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Medical Bulletin

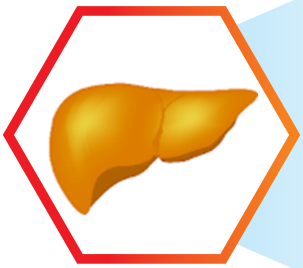
BLUE CROSS LIFE SCIENCES Division of Blue Cross Laboratories Pvt Ltd.

MULTIFACETED IMPACT OF STATIN USE ON FATTY LIVER DISEASE

The overall prevalence of metabolic associated fatty liver disease (MAFLD) is estimated at 25% of the general population in developed countries and is a major health concern. According to the definition proposed in 2020, MAFLD affects the following subjects: overweight/obese individuals with type 2 diabetes mellitus (T2DM) and normal weight persons fulfilling at least 2 criteria, mainly metabolic ones. The diagnosis of MAFLD is significant for patients' prognosis, as the disease accelerates the development of cardiovascular complications and, on the other hand, cardiometabolic conditions are risk factors for the development of fatty liver diseases. The fairly high prevalence of non-alcoholic steatohepatitis (NASH) is a significant observation, as this condition precedes the development of serious hepatological consequences in patients with MAFLD.

The high prevalence of cardiovascular conditions in patients with MAFLD is a result of the complex correlation between hepatic steatosis and classical and non-classical cardiovascular risk factors, commonly observed in this particular population. The majority of patients with MAFLD demonstrate insulin resistance, hypertension, dyslipidemia, overweight, or obesity. Patients with MAFLD demonstrate proatherogenic lipid profiles, characterized by high triglyceride levels, low-density lipoprotein cholesterol (LDL-C), reduced HDL-C, and high apolipoprotein B (apoB) levels. 2019 ESC guidelines on dyslipidemia in patients with metabolic disorders, indicated the apoB assay may be an alternative to LDL-C and preferred to non-HDL-C level assay.

CLASSIC CARDIOVASCULAR RISK FACTORS



- obesity
- hypertension
- dyslipidemia
- type 2 diabetes mellitus /pre-diabetes

Due to the common prevalence of cardiovascular conditions in patients with MAFLD, they usually present with high cardiovascular risk and require lipid-lowering agents. In patients with MAFLD, statin therapy is very effective in reducing the risk of cardiovascular morbidity and mortality, compared to patients not using statins.

The selection of a lipid-lowering drug and its dose in patients with dyslipidemia and MAFLD should be guided by its efficacy in achieving the LDL-C target values, as defined for a given cardiovascular risk group. According to an expert opinion, rosuvastatin is the preferred statin in patients with liver disease due to its pharmacokinetic profile.

The pleiotropic effects of statins go beyond their cardiovascular-protective ability and consist of anti-inflammatory, anti-thrombotic and anti-fibrotic properties and may thus inhibit progression from simple steatosis to fibrosis and non-alcoholic steatohepatitis (NASH).

The antifibrotic action of statins may be due to the inhibition of the paracrine signaling between hepatocytes and hepatic stellate cells deactivating the stellate cells, which in turn inactivates fibrogenesis.

In one of the consensus statements by experts it was agreeable that all patients with MAFLD should be considered for statin treatment due to their increased CVD risk. Statin treatment in MAFLD patients with mild-to-moderate abnormal serum liver enzymes is safe and may improve liver enzyme levels and reduce CVD morbidity and mortality. Importantly, clinicians are commonly concerned about drug-induced liver injury, but statin use is not associated with abnormal serum liver enzyme levels in patients with hepatic steatosis. Based on this, statins are thought to reduce the risk of CVD in MAFLD patients with dyslipidemia. Results from several clinical studies demonstrated that among those with metabolic dysfunction, the use of statins was significantly associated with a lower prevalence of NASH and fibrosis. Amongst statins, rosuvastatin is distinguished by its pronounced hepatic selectivity and lipid-lowering efficacy.

Rosuvastatin, a widely used statin, significantly reduced intrahepatocellular lipid (IHCL) as in moderate to severe MAFLD. The extent of IHCL reduction was clearly correlated with the degree of improvements in key lipid parameters, including low density lipoprotein-C (LDL-C), apolipoprotein-B (ApoB), triglycerides (TGs), and free fatty acids (FFAs). In one of the recent prospective, randomized, open-label study, strong evidence supporting the effectiveness of rosuvastatin, administered at a dosage of 10 mg/day for a 52-week duration, and significantly reduced the IHCL in individuals diagnosed with MAFLD.

Thus in Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), statin therapy, while primarily known for reducing cardiovascular risk, shows promise in potentially improving liver health, reducing inflammation, and even regressing steatotic lesions.

Source:*Wang et al;Diabetes & Metabolic Syndrome: Clinical Research & Reviews 18 (2024) 103126.Iwona Gorczyca, et.al;journals.viamedica.pl/polish_heart_journal,Vol 81, No 2, 2023; Ibrahim Ayada, et.al; the lancet, Vol. 87 January, 2023; Xiao-Dong Zhou et.al; Hepatology International (2023) 17:773–791.*

IMPACT OF FIXED COMBINATION OF METFORMIN AND PIOGLITAZONE ON INSULIN RESISTANCE OF PATIENTS WITH TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM), accounting for >90% of patients with diabetes, is a chronic disease characterized by insulin resistance or relative insulin deficiency. Previous epidemiological studies have revealed that the global prevalence of T2DM has significantly increased over the last four decades.

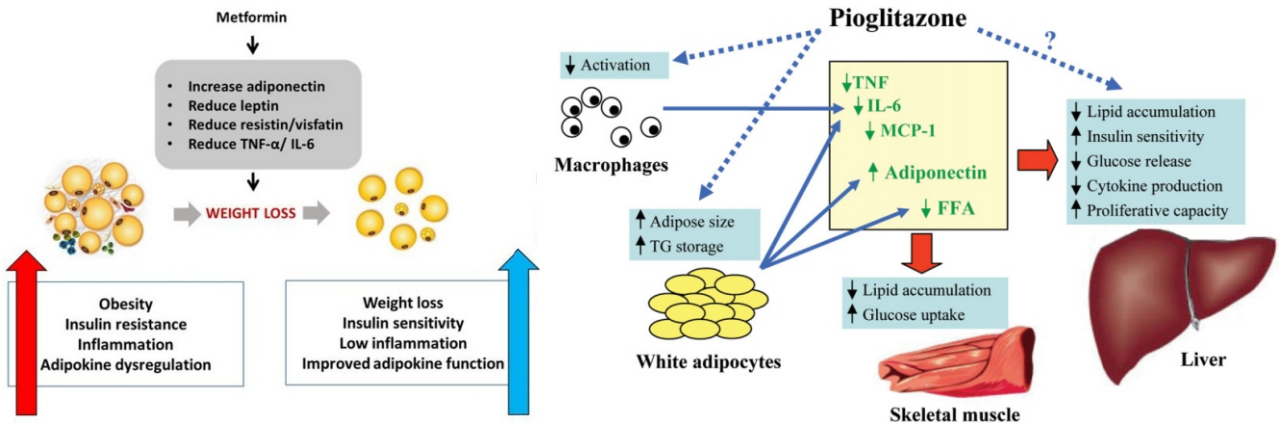
Patients with diabetes are susceptible to both microvascular and macrovascular complications, which lead to a long-term health damage and enormous economic losses. Massive studies have uncovered the fundamental pathophysiological mechanisms of insulin resistance underlying the development of T2DM. Insulin resistance is a complex condition where insulin-dependent cells, such as skeletal muscle cells and adipocytes, respond inappropriately to normal insulin levels, and thus more insulin is needed to maintain normal function. Obesity and visceral adiposity are common habitual factors aggravating insulin resistance & progression of insulin resistance worsens the burden on beta cells and contributes to hyperinsulinemia and frank diabetes. Moreover, insulin resistance has been demonstrated to be associated with an increased risk of cardiovascular events in patients with diabetes. Therefore, insulin resistance should be ameliorated early for the optimal management of T2DM.

Therapies for insulin resistance have stagnated for a number of years due to a lack of knowledge of underlying mechanisms and specific molecular drug targets. Previous studies revealed that increased glucose-fatty acid cycle, O-GlcNAcylation of key enzymes in the hexosamine biosynthesis pathway, ectopic lipid accumulation, and inflammation and endoplasmic reticulum stress associated with insulin resistance. Therefore, stimulation of fat oxidation and muscle mass and inhibition of hepatic fat synthesis with novel molecular compounds might provide an alternative strategy for insulin resistance.

Pioglitazone is a powerful insulin sensitizer that directly improves insulin sensitivity through activating insulin signaling on muscle cells. Advantages of pioglitazone, such as durable responsiveness, low risk of hypoglycemia, flexible combination with additional agents, and little influence of renal function. In patients with prediabetes, pioglitazone treatment may delay the development of T2DM with sparse serious adverse events and cardiovascular complications, according to a recent meta-analysis. Emerging evidence has also demonstrated the protective effect of a low dose of pioglitazone on liver steatosis and inflammation independent of glycemic control in patients with T2DM.

Moreover, pioglitazone can reduce the risk of myocardial infarction and ischemic stroke in primary and secondary prevention without proven direct harm on the myocardium. In vitro studies have confirmed that pioglitazone shows solid benefits on cardiomyocyte electrophysiology, ischemia-reperfusion injury, and cardiac remodeling.

Metformin is a very modest insulin sensitizer in muscle and a powerful drug targeting glucose production in liver which also provides cardiovascular protection in patients with T2DM.



Synergistic action of Metformin and Pioglitazone for reducing the insulin resistance

Metformin and pioglitazone improve insulin sensitivity through different molecular and organ-specific mechanisms. The synergistic action of metformin and pioglitazone provides a rationale for the combination of both drugs in treatment of insulin resistance. In addition to the benefits over glycemic control, improvements in diabetic dyslipidemia, inflammation, and cardiovascular events have been reported. Therefore, the fixed-dose combination of pioglitazone and metformin serves as a more convenient option for control of T2DM based on the bioequivalence between the fixed-dose combination and co-administration of individual medication.

Clinically, lean individuals with insulin resistance are not uncommon and combination of metformin and pioglitazone may be optimal option, especially for those with cardiovascular complications, poor lipid control, and low body weight.

Pioglitazone-metformin combination therapy is associated with significantly decreased levels of HOMA-IR providing greater improvement in insulin resistance when compared with metformin monotherapy in patients with T2DM.

Source: *Sun R. et al; Diabetes, Metabolic Syndrome and Obesity 2023:16*

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