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Abstract - Impact of peroxisome proliferator-activated receptor agonists on myosteatosis in the context of metabolic dysfunction-associated steatotic liver disease

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Introduction

A growing body of evidence suggests that metabolic dysfunction-associated steatotic liver disease (MASLD) could be associated with fatty infiltration of skeletal muscles, known as myosteatosis. Myosteatosis is implicated in the development of insulin resistance by altering the insulin signalling pathway, could affect muscle function and possibly contributes to the severity of liver damage. A combination of peroxisome proliferator-activated receptor (PPAR) agonists is currently being evaluated as a promising treatment for metabolic dysfunction-associated steatohepatitis (MASH), the inflammatory stage of MASLD. However, the effect of pan-PPAR agonists on myosteatosis remains to be determined.

Aim

The aim of this systematic review is to evaluate the effect of PPAR agonists and their combination on myosteatosis in the context of MASLD.

Methods

We searched for combination of terms including NAFLD, MAFLD, NASH, PPAR agonist, muscle fat and intramyocellular lipids published until March 2023 using PubMed and EMBASE. Only original articles have been retained. Articles were carefully selected and examined in order to identify relevant results that align with our research topic.

Results

Our search yielded 34 results. After reading the titles and removing duplicates, 24 articles were evaluated according to our inclusion criteria. Eleven original manuscript articles were retained to answer our research question.
The impact of the PPARα agonist on myosteatosis was assessed by triglyceride extraction in two preclinical studies in rats on a high-fat diet (HFD) and in insulin-resistant mice, and by proton magnetic resonance spectroscopy (MRS) in a clinical study in healthy and insulin-resistant elderly subjects. In rats fed a HFD, a two-week treatment significantly reduced quadriceps muscle triglyceride levels (-34%), as well as liver triglyceride levels (-54%), compared with controls. In insulin-resistant rats, it reduced quadriceps muscle (-44%) and liver (-40%) triglyceride levels compared to untreated rats. In a clinical study, a 60-day course of the PPARα agonist fenofibrate had no significant impact on soleus intramyocellular lipids (IMCL) or liver fat content in either insulin-resistant subjects or the healthy elderly group.
In two studies on myocytes, treatment with PPARδ agonist increased the expression of the fatty acid oxidation genes CD36 and CPT1b.
PPARγ agonists have been the subject of two preclinical studies and one clinical study. In the first preclinical study in Zucker diabetic fatty (ZDF) rats, treatment for one week with the PPARγ agonist rosiglitazone reduced IMCL (-40%) and hepatic steatosis (-89%) assessed by MRS and compared with the control group of ZDF rats, but had no impact on extramyocellular lipids. In a second preclinical study on ZDF rats, the PPARγ agonist pioglitazone reduced anterior tibial IMCL (-43%) assessed by proton MRS. In contrast, one year's treatment with rosiglitazone significantly increased the surface area of low density muscles (suggesting muscle fat infiltration) assessed by CT scan in patients with type 2 diabetes, while no change was observed in the placebo group.
Combinations of PPAR agonists were evaluated in two preclinical studies and one clinical study. In the first preclinical study in ZDF rats on a HFD, cevoglitazar (a dual PPARα/γ agonist) significantly reduced the IMCL of the tibialis anterior, comparable to treatment with the PPARα agonist fenofibrate and the PPARγ agonist pioglitazone alone. Only fenofibrate and cevoglitazar significantly reduced hepatocellular lipids (MRS). In another preclinical study in ZDF rats, the combination of fenofibrate (PPARα) and rosiglitazone (PPARγ) did not significantly reduce gastrocnemius muscle triglyceride content (assessed by triglyceride extraction), but did with fenofibrate alone. In addition, gastrocnemius intramuscular triglyceride content was increased in ZDF rats treated with rosiglitazone alone. In contrast, in the latest clinical trial in type 2 diabetic patients, a 4-month treatment with the PPARα/γ agonist muraglitazar significantly decreased IMCL of the tibialis anterior as well as liver fat content assessed by MRS.

Conclusions

PPAR agonists, and more specifically their combination, are a promising treatment for MASH and could also have a positive impact on reducing myosteatosis. The few discrepancies noted between the studies could be explained by the different techniques used to assess myosteatosis and the possible adipogenic effect of PPARγ agonists. Further clinical research is required to fully evaluate the efficacy of these treatments on both MASH components and myosteatosis. We believe that myosteatosis should be adequately evaluated in future studies on MASLD/MASH.