP1B1-, OATP1B3- and OATP2B1-mediated BSP uptake were determined. These in vitro results demonstrate that several oral antidiabetic drugs may influence hepatic OATP-mediated drug uptake. The in vivo consequences of these results have to be analysed in further studies [41].

Evidence suggests that obesity and insulin resistance are the major factors that contribute to the development of NAFLD. In comparing the factors that contribute to the buildup of excess calories in obesity, an imbalance of energy homeostasis can be considered as the basis. Among the peripheral signals that are generated to regulate the uptake of food, signals from adipose tissue are of major relevance and involve the maintenance of energy homeostasis through processes such as lipogenesis, lipolysis, and oxidation of fatty acids. Advances in research on adipose tissue suggest an integral role played by adipokines in NAFLD. Cytokines secreted by adipocytes, such as tumor necrosis factor-α, transforming growth factor-β, and interleukin-6, are implicated in NAFLD [42]. CBP could be phosphorylated in white blood cells (WBCs), and CBP phosphorylation in the liver and in WBCs of mice had a similar pattern of change during a fasting time course experiment. These data suggests that CBP phosphorylation in WBCs may be used as a biomarker of metformin action in the liver [43].

DPP-4 is a promising in situ marker of biliary functionality not only of normal but also of fatty rats. The approach, initially devised to investigate the behaviour of the liver during the various phases of transplantation, appears to have a much higher potentiality as it could be further exploited to investigate any pathological or stressful conditions involving the biliary tract (i.e., metabolic syndrome and cholestasis) and the response of the biliary tract to therapy and/or to surgery [44].

Pioglitazone hydrochloride is an insulin sensitizer in the TZD family and glimepiride is an insulin secretagogue in the SU family. This article reviews mechanisms of action and clinical data behind the use of these two commonly used oral hypoglycemic agents with documented efficacy and good safety profile of once-daily administration, alone or in combination with insulin or metformin, in the management of Type 2DM in terms of glycemic and non-glycemic effects, tolerability and side effects, and impact on vascular health [45]. Trigonelline was successful in improving glycemic control, metabolic parameters, and liver function in diabetic rats. It is therefore suggested that Trigonelline may be a potential agent for the treatment of type 2 DM [46].

CONCLUSIONS

Among the various antidiabetic drugs used, lower doses are being prescribed for drugs like Glipizide, glinides and glimepiside all of which has the effect of inducing hypoglycemia. They all have long lasting action. The drug of choice has been metformin which not only stimulate insulin action but also act as lipid lowering agent and rarely cause hypoglycemia. However, frequent monitoring of liver function is a must if one uses on a long term basis as some liver enzymes are said to be altered. Other drugs to have their own tolerability and some side effects. The contents of this review article will certainly be useful for diabetologists to decide on the choice of drugs to be used for the type of Diabetic patients they treat. Further research scholars could make use of this article to expand their field in Diabetes Mellitus.

CONFLICT OF INTEREST

The authors have no conflict of interests and all authors were equally involved in compiling this review article. There is no financial conflict involved in preparing and submitting this manuscript.

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