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Metformin in the management of non-alcoholic fatty liver disease: current evidence and future perspectives

Metformina en el manejo del hígado graso no alcohólico: evidencia actual y perspectivas futuras

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), linked to obesity and type 2 diabetes, affects nearly one billion people globally, with rising prevalence due to both improved diagnostics and increasing incidence. In Mexico, NAFLD prevalence may exceed 50%. A particular study was conducted on 505 young adults, where 47% were at risk for non-alcoholic steatohepatitis (NASH), and 67.8% showed abnormal liver stiffness or confirmed NASH. NAFLD management requires a comprehensive approach, from early-stage lifestyle changes to targeted pharmacological treatments for advanced fibrosis or cirrhosis. Metformin, a widely used diabetes medication, shows promise in NAFLD by improving liver damage markers and insulin resistance and potentially reducing hepatocellular carcinoma risk, though evidence of significant liver histological improvements is limited. This article explores metformin's role in NAFLD treatment, focusing on its potential impact in Mexico and beyond.

RESUMEN

La enfermedad por hígado graso no alcohólico (NAFLD, por sus siglas en inglés), asociada con la obesidad y la diabetes tipo 2, afecta a casi mil millones de personas a nivel mundial, con una prevalencia en aumento debido a tanto mejoras en los métodos diagnósticos como al incremento en su incidencia. En México, la prevalencia de la NAFLD podría superar el 50%. Un estudio realizado en 505 adultos jóvenes encontró que el 47% estaba en riesgo de esteatohepatitis no alcohólica (NASH, por sus siglas en inglés) y que 67.8% presentaba rigidez hepática anormal o un diagnóstico confirmado de NASH. El manejo de la NAFLD requiere un enfoque integral, desde cambios en el estilo de vida en las etapas iniciales hasta tratamientos farmacológicos dirigidos para fibrosis o cirrosis avanzadas. La metformina, un medicamento ampliamente utilizado para la diabetes, muestra potencial en la NAFLD al mejorar los marcadores de daño hepático y la resistencia a la insulina, y podría reducir el riesgo de carcinoma hepatocelular, aunque la evidencia sobre mejoras histológicas significativas en el hígado es limitada. Este artículo analiza el papel de la metformina en el tratamiento de la NAFLD, con énfasis en su posible impacto en México y a nivel global.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a growing global concern, with prevalence linked to significant clinical and economic impact. It is estimated that this condition affects almost a third of the population worldwide. It is recognized as the most common liver disease in Western countries. A study based on data from the National Health and Nutrition Examination Survey in the United States showed that NAFLD prevalence was highest amongst Mexican Americans; the estimated prevalence of the disease could surpass 50%

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amongst this population.[1] Although national studies are lacking, the Mexican population is prone to this condition. A study conducted on 505 young Mexican adults showed that 47% were at risk of non-alcoholic steatohepatitis (NASH), and among them, 67.8% presented with abnormal liver stiffness or a confirmed diagnosis of NASH.[2] The burden of NAFLD is not only due to increased awareness and advances in diagnosis but also to a true rise in its occurrence, particularly parallel to rising obesity and type 2 diabetes rates, with estimates suggesting that approximately one billion people worldwide may be affected by NAFLD *(Figure 1)*.[3] Therefore, a simplified approach to prevention, diagnosis, and treatment is needed.[4] Lifestyle interventions, such as dietary changes and exercise, can be effective in the early stages of the disease, but as it progresses, there is a growing demand to develop pharmacological agents targeting advanced stages like fibrosis or cirrhosis.[5]

Exploring metformin as a possible therapeutic option for NAFLD and non-alcoholic steatohepatitis (NASH) is of great relevance. Metformin has been shown to have beneficial effects on NAFLD by protecting against cardiac ischemia-reperfusion injury, atherosclerosis, and pancreatic β-cell dysfunction induced by oxidative stress[6] Moreover, metformin has demonstrated therapeutic effects in NAFLD patients by improving markers such as Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG), and insulin resistance. Furthermore, insulin resistance plays a key role in the development of NAFLD and contributes to its progression from simple fatty liver to more severe conditions such as steatohepatitis, cirrhosis, and hepatocellular carcinoma. It is also recognized as a common feature in individuals with type 2 diabetes and a significant factor in its underlying pathophysiology.[7]

Studies have indicated that metformin could be a promising treatment option for NASH, with potential efficacy demonstrated in pediatric pilot data.[8] Additionally, metformin has been suggested to reduce the risk of hepatocellular carcinoma (HCC) and protect against NASH-related HCC, highlighting its potential to prevent liver cancer.[9] However, it is important to note that while metformin has weight loss and insulin-sensitizing properties, evidence supporting its efficacy in improving liver histology in NAFLD or NASH is still lacking.[10]

The purpose of the review article is to critically examine and consolidate existing knowledge on the use of metformin in the context of NAFLD.

MECHANISM OF ACTION

Metformin is a widely used oral antidiabetic medication known for its effectiveness in managing type 2 diabetes. Its mechanism of action involves several processes that contribute to its effects. Pharmacokinetically, metformin is well absorbed orally, with peak plasma

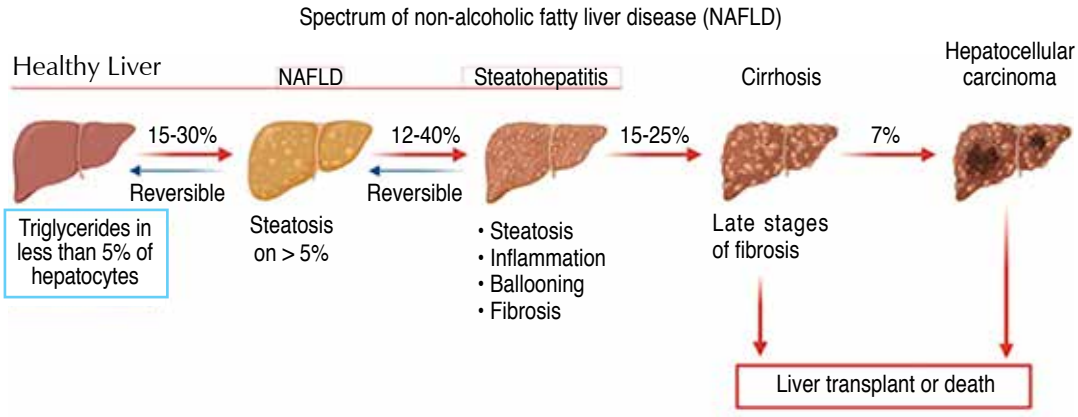

Figure 1: Spectrum of non-alcoholic fatty liver disease in NAFLD. Liver abnormalities progress from steatosis to NASH. NASH is a progressive condition that can further advance to cirrhosis and hepatocellular carcinoma (HCC). HCC = hepatocellular carcinoma. NAFLD = non-alcoholic fatty liver disease. NASH = non-alcoholic steatohepatitis.

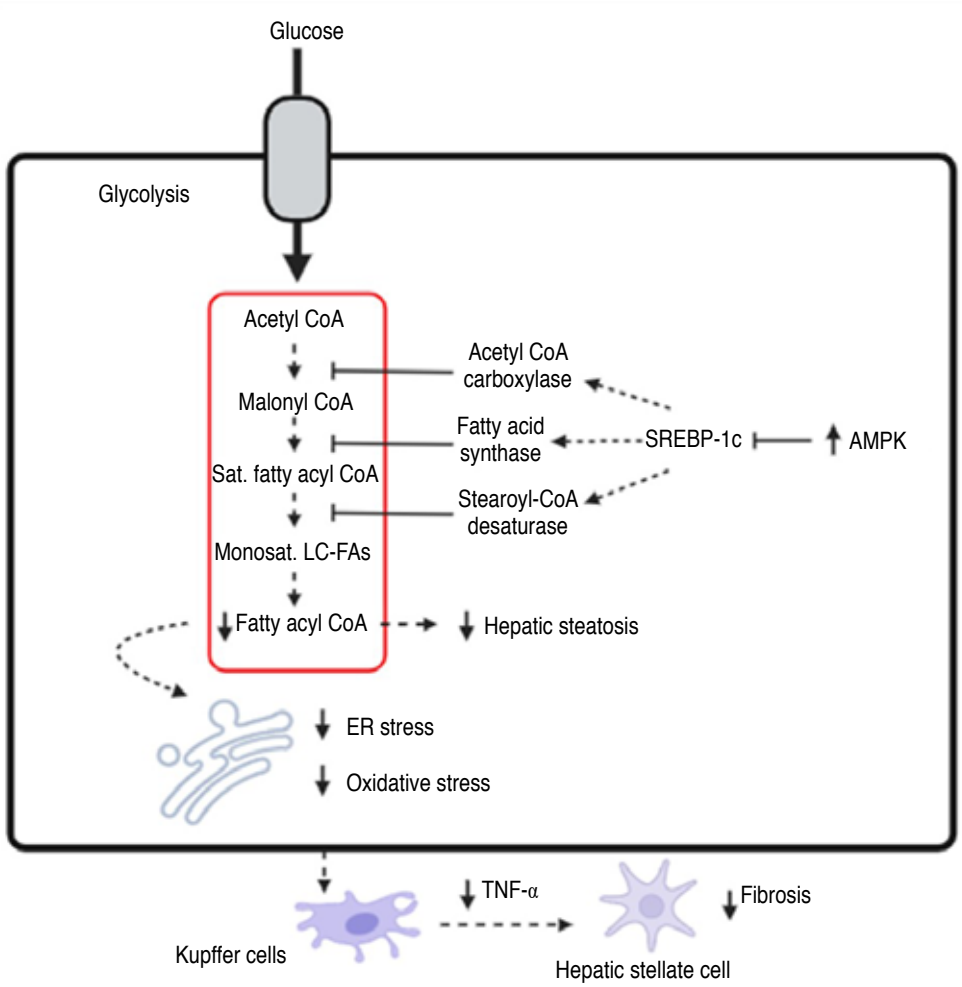

Figure 2: Metformin mechanism of action in NAFLD. Lipogenic gene expression of proteins involved in hepatic lipogenesis, including sterol regulatory element-binding protein 1 (SREBP-1c), acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase, are reduced with metformin treatment. It is speculated that these changes are related to the activation of AMPK. The resulting decrease in monounsaturated long-chain fatty acids (LC-FAs) and fatty acyl CoA also decreases hepatic steatosis by decreasing lipid-induced endoplasmic reticulum (ER) stress and decreasing substrates for fatty acid β-oxidation. Finally, reduction in oxidative stress and endoplasmic reticulum stress reduces alpha tumor necrosis factor produced by Kupffer cells, reducing hepatic stellate cell activation and resulting in a reduction of inflammation and fibrosis.

AMPK = AMP-activated protein kinase. CoA = coenzyme A. ER = endoplasmic reticulum. LC-FAs = long-chain fatty acids. NAFLD = non-alcoholic fatty liver disease. SREBP-1c = sterol regulatory element-binding protein 1. TNF-α = Tumor Necrosis Factor alpha.

concentrations reached 2 to 3 hours after administration.[11,12] It has minimal protein binding and is primarily excreted unchanged in the urine, with a half-life of approximately 6 hours.[13,14] Pharmacodynamically, metformin reduces hepatic glucose production by inhibiting gluconeogenesis, leading to lower blood glucose levels and improved insulin sensitivity.[15-17] Additionally, metformin activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy metabolism, playing a crucial role in mediating its effects on glucose and lipid metabolism.[18,19] Metformin's activation of AMPK reduces lipogenesis by inhibiting acetyl-CoA carboxylase (ACC) and decreases fatty acid oxidation, which helps to reduce the accumulation of hepatic fat, a hallmark of NAFLD progression *(Figure 2)*. By

improving mitochondrial function and reducing oxidative stress, metformin further prevents the development of steatohepatitis.[20]

Finally, by these pathways, metformin can reduce fasting and postprandial blood glucose levels by enhancing insulin sensitivity and decreasing hepatic glucose production. It also influences metabolic pathways related to glucose and lipid metabolism, contributing to its overall therapeutic effects.[21,22] Metformin's impact on glucose metabolism is further enhanced by its modulation of the cellular redox balance, affecting various metabolic pathways and cellular processes.[20]

METFORMIN AND NAFLD: KEY STUDIES

NAFLD is a spectrum of liver disorders characterized by excessive fat accumulation in the liver without significant alcohol consumption. One of the driving forces in NAFLD is insulin resistance, which results in increased lipolysis, leading to an influx of free fatty acids into the liver. This excess fat, combined with impaired mitochondrial function, promotes oxidative stress and inflammation, progressing from simple steatosis (fatty liver) to NASH, where inflammation and liver cell damage occur. Over time, this can lead to fibrosis, cirrhosis, and eventually hepatocellular carcinoma.[6]

Diagnosing NAFLD is challenging due to the absence of specific symptoms in the early stages. It is often identified incidentally during imaging for other conditions or through elevated liver enzymes in blood tests. However, the gold standard remains liver biopsy, which can differentiate between simple steatosis and NASH. Non-invasive diagnostic methods are under development, but current limitations in distinguishing disease stages hinder early intervention.[6,23]

Current treatments for NAFLD primarily revolve around lifestyle modifications, such as weight loss through diet and exercise, which remain the cornerstone of management. No specific pharmacological treatment for NAFLD has been approved yet. The limitations in treating advanced stages of the disease, such as cirrhosis or hepatocellular carcinoma, highlight the urgent need for more targeted therapies.[6,23]

In this context, metformin, a widely used drug for type 2 diabetes, has gained attention for its potential benefits in treating NAFLD. Given its effects on insulin sensitivity and hepatic glucose production, metformin could address some of the underlying drivers of NAFLD progression.

Several key studies have demonstrated the positive effects of metformin in treating NAFLD, showing improvements in liver enzyme levels and metabolic parameters. A study by Zhou et al.[6] demonstrated the therapeutic effect of metformin in treating NASH by reducing hepatic glucose production. Another study by Woo et al.[23] found that metformin had beneficial effects on improving histological parameters such as inflammation, steatosis, and fibrosis in patients with NAFLD. Feng et al.[24] compared the effects of gliclazide, liraglutide, and metformin in patients with type 2 diabetes (T2DM) and NAFLD, showing metformin's positive impact on both diabetes and NAFLD treatment. A study by Zhang et al.[9] highlighted metformin's protective mechanisms in hepatocytes and immune cells against NAFLD-related hepatocellular carcinoma (HCC). Pinyopornpanish et al.[25] found that metformin, in combination with diet, improved insulin resistance in NAFLD patients, indicating positive effects on metabolic parameters. Additionally, Green et al.[26] conducted a meta-analysis and network pharmacology study supporting metformin's efficacy in treating NAFLD, emphasizing its potential benefits on liver enzymes and glucose metabolism. These studies suggest that metformin's benefits in reducing hepatic steatosis are particularly evident in individuals with higher BMIs, potentially due to its pronounced effects on improving insulin sensitivity and reducing liver fat content.

However, while metformin has shown promise in treating NAFLD, there are challenges and limitations to its efficacy. Not all patients experienced the same degree of improvement in liver enzymes, histology, or metabolic parameters in these studies.[6,23] Metformin may be more effective in the early stages of NAFLD and might have limited efficacy in advanced disease stages, particularly in cases of severe fibrosis or cirrhosis.

Adverse effects, especially gastrointestinal side effects like diarrhea, nausea, and abdominal discomfort, are associated with metformin and may affect patient adherence.[9,25] While it showed improvements in liver enzymes and metabolic parameters, its impact on histological changes in the liver, such as fibrosis regression, was unclear.[27,28] Studies used a wide range of doses, indicating that the optimal dose and duration of metformin treatment for NAFLD are still under investigation, and individualized treatment approaches may be necessary for optimal outcomes. However, efficacy in reducing intrahepatic lipids has been demonstrated *in vivo* studies with mice, where a dose of 3 mg/kg/day orally for 5 weeks showed a decrease in hepatic triglycerides and total cholesterol and increased AMPK activity. A dose of 300 mg/kg/day orally for 6 weeks improved liver histology and delayed NAFLD development, as well as reduced NAFLD activity scores.[25]

FUTURE PERSPECTIVES

Conducting long-term studies to evaluate the sustained effects of metformin on liver enzymes, histology, and metabolic parameters in NAFLD patients is essential to determine treatment durability. Comparative studies are crucial to assess metformin's efficacy against other treatment modalities, such as lifestyle interventions, other medications, or combination therapies, to identify the most effective approach for managing NAFLD. Mechanistic studies play a vital role in investigating the underlying mechanisms of metformin action in NAFLD, including its effects on hepatic metabolism, inflammation, fibrosis, and immune response, thus elucidating the pathways involved in its therapeutic effects. Additionally, imaging studies using advanced modalities like MRI or spectroscopy are important for assessing changes in liver fat content, fibrosis, and inflammation in response to metformin treatment.[6,23,24,29]

Emerging biomarkers, such as cytokeratin-18 (CK-18) and Patatin-like phospholipase domain-containing protein 3 (PNPLA3) variants, show promise in providing non-invasive means to assess disease severity and progression in NAFLD patients. These markers may soon play a crucial role in identifying individuals at higher risk for fibrosis or hepatocellular carcinoma.

In patients with NAFLD, elevated levels of CK-18 fragments in the blood correlate with increased hepatocyte apoptosis, which is a hallmark of disease progression from simple steatosis to NASH. The ability of CK-18 to differentiate between these stages is important since NASH is associated with a higher risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma. This provides the potential to replace invasive liver biopsies in diagnosing and monitoring NASH. Elevated CK-18 levels have been validated in multiple studies as a marker of liver inflammation and fibrosis severity, making it a useful tool in both clinical trials and clinical practice for evaluating the efficacy of treatments like metformin. For instance, CK-18 could help identify NAFLD patients who are more likely to benefit from metformin therapy based on the extent of liver cell injury and disease progression.[30]

Meanwhile, PNPLA3 is a gene that encodes a protein involved in lipid metabolism. Variants in the PNPLA3 gene, particularly the I148M polymorphism, have been strongly associated with the development and progression of NAFLD. This variant is associated with an increased accumulation of triglycerides in hepatocytes, which exacerbates liver fat deposition and contributes to the progression of NAFLD. Patients with this variant are at higher risk of developing more severe forms of NAFLD, including NASH, fibrosis, cirrhosis, and hepatocellular carcinoma.[30]

The identification of PNPLA3 variants in patients could serve as a genetic biomarker for assessing disease risk and severity. Screening for PNPLA3 variants might help in stratifying NAFLD patients based on their risk for progression to severe fibrosis or HCC. This could be particularly useful for personalized treatment approaches, as individuals carrying this variant may require more aggressive management, including the consideration of therapies like metformin.[30]

Novel biomarkers hold significant potential for guiding the treatment of NAFLD. For example, elevated CK-18 levels may serve as an indicator for intensifying therapeutic interventions in patients at higher risk of

disease progression. Similarly, identifying the PNPLA3 variant in patients could facilitate early implementation of lifestyle modifications and targeted pharmacological treatments, such as metformin, to mitigate disease progression and reduce the risk of severe complications, including cirrhosis and hepatocellular carcinoma (HCC). These advancements pave the way for more personalized and effective management strategies in NAFLD care.[30]

The treatment landscape of NAFLD is evolving, focusing on identifying effective strategies for managing this condition. We are entering an era of precision medicine, so future studies should explore the potential role of genetic factors in determining individual responses to metformin treatment in NAFLD patients, leading to personalized treatment approaches.

CONCLUSION

Long-term studies are essential to evaluate metformin's effects on liver enzymes, histology, and metabolic parameters in NAFLD. Comparative studies should assess its efficacy against lifestyle interventions, other medications, or combination therapies. Mechanistic studies will further elucidate metformin's impact on hepatic metabolism, inflammation, and fibrosis.

In conclusion, while metformin shows promise for NAFLD treatment, its efficacy is context-dependent, with benefits primarily seen in early-stage disease. It holds potential for integration into a precision medicine framework, particularly when combined with other therapies or targeted interventions. Further research is warranted to establish optimal dosing, duration, and combination strategies, paving the way for personalized treatment approaches that address the complexities of NAFLD management.

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