Metformin improves aspects of obesity-associated NAFLD

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Nonalcoholic fatty liver disease (NAFLD) is known to have an intricate relationship with other metabolic diseases such as insulin resistance and obesity. While numerous studies have shown that metformin, an insulin-sensitizing agent, has beneficial effects on NAFLD, the mechanisms underlying metformin actions on NAFLD remain to be elucidated. In a recent study, the effects of metformin on the aspects of NAFLD were examined. In mice of diet-induced obesity (DIO), metformin treatment reduced hepatic steatosis and inflammation and increased the phosphorylation of liver AMP-activated protein kinase (AMPK). In the in vitro systems, metformin exhibited direct effects on hepatocyte and macrophage inflammatory responses. However, metformin appeared to have limited effects on altering adipose tissue lipid accumulation and inflammatory status. Together, metformin improves the aspects of NAFLD by reducing hepatic steatosis, and by decreasing liver inflammation due to the direct effects on suppressing hepatocyte and macrophage inflammatory responses, which all are independent of altering adiposity and adipose tissue inflammatory status.

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Non-alcoholic fatty liver disease (NAFLD) is a clinical manifestation which encompasses the whole spectrum of liver diseases including hepatic steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis without significant alcohol consumption [1]. While simple steatosis is generally considered as histologically benign, it could progress to NASH during overt liver necroinflammation, and could eventually progress to cirrhosis, liver failure and liver cancer [2]. The pathophysiology of NAFLD includes altered fatty acid metabolism and inflammatory pathways that are associated with cross-talk among residing hepatic populations, macrophages, adipose tissue, and perhaps the gut [2-4]. Since NAFLD is highly prevalent in obese and type 2 diabetic individuals [5, 6], metformin, an anti-diabetic drug and an insulin sensitizer, has been suggested in managing NAFLD. Using diet-induced obesity (DIO) mice that also display hepatic steatosis and inflammation, Woo et al. examined the effects of metformin on the aspects of NAFLD and elucidated the mechanisms underlying the beneficial effects of metformin.

Metformin treatment decreases liver fat accumulation and increases liver AMPK activation

Much evidence has shown the favorable effects of metformin on decreasing hepatic steatosis, likely through activating hepatic AMP-activated protein kinase (AMPK) [7, 8]. AMPK is an energy-sensing switch that is involved in glucose, lipid and protein metabolism. Since the discovery of AMPK, extensive research has been performed to address the signaling mechanisms of AMPK and its potential role in mediating different metabolic disease states [9]. Indeed, one of the roles that AMPK plays in human disease is highly associated with lipid metabolism in NAFLD [10], and that metformin is capable of increasing the activation of AMPK, leading to the activation of downstream cascades that results in improved hepatic lipid metabolism and decreased steatosis levels. This mechanistic action of metformin is further confirmed by a recent study [8], in which improvement of
hepatic lipid metabolism is accompanied by increased liver AMPK activation in DIO mice. Consistently, the phosphorylation of liver acetyl-coA carboxylase (ACC), a key enzyme of lipogenesis and also a substrate enzyme of AMPK, is significantly increased. These results indicate a decrease in ACC activity in response to the treatment of metformin. In addition, there is a significant decrease in hepatic mRNA levels of ACC and fatty acid synthase (FAS) in the metformin treated obese mice. These events signify a likely decrease in hepatic lipogenesis, and bring about a decrease in hepatic steatosis in the obese mice.

Metformin treatment suppresses proinflammatory responses in both hepatocytes and macrophages

Simple steatosis is a more benign form of NAFLD whereas NASH is the more severe form. As proposed by Tilg and Moschen [2], hepatic steatosis does not necessarily precede NASH, but NASH could at times lead to the development of hepatic steatosis. Nevertheless, liver inflammation is a key factor that leads to histological damage and the progression of NASH. Therefore, any agent that could inhibit or slow the progression of inflammation would be potentially beneficial for managing NAFLD. However, relative to the studies on how metformin improves hepatic steatosis, there are very limited studies that address the effect of metformin on liver inflammation. In elucidating metformin action on liver inflammation, Woo et al. provided evidence to support that metformin can directly suppress hepatocyte and macrophage inflammatory responses [8]. This is crucial because, firstly, Woo et al. validated that metformin ameliorates liver inflammation in obese mice. Secondly, in the subsequent studies using H4IIE cells (rat hepatoma cells) and bone marrow-derived macrophages (BMDMs), Woo et al. showed that metformin treatment blunted c-Jun N-terminal protein kinase 1 (JNK) and nuclear factor-κB (NF-κB) signaling under lipopolysaccharide (LPS)-treated conditions. In addition, metformin treatment markedly decreased the effect of LPS on stimulating mRNA expression levels of IL-1β, IL-6, and TNF-α in BMDMs. Notably, AMPK signaling in hepatocytes was markedly increased within the same study. This implies a potential link between hepatocyte AMPK and liver inflammation given that AMPK has been widely discussed as an upstream inhibitor of the inflammatory NF-κB cascade [11]. Thus, metformin acts to directly suppress hepatocyte and macrophage inflammatory responses during the pathology of liver inflammation. However, it remains to be determined to which extent metformin action on hepatocytes versus macrophages/Kupffer cells contributes to suppression of liver inflammation during NAFLD.

Metformin treatment shows no effects on adiposity and adipose tissue inflammation

Obesity-associated adipose tissue dysfunction contributes to the pathogenesis of NAFLD [12]. Woo et al. postulated that metformin could benefit NAFLD also by improving adipose phenotype. However, this was not the case. Compared with the control, metformin showed limited effects on adipose tissue – metformin affects neither adiposity nor the inflammatory status of adipose tissue in the obese mice. The underlying mechanisms are unknown, but could be attributable to limited effect of metformin on adipose tissue AMPK phosphorylation. Although metformin has been reported to decrease body weight in animal models and human subjects [13], this weight-lowering effect of metformin is likely secondary to a decrease in food intake [14], but not due to metformin actions on adipose tissue.

Conclusion

In summary, the study by Woo et al. provided evidence to support that metformin has beneficial effects on decreasing hepatic steatosis and inflammation in NAFLD. The beneficial effects of metformin on NAFLD are attributable to metformin actions on improving lipid metabolism in hepatocytes and on suppressing inflammatory responses in hepatocytes and macrophages, but are independent of altering adiposity and adipose tissue inflammation.

References


