

## Current role of fenofibrate in the prevention and management of non-alcoholic fatty liver disease

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) is a common health problem with a high mortality burden due to its liver- and vascular-specific complications. It is associated with obesity, high-fat diet as well as with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS). Impaired hepatic fatty acid (FA) turnover together with insulin resistance are key players in NAFLD pathogenesis. Peroxisome proliferator-activated receptors (PPARs) are involved in lipid and glucose metabolic pathways. The novel concept is that the activation of the PPAR $\alpha$  subunit may protect from liver steatosis. Fenofibrate, by activating PPAR $\alpha$ , effectively improves the atherogenic lipid profile associated with T2DM and MetS. Experimental evidence suggested various protective effects of the drug against liver steatosis. Namely, fenofibrate-related PPAR $\alpha$  activation may enhance the expression of genes promoting hepatic FA  $\beta$ -oxidation. Furthermore, fenofibrate reduces hepatic insulin resistance. It also inhibits the expression of inflammatory mediators involved in non-alcoholic steatohepatitis pathogenesis. These include tumor necrosis factor- $\alpha$ , intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1. Consequent-

ly, fenofibrate can limit hepatic macrophage infiltration. Other liver-protective effects include decreased oxidative stress and improved liver microvasculature function. Experimental studies showed that fenofibrate can limit liver steatosis associated with high-fat diet, T2DM and obesity-related insulin resistance. Few studies showed that these benefits are also relevant even in the clinical setting. However, these have certain limitations. Namely, these were uncontrolled, their sample size was small, fenofibrate was used as a part of multi-factorial approach, while histological data were absent. In this context, there is a need for large prospective studies, including proper control groups and full assessment of liver histology.

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**Key words:** Fenofibrate; Non-alcoholic fatty liver disease; Steatohepatitis; Peroxisome proliferator-activated receptors

**Core tip:** Non-alcoholic fatty liver disease (NAFLD) is a common health problem associated with increased liver- and vascular-specific complications. Dyslipidemia, predominantly hypertriglyceridemia, and insulin resistance play a key role in its pathogenesis. Fenofibrate, by activating peroxisome proliferator-activated receptors appears to decrease liver steatosis in experimental animal studies. This benefit can be attributed to its lipid-lowering potency, together with anti-inflammatory and anti-oxidant actions. Also, fenofibrate increases adiponectin levels and the expression of its liver-active receptor. A potential protective role of fenofibrate against NAFLD has also been implied by few small clinical studies. However, this benefit should be further assessed.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a cluster of liver disorders associated with hepatic lipid accumulation (steatosis) in the absence of viral hepatitis or alcohol abuse<sup>[1]</sup>. These include a histological spectrum ranging from steatosis alone to non-alcoholic steatohepatitis (NASH)<sup>[1]</sup>. In NASH, beyond lipid accumulation, necroinflammation and fibrosis exist<sup>[2,3]</sup>. Approximately 29% of NASH patients will develop cirrhosis within 10 years<sup>[4]</sup>. End-stage liver disease and hepatocellular carcinoma are liver-specific endpoints of NAFLD<sup>[3-5]</sup>.

NAFLD is a common health problem affecting up to 35% of the population in several countries<sup>[5]</sup>. It is estimated that 19% of the United States adult population, corresponding to 28.8 million individuals, exhibit ultrasonographic findings of NAFLD<sup>[6]</sup>. Increased body weight considerably increases the risk of this abnormality. Among 257 Italian individuals obesity was associated with a 4.6-fold increased risk of hepatic steatosis<sup>[7]</sup>. Considering current obesity epidemic it is expected that NAFLD prevalence will rise.

NAFLD is typically asymptomatic<sup>[8]</sup>. Non-specific complaints include fatigue, malaise and right upper quadrant discomfort<sup>[8]</sup>. Elevation of aminotransferase activities, especially of alanine aminotransferase (ALT) and  $\gamma$ -glutamyltranspeptidase ( $\gamma$ GT), are markers of hepatocellular damage<sup>[9,10]</sup>. Lipid accumulation in the liver is identified by non-invasive imaging techniques, including ultrasound and magnetic resonance imaging (MRI)<sup>[9]</sup>. However, these techniques cannot discriminate between simple liver steatosis and NASH. In this context, liver biopsy remains the “gold standard”<sup>[11]</sup>.

From a pathophysiological viewpoint, NAFLD is associated with imbalanced influx *vs* removal of triglycerides (TG) in the liver<sup>[1]</sup>. In this context, TG accumulation > 55 mg/g measured by MRI or by histological examination is its key diagnostic feature<sup>[12,13]</sup>. Fatty acids (FA) account for approximately 60% of TG in the liver of NAFLD patients, while approximately 15% originate from dietary fat<sup>[14]</sup>. *De novo* production is responsible for the rest 25%<sup>[14]</sup>.

Insulin resistance plays a key role in the pathogenesis of NAFLD<sup>[2,15,16]</sup>. This can be attributed to enhanced hepatic FA flux and uptake<sup>[2,15,16]</sup>. Insulin resistance results in hyperinsulinemia and increased circulating levels of free FA, which enter hepatocyte cytoplasm to create TG<sup>[2,15,16]</sup>. Furthermore, high plasma insulin and glucose levels might stimulate transcription factors associated with enhanced hepatic lipogenesis<sup>[17-19]</sup>. In the clinical setting, these abnormalities are mirrored by increased circulating concentration of TG-rich lipoproteins and hypertriglyceridemia. NAFLD is commonly noted in insulin resistant states, including type 2 diabetes (T2DM) and metabolic syndrome (MetS)<sup>[20-27]</sup>. Interestingly, it was suggested

that raised activities of ALT or  $\gamma$ GT may predict future development of MetS or T2DM<sup>[20-24]</sup>. In this context, NAFLD has been considered as the “hepatic component of MetS”.

It was suggested that NAFLD increases the risk of cardiovascular (CV) events<sup>[20,28,29]</sup>. In prospective studies, raised serum activity of liver enzymes independently predicted CV events and/or total and CV mortality<sup>[20]</sup>. For example,  $\gamma$ GT activity was raised in 163 patients admitted with an acute ischemic/non-embolic stroke compared with 166 healthy individuals<sup>[30]</sup>. Interestingly, patients at the highest quartile for  $\gamma$ GT activity had a 4.7-fold higher risk of ischemic stroke than those at the lowest quartile<sup>[30]</sup>. This association was relevant after adjustment for the presence of established CV risk factors<sup>[30]</sup>. In accordance with these findings, elevated ALT activity was associated with increased CV- and diabetes-related mortality in 37085 Korean subjects<sup>[31]</sup>. Furthermore, NAFLD patients may exhibit enhanced subclinical atherosclerosis compared with non-steatotic individuals<sup>[28]</sup>. This may be explained at least in part by the coexistence of NAFLD with an atherogenic risk profile characterized by hyperlipidemia, dysglycemia and hypertension<sup>[32]</sup>. Also, in NAFLD the liver overproduces various atherogenic factors, including inflammatory cytokines, coagulation factors and molecules that increase blood pressure<sup>[32]</sup>.

To date, an established treatment of NAFLD is gradual weight loss. It was shown that dietary intervention or bariatric surgery improved liver function tests and liver histology in patients with NASH<sup>[33-35]</sup>. Also, weight reduction by orlistat might be useful<sup>[36,37]</sup>. Among 50 overweight subjects dietary intervention together with vitamin E and orlistat achieved significant weight loss<sup>[37]</sup>. Reduction  $\geq$  5 and 9% was associated with improved insulin resistance and hepatic histological findings, respectively<sup>[37]</sup>. Also, vitamin E as a potent antioxidant can improve liver histology in non-diabetic NASH. In this context, it is considered a first-line pharmacotherapy for this patient population<sup>[38]</sup>. Furthermore, pioglitazone can be useful for patients with biopsy-proven NASH<sup>[38]</sup>. However, it should be acknowledged that most patients on pioglitazone in clinical trials were non-diabetic. Also, long-term safety and efficacy has not been evaluated<sup>[38]</sup>.

## NAFLD AND LIPID-LOWERING DRUGS

Interest is increasing regarding the effect of lipid-lowering drugs on NAFLD. Long-term statin treatment has been associated with significant decreases or even normalization of serum aminotransferase activities in patients with NAFLD and dyslipidemia<sup>[39-41]</sup>. Liver steatosis assessed by either imaging techniques or biopsy was also diminished<sup>[40,41]</sup>. Interestingly, this benefit appears to be associated with greater vascular risk reduction. The Greek Atorvastatin and Coronary Heart Disease Evaluation study included 1600 patients with established coronary heart disease (CHD). These were randomized to atorvastatin or “usual” medical care to achieve low density

lipoprotein cholesterol (LDL-C) goal < 100 mg/dL<sup>[42]</sup>. Atorvastatin was more effective in reducing total and CV mortality as well as coronary morbidity compared with “usual” care<sup>[42]</sup>. A *post hoc* analysis of this study included 437 patients with moderately abnormal liver function tests at baseline possibly associated with NAFLD<sup>[43]</sup>. NAFLD was assumed in patients with moderately elevated aminotransferase activities (< 3x the upper limit of normal) together with relevant ultrasonographic findings, after excluding other causes of abnormal liver function tests<sup>[43]</sup>. Statin (mainly atorvastatin) treatment was associated with substantial improvements of aminotransferase activities, whereas non-statin use with further increases<sup>[43]</sup>. Interestingly, among patients with abnormal liver function tests those who received a statin experienced a greater reduction of CV events (69% relative risk reduction,  $P < 0.0001$ ) compared with those who did not receive a statin<sup>[43]</sup>. Furthermore, among statin-treated patients, those with abnormal liver function tests had fewer CV events compared with those with normal liver function tests (39% relative risk reduction,  $P < 0.0001$ )<sup>[43]</sup>. However, these promising findings have limitations including the *post hoc* analysis and small number of patients. Furthermore, liver biopsy was not performed.

Ezetimibe antagonizes cholesterol absorption by inhibiting Niemann-Pick C1 like-1 protein (NPC1L1)<sup>[44]</sup>. This protein is expressed by both enterocytes and hepatocytes. It was suggested that ezetimibe may be useful for the management of NAFLD by inhibiting hepatic cholesterol accumulation<sup>[45]</sup>. This can be better achieved by combinations of ezetimibe with drugs facilitating weight loss or enhancing insulin sensitivity<sup>[45]</sup>.

Fibrates are first-line drugs for reducing TG levels. In this context, they are commonly used for correcting lipid abnormalities in obese patients with MetS and T2DM<sup>[46-48]</sup>. Their hypolipidemic action is attributed to activation of the peroxisome proliferator-activated receptors (PPAR), particularly PPAR $\alpha$ <sup>[49]</sup>. PPARs control the transcription of genes regulating lipid and glucose metabolism<sup>[50]</sup>. These receptors may also modulate hepatic lipid homeostasis, inflammation and fibrosis, by directing the proliferative and inflammatory response of specific cell types<sup>[50]</sup>.

PPAR $\alpha$  isotype is highly expressed in metabolically active tissues, including the liver, muscle, intestine and brown adipose tissue<sup>[51]</sup>. PPAR $\alpha$  is predominantly expressed by hepatocytes and decreases hepatic lipid accumulation<sup>[50,51]</sup>. This is mostly attributed to a regulation of the FA transport and  $\beta$ -oxidative degradation. PPAR $\alpha$  also controls inflammatory responses by inhibiting inflammatory gene expression induced by nuclear factor kappa B (NF- $\kappa$ B)<sup>[50,51]</sup>. Furthermore, it can limit interleukin (IL)-1-associated C-reactive protein expression<sup>[50,52]</sup>. In this regard, it has been shown that PPAR $\alpha$  deficient mice are susceptible to hepatic steatosis and NASH<sup>[53-55]</sup>.

The current concept is that PPAR $\alpha$  activation may prevent these abnormalities<sup>[50,53]</sup>. Interestingly, PPAR $\alpha$  agonism reversed steatohepatitis in mice, suggesting a

potential curative role against NASH<sup>[56]</sup>. This benefit might be attributed to a downregulated expression of inflammatory genes<sup>[55]</sup>. Also, PPAR $\alpha$  activation may reverse fibrosis by reducing the expression of fibrotic markers and the number of stellate cells<sup>[56]</sup>.

## FENOFIBRATE AND NAFLD

Fenofibrate is one of the most used fibrates. This drug alone or in combination with statins improves the atherogenic serum lipid profile, by significantly reducing TG, while raising HDL-C levels<sup>[57-59]</sup>. Also, it appears to exert anti-inflammatory and anti-thrombotic actions, while improving endothelial function, particularly in patients with MetS and T2DM<sup>[47,60-63]</sup>. In this context, large clinical trials suggest that fenofibrate declines atherosclerosis progression and the risk of vascular events in patients with T2DM and dyslipidemia<sup>[64,65]</sup>. However, this benefit should be further assessed.

Interestingly, fenofibrate may improve insulin sensitivity by limiting lipid accumulation in several tissues, including the liver and muscles<sup>[66-69]</sup>. This can also be attributed to increased adiponectin together with reduced expression and plasma levels of several other adipokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), leptin, resistin and plasminogen activator inhibitor (PAI)-1<sup>[66,70,71]</sup>. Considering its hypolipidemic and insulin-sensitizing actions it could be assumed that fenofibrate is useful for the prevention and management of NAFLD. Herein, we discuss the role of fenofibrate as a potential treatment option for NAFLD.

### Mechanistic implications

Animal studies suggested a protective role of fenofibrate against NAFLD providing explanatory mechanisms. Fenofibrate prevented from high-fat diet-induced hepatic TG accumulation<sup>[72-75]</sup>. Consequently, all histological findings of NAFLD, including hepatic steatosis, necroinflammation and collagen deposition, were reversed<sup>[72-74]</sup>. These benefits were associated with its lipid-lowering together with anti-inflammatory properties. Namely, fenofibrate prevented from diet-associated weight gain and increases in circulating TG and free FA<sup>[72,73]</sup>. It was suggested that PPAR $\alpha$  activation by fenofibrate enhances hepatic FA turnover. Namely, it increased mRNA expression of FA  $\beta$ -oxidation enzymes in obese rats with T2DM<sup>[76]</sup>. These include FA transport protein, FA binding protein, carnitine palmitoyltransferase II, as well as medium- and long-chain acyl-CoA dehydrogenase and acyl-CoA oxidase<sup>[76,77]</sup>.

A high-fat diet-associated increase in the liver inflammatory gene expression may be ameliorated by fenofibrate<sup>[74]</sup>. Importantly, this effect was relevant immediately after treatment initiation, before liver steatosis occur. This finding implies a potential protective role of fenofibrate against liver inflammation resulting in NASH<sup>[74]</sup>. TNF- $\alpha$  plays a key role in NASH pathogenesis. Its plasma levels can be decreased by fenofibrate<sup>[72]</sup>. It appears that TNF- $\alpha$  hepatic expression is reduced by PPAR $\alpha$  activation<sup>[73]</sup>.

Macrophage infiltration of the liver may be also limited<sup>[72,74]</sup>. Inhibition of the liver expression of monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1 may help explain this benefit<sup>[75]</sup>. This action is PPAR $\alpha$ -dependent<sup>[75]</sup>. Anti-inflammatory properties of fenofibrate imply a protective effect against NASH.

Anti-oxidant actions may account for anti-steatotic effects of fenofibrate on the liver<sup>[73,78]</sup>. Fenofibrate reduced hepatic steatosis in mice developing hereditary NAFLD without obesity<sup>[78]</sup>. Increased expression of genes facilitating FA turnover, while reducing hepatic lipid peroxidation, were mechanisms explaining this benefit<sup>[78]</sup>.

Reducing hepatic insulin resistance may also account for protective effects of fenofibrate against NAFLD<sup>[72,73,76,79]</sup>. This may be mediated by enhanced FA  $\beta$ -oxidation together with eliminated accumulation of diacylglycerols, which have an impact on insulin signaling<sup>[79]</sup>. In this context, fenofibrate improved liver steatosis in animal models of obesity-related T2DM and hepatic insulin resistance<sup>[76,79]</sup>. Likewise, in a NASH animal model with obesity, dyslipidemia and insulin resistance fenofibrate improved insulin sensitivity and hepatic morphology, while decreasing ALT activity<sup>[77]</sup>. In this regard fenofibrate was more effective than rosiglitazone<sup>[77]</sup>. Therefore, PPAR $\alpha$  might be preferred over PPAR $\gamma$  activation for treating insulin resistance-associated NASH.

High-fat diet may adversely affect hepatic microvasculature by narrowing sinusoids and reducing hepatic microcirculatory perfusion<sup>[80]</sup>. Consequently, oxygenation of portal venules may be disturbed. It was suggested that these abnormalities promote the development of NAFLD<sup>[80]</sup>. It was suggested that PPAR $\alpha$  agonists exert beneficial effects on the microcirculation of several tissues, including the retina, kidney and nerves<sup>[80]</sup>. It appears that PPAR $\alpha$  activation inhibits various mediators of vascular damage, including lipotoxicity, inflammation, reactive oxygen species generation, endothelial dysfunction and thrombosis<sup>[80]</sup>. Also, it can influence intracellular signalling pathways associated with microvascular complications<sup>[80]</sup>. In this context, fenofibrate was associated with a slower progression of retinopathy and albuminuria in the clinical setting of T2DM<sup>[64,80-82]</sup>. It was shown that fenofibrate exerts beneficial effects on the liver microvascular environment and oxygen metabolism. Namely, it remarkably improved microvascular patency and tissue oxygenation in high-fat diet-induced NAFLD mice<sup>[83]</sup>. These findings imply a potential protective effect of the drug against T2DM-related hepatic steatosis.

Another experimental study investigated a cross-link between anti-steatotic and anti-atherosclerotic effects of fenofibrate<sup>[84]</sup>. Microparticles are small membrane vesicles produced by activated and apoptotic cells, being not only biomarkers, but also functional actors in NAFLD and atherosclerosis. In mice with atherosclerosis and NAFLD, fed with Western diet, the expression of microparticles was increased in atherosclerotic lesions and the liver<sup>[84]</sup>. Fenofibrate was associated with reduced expression of

microparticles in atherosclerotic lesions, but not in the liver<sup>[84]</sup>. Therefore, limiting microparticle expression might not help explain the protective role of fenofibrate against NAFLD.

Adiponectin is an adipokine with various functions associated with insulin sensitivity and inflammation<sup>[85-87]</sup>. Reduced adiponectin levels have been associated with increased insulin resistance and risk of vascular events<sup>[85]</sup>. Patients with MetS and/or T2DM have low circulating adiponectin levels<sup>[86,87]</sup>. These are also decreased in patients with NAFLD, possibly due to enhanced hepatic insulin resistance together with declined FA  $\beta$ -oxidation<sup>[88,89]</sup>. In contrast, recombinant adiponectin administration exerted protective effects against NAFLD in mice<sup>[90]</sup>. These were attributed to increased  $\beta$ -oxidation and limited hepatic synthesis of FA<sup>[90]</sup>. Also, liver production and plasma levels of TNF- $\alpha$  may be reduced<sup>[90]</sup>. Adiponectin downregulated aldehyde oxidase 1 *in vivo*<sup>[91]</sup>. This enzyme produces reactive oxygen species that promote cell damage and fibrogenesis<sup>[91]</sup>. Its activity is high in obesity-related hepatic steatosis<sup>[91]</sup>. Adiponectin also inhibited hepatic fibrosis by downregulating connective tissue growth factor *in vitro*<sup>[92]</sup>. This molecule promotes liver fibrosis by activating transforming growth factor (TGF)  $\beta$ <sup>[92]</sup>. PPAR $\alpha$  activation appears to play a key role in these benefits of adiponectin; thus fenofibrate exhibited the same properties<sup>[91,92]</sup>. Also, clinical and experimental studies showed that fenofibrate increases adiponectin plasma levels<sup>[93,94]</sup>. This was associated with vascular benefits of the drug and the rise in HDL-C levels<sup>[93,94]</sup>.

Except for adiponectin, its liver-specific R2 receptor (AdipoR2) appears to play a role in steatosis and inflammation. At the cellular/molecular level AdipoR2 mRNA was reduced in liver samples of patients with NASH<sup>[95,96]</sup>. It was suggested that AdipoR2 may be protective against steatosis-related hepatic insulin resistance<sup>[97]</sup>. In contrast, impairment of its expression was associated with decreases PPAR $\alpha$  signaling pathways<sup>[97]</sup>. FA load and endoplasmic reticulum stress decreased AdipoR2 levels *in vitro*<sup>[98]</sup>. Fenofibrate preserved AdipoR2 levels, while preventing from TG accumulation and endoplasmic reticulum stress<sup>[98]</sup>.

### Clinical evidence

Few clinical studies assessed the effect of fenofibrate on biochemical and imaging surrogates of NAFLD. A study included 186 patients with MetS and both biochemical and ultrasonographic evidence of NAFLD<sup>[99]</sup>. These received lifestyle advice and treatment for hypertension, impaired fasting glucose (metformin) and obesity (orlistat)<sup>[99]</sup>. For the management of dyslipidemia study participants were randomized to atorvastatin 20 mg/d or micronized fenofibrate 200 mg/d monotherapy or their combination. After 54 wk the percentage of patients having no longer biochemical or ultrasonographic evidence of NAFLD was 67%, 42% and 70% for atorvastatin, fenofibrate and combination, respectively<sup>[99]</sup>. Interestingly, each treatment option was independently associated with this benefit.

Other variables independently predicting hepatic steatosis elimination included corrections of low-grade inflammation (high-sensitivity C-reactive protein), anthropometric variables (waist circumference and body weight), the serum lipid profile (TG, LDL-C and total cholesterol levels), systolic blood pressure and glucose levels<sup>[99]</sup>. This study highlighted a potential role of multifactorial treatment, including fenofibrate, in reducing hepatic steatosis associated with MetS. However, these results should be considered under certain limitations. For example, no placebo group was included. Furthermore, no biopsy, which is the “gold standard” for NAFLD diagnosis and staging, was performed<sup>[99]</sup>. Another small study included 15 patients with T2DM randomized to fenofibrate or pioglitazone<sup>[100]</sup>. Pioglitazone significantly improved glucose homeostasis and reduced fasting TG and free fatty acid (FFA) concentrations. These changes were associated with decreased hepatic fat content assessed by MRI<sup>[100]</sup>. However, these changes were not relevant in fenofibrate-treated patients. Adding pioglitazone on fenofibrate decreased insulin resistance as well as FFA and TG levels, thereby reducing hepatic fat content<sup>[100]</sup>. This finding implies the efficacy of multifactorial treatment in restricting hepatic steatosis in T2DM, as well. In contrast, adding fenofibrate on top of pioglitazone failed to significantly decrease insulin resistance, while lowering circulating TG and FFA levels. These changes were not associated with significantly reduced hepatic steatosis<sup>[100]</sup>. Considering these, improving insulin resistance by PPAR $\gamma$  activation might be preferred over reducing TG levels for the management of T2DM-related NAFLD.

Another study included 16 patients with biopsy-confirmed NAFLD. These were treated with fenofibrate (200 mg/d) for 48 wk<sup>[101]</sup>. Fenofibrate was associated with significant improvement of the serum lipid profile and insulin sensitivity. Alkaline phosphatase and  $\gamma$ GT activities were significantly reduced<sup>[101]</sup>. The proportion of patients with abnormal aminotransferase activities (> 45 IU/L) was also decreased: 93.7% at baseline *vs* 62.5% following treatment for ALT; 50% at baseline *vs* 18.7% following treatment for AST<sup>[101]</sup>. Interestingly, a control liver biopsy at the end of the study showed a significantly decreased grade of hepatocellular ballooning degeneration compared with baseline. However, the grade of steatosis, lobular inflammation, fibrosis and NAFLD activity score did not change significantly<sup>[101]</sup>.

Data from large clinical trials are lacking. This may be attributed to the exclusion of patients with chronic liver disease due to transient increases in aminotransferase activities associated with fibrate treatment<sup>[102]</sup>. Although these elevations occur without any other signal of hepatotoxicity, moderate increases in liver function tests are an indication of adverse effect reaction in large clinical trials. This was also relevant for fenofibrate trials, including the Fenofibrate Intervention and Event Lowering in Diabetes study<sup>[64]</sup>. Also, it was suggested that aminotransferases may be direct PPAR $\alpha$  target genes<sup>[103,104]</sup>. This implies that fibrate-induced elevations in plasma aminotransferase

activities are a mechanism-related treatment effect. In this context, aminotransferase activities might be problematic as surrogates of NAFLD in studies assessing drug effects on liver steatosis.

## CONCLUSION

NAFLD is a common health problem associated with increased liver-specific as well as CV morbidity and mortality. Impaired FA turnover, often associated with insulin resistance, is its pathophysiological hallmark. In the presence of inflammation hepatic steatosis can progress to NASH and eventually cirrhosis. Weight loss, vitamin E and pioglitazone can be useful for the management of this abnormality, while the role of lipid-lowering drugs is being investigated.

PPAR $\alpha$  plays a role in the pathogenesis of NAFLD by regulating lipid and glucose metabolic pathways. The novel concept is that PPAR $\alpha$  activation may be protective and therapeutic against NAFLD. Experimental data suggested such a role of fenofibrate in the setting of high-fat diet, obesity, insulin resistance and T2DM. An improved FA turnover can help explain this benefit. Indeed, fenofibrate appears to enhance the expression of genes promoting FA  $\beta$ -oxidation. Also, its anti-inflammatory together with anti-oxidant actions may prevent from NASH-related necroinflammation, apoptosis and fibrosis. These are attributed to inhibited expression of inflammatory mediators, including TNF- $\alpha$ , MCP-1, VCAM-1 and ICAM-1, together with reduced lipid peroxidation and reactive oxygen species formation. Also, it was suggested that insulin resistance is also improved by fenofibrate. All these effects appear to be PPAR $\alpha$ -dependent. Furthermore, fenofibrate increases the expression and plasma levels of adiponectin, while preserving its liver-active receptor. Beyond insulin-sensitizing effects this adipokine enhances FA hepatic  $\beta$ -oxidation and exerts various anti-inflammatory and anti-fibrotic effects on the liver.

Data are inconclusive regarding the effect of fenofibrate on NAFLD surrogates in the clinical setting. Fenofibrate treatment as a part of multifactorial approach may be useful in MetS and T2DM. In this regard, insulin-sensitizing may be more important than lipid-lowering effects of the drug. However, this benefit should be further established by histological studies. Other limitations of available clinical studies include small sample size and the use of fenofibrate in combination with other strategies. In this context, there is a need for large prospective studies, including proper control groups and full assessment of liver histology.

## REFERENCES

- 1 **Angulo P**, Lindor KD. Non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002; **17** Suppl: S186-S190 [PMID: 12000605 DOI: 10.1046/j.1440-1746.17.s1.10.x]
- 2 **Diakou MC**, Liberopoulos EN, Mikhailidis DP, Tsianos EV, Burroughs AK, Elisaf MS. Pharmacological treatment of non-alcoholic steatohepatitis: the current evidence. *Scand J Gastroenterol* 2007; **42**: 139-147 [PMID: 17327932 DOI: 10.1080

- /00365520601058395]
- 3 **Cuadrado A**, Orive A, García-Suárez C, Domínguez A, Fernández-Escalante JC, Crespo J, Pons-Romero F. Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. *Obes Surg* 2005; **15**: 442-446 [PMID: 15826485 DOI: 10.1381/0960892053576596]
  - 4 **Caldwell S**, Argo C. The natural history of non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 162-168 [PMID: 20460906 DOI: 10.1159/000282081]
  - 5 **Bellentani S**, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). *Ann Hepatol* 2009; **8** Suppl 1: S4-S8 [PMID: 19381118 DOI: 10.1002/cld.27]
  - 6 **Lazo M**, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic Fatty liver disease in the United States: the third national health and nutrition examination survey, 1988-1994. *Am J Epidemiol* 2013; **178**: 38-45 [PMID: 23703888 DOI: 10.1093/aje/kws448]
  - 7 **Bellentani S**, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, Cristanini G, Tiribelli C. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med* 2000; **132**: 112-117 [PMID: 10644271 DOI: 10.7326/0003-4819-132-2-200001180-00004]
  - 8 **Falck-Ytter Y**, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001; **21**: 17-26 [PMID: 11296693 DOI: 10.1055/s-2001-12926]
  - 9 **Parekh S**, Anania FA. Abnormal lipid and glucose metabolism in obesity: implications for nonalcoholic fatty liver disease. *Gastroenterology* 2007; **132**: 2191-2207 [PMID: 17498512 DOI: 10.1053/j.gastro.2007.03.055]
  - 10 **Donati G**, Stagni B, Piscaglia F, Venturoli N, Morselli-Labate AM, Rasciti L, Bolondi L. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. *Gut* 2004; **53**: 1020-1023 [PMID: 15194655 DOI: 10.1136/gut.2003.027086]
  - 11 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219 [PMID: 12717402 DOI: 10.1053/jhep.2003.50193]
  - 12 **Szczepaniak K**, Person WB, Hadzi D. Experimental matrix isolation study and quantum-mechanics-based normal-coordinate analysis of the anharmonic infrared spectrum of picolinic acid N-oxide. *J Phys Chem A* 2005; **109**: 6710-6724 [PMID: 16834024 DOI: 10.1021/jp058089o]
  - 13 **Brunt EM**. Grading and staging the histopathological lesions of chronic hepatitis: the Knodell histology activity index and beyond. *Hepatology* 2000; **31**: 241-246 [PMID: 10613753 DOI: 10.1002/hep.510310136]
  - 14 **Donnelly KL**, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest* 2005; **115**: 1343-1351 [PMID: 15864352 DOI: 10.1172/JCI23621]
  - 15 **Angelico F**, Del Ben M, Conti R, Francioso S, Feole K, Fiorello S, Cavallo MG, Zalunardo B, Lirussi F, Alessandri C, Violi F. Insulin resistance, the metabolic syndrome, and non-alcoholic fatty liver disease. *J Clin Endocrinol Metab* 2005; **90**: 1578-1582 [PMID: 15598693 DOI: 10.1210/jc.2004-1024]
  - 16 **Abdeen MB**, Chowdhury NA, Hayden MR, Ibdah JA. Non-alcoholic steatohepatitis and the cardiometabolic syndrome. *J Cardiometab Syndr* 2006; **1**: 36-40 [PMID: 17675901 DOI: 10.1111/j.0197-3118.2006.05523.x]
  - 17 **Kim JB**, Sarraf P, Wright M, Yao KM, Mueller E, Solanes G, Lowell BB, Spiegelman BM. Nutritional and insulin regulation of fatty acid synthetase and leptin gene expression through ADD1/SREBP1. *J Clin Invest* 1998; **101**: 1-9 [PMID: 9421459 DOI: 10.1172/JCI1411]
  - 18 **Tobin KA**, Ulven SM, Schuster GU, Steineger HH, Andresen SM, Gustafsson JA, Nebb HI. Liver X receptors as insulin-mediating factors in fatty acid and cholesterol biosynthesis. *J Biol Chem* 2002; **277**: 10691-10697 [PMID: 11781314 DOI: 10.1074/jbc.M109771200]
  - 19 **Dentin R**, Girard J, Postic C. Carbohydrate responsive element binding protein (ChREBP) and sterol regulatory element binding protein-1c (SREBP-1c): two key regulators of glucose metabolism and lipid synthesis in liver. *Biochimie* 2005; **87**: 81-86 [PMID: 15733741 DOI: 10.1016/j.biochi.2004.11.008]
  - 20 **Lioudaki E**, Ganotakis ES, Mikhailidis DP. Liver enzymes: potential cardiovascular risk markers? *Curr Pharm Des* 2011; **17**: 3632-3643 [PMID: 22074433 DOI: 10.2174/138161211798220945]
  - 21 **Zhang Y**, Lu X, Hong J, Chao M, Gu W, Wang W, Ning G. Positive correlations of liver enzymes with metabolic syndrome including insulin resistance in newly diagnosed type 2 diabetes mellitus. *Endocrine* 2010; **38**: 181-187 [PMID: 20972737 DOI: 10.1007/s12020-010-9369-6]
  - 22 **Marchesini G**, Avagnina S, Barantani EG, Ciccarone AM, Corica F, Dall'Aglia E, Dalle Grave R, Morpurgo PS, Tomasi F, Vitacolonna E. Aminotransferase and gamma-glutamyl-transpeptidase levels in obesity are associated with insulin resistance and the metabolic syndrome. *J Endocrinol Invest* 2005; **28**: 333-339 [PMID: 15966506]
  - 23 **Forlani G**, Di Bonito P, Mannucci E, Capaldo B, Genovese S, Orrasch M, Scaldaferrri L, Di Bartolo P, Melandri P, Dei Cas A, Zavaroni I, Marchesini G. Prevalence of elevated liver enzymes in Type 2 diabetes mellitus and its association with the metabolic syndrome. *J Endocrinol Invest* 2008; **31**: 146-152 [PMID: 18362506]
  - 24 **Haffner SM**. Relationship of metabolic risk factors and development of cardiovascular disease and diabetes. *Obesity* (Silver Spring) 2006; **14** Suppl 3: 121S-127S [PMID: 16931493 DOI: 10.1038/oby.2006.291]
  - 25 **Tominaga K**, Fujimoto E, Suzuki K, Hayashi M, Ichikawa M, Inaba Y. Prevalence of non-alcoholic fatty liver disease in children and relationship to metabolic syndrome, insulin resistance, and waist circumference. *Environ Health Prev Med* 2009; **14**: 142-149 [PMID: 19568858 DOI: 10.1007/s12199-008-0074-5]
  - 26 **Almeda-Valdés P**, Cuevas-Ramos D, Aguilar-Salinas CA. Metabolic syndrome and non-alcoholic fatty liver disease. *Ann Hepatol* 2009; **8** Suppl 1: S18-S24 [PMID: 19381120]
  - 27 **Targher G**, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. *Semin Thromb Hemost* 2009; **35**: 277-287 [PMID: 19452403 DOI: 10.1055/s-0029-1222606]
  - 28 **Lizardi-Cervera J**, Aguilar-Zapata D. Nonalcoholic fatty liver disease and its association with cardiovascular disease. *Ann Hepatol* 2009; **8** Suppl 1: S40-S43 [PMID: 19381123 DOI: 10.4254/wjh.v2.i4.139]
  - 29 **Misra VL**, Khashab M, Chalasani N. Nonalcoholic fatty liver disease and cardiovascular risk. *Curr Gastroenterol Rep* 2009; **11**: 50-55 [PMID: 19166659 DOI: 10.1007/s11894-009-0008-4]
  - 30 **Korantzopoulos P**, Tzimas P, Kalantzi K, Kostapanos M, Vemmos K, Goudevenos J, Elisaf M, Milionis H. Association between serum gamma-glutamyltransferase and acute ischemic nonembolic stroke in elderly subjects. *Arch Med Res* 2009; **40**: 582-589 [PMID: 20082873 DOI: 10.1016/j.armed.2009.07.012]
  - 31 **Yun KE**, Shin CY, Yoon YS, Park HS. Elevated alanine aminotransferase levels predict mortality from cardiovascular disease and diabetes in Koreans. *Atherosclerosis* 2009; **205**: 533-537 [PMID: 19159884 DOI: 10.1016/j.atherosclerosis.2008.12.012]
  - 32 **Edens MA**, Kuipers F, Stolk RP. Non-alcoholic fatty liver disease is associated with cardiovascular disease risk markers. *Obes Rev* 2009; **10**: 412-419 [PMID: 19413701 DOI: 10.1111/j.1467-789X.2009.00594.x]

- 33 **Lam BP**, Younossi ZM. Treatment regimens for non-alcoholic fatty liver disease. *Ann Hepatol* 2009; **8** Suppl 1: S51-S59 [PMID: 19381125]
- 34 **Kim HK**, Park JY, Lee KU, Lee GE, Jeon SH, Kim JH, Kim CH. Effect of body weight and lifestyle changes on long-term course of nonalcoholic fatty liver disease in Koreans. *Am J Med Sci* 2009; **337**: 98-102 [PMID: 19214024 DOI: 10.1097/MAJ.0b013e3181812879]
- 35 **Mummadi RR**, Kasturi KS, Chennareddygar S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2008; **6**: 1396-1402 [PMID: 18986848 DOI: 10.1016/j.cgh.2008.08.012]
- 36 **Assy N**, Hussein O, Abassi Z. Weight loss induced by orlistat reverses fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis. *Gut* 2007; **56**: 443-444 [PMID: 17339254 DOI: 10.1136/gut.2006.106021]
- 37 **Harrison SA**, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. *Hepatology* 2009; **49**: 80-86 [PMID: 19053049 DOI: 10.1002/hep.22575]
- 38 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]
- 39 **Gómez-Domínguez E**, Gisbert JP, Moreno-Monteaudo JA, García-Buey L, Moreno-Otero R. A pilot study of atorvastatin treatment in dyslipemid, non-alcoholic fatty liver patients. *Aliment Pharmacol Ther* 2006; **23**: 1643-1647 [PMID: 16696815 DOI: 10.1111/j.1365-2036.2006.02926.x]
- 40 **Hyogo H**, Tazuma S, Arihiro K, Iwamoto K, Nabeshima Y, Inoue M, Ishitobi T, Nonaka M, Chayama K. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. *Metabolism* 2008; **57**: 1711-1718 [PMID: 19013295 DOI: 10.1016/j.metabol.2008.07.030]
- 41 **Hyogo H**, Yamagishi S, Maeda S, Kimura Y, Ishitobi T, Chayama K. Atorvastatin improves disease activity of non-alcoholic steatohepatitis partly through its tumour necrosis factor- $\alpha$ -lowering property. *Dig Liver Dis* 2012; **44**: 492-496 [PMID: 22265683 DOI: 10.1016/j.dld.2011.12.013]
- 42 **Athyros VG**, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, Demitriadis DS, Kontopoulos AG. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002; **18**: 220-228 [PMID: 12201623 DOI: 10.1185/030079902125000787]
- 43 **Athyros VG**, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelis ED, Theocharidou E, Karagiannis A, Mikhailidis DP. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet* 2010; **376**: 1916-1922 [PMID: 21109302 DOI: 10.1016/S0140-6736(10)61272-X]
- 44 **Kostapanos MS**, Mikhailidis DP, Elisaf MS. Adding ezetimibe to statin treatment: is LDL-C lowering the only benefit? *Future Cardiol* 2012; **8**: 813-817 [PMID: 23176685 DOI: 10.2217/fca.12.64]
- 45 **Filippatos TD**, Elisaf MS. Role of ezetimibe in non-alcoholic fatty liver disease. *World J Hepatol* 2011; **3**: 265-267 [PMID: 22059109 DOI: 10.4254/wjh.v3.i10.265]
- 46 **Filippatos TD**, Kiortsis DN, Liberopoulos EN, Georgoula M, Mikhailidis DP, Elisaf MS. Effect of orlistat, micronised fenofibrate and their combination on metabolic parameters in overweight and obese patients with the metabolic syndrome: the FenOrli study. *Curr Med Res Opin* 2005; **21**: 1997-2006 [PMID: 16368051 DOI: 10.1185/030079905X75078]
- 47 **Filippatos TD**, Gazi IF, Liberopoulos EN, Athyros VG, Elisaf MS, Tselepis AD, Kiortsis DN. The effect of orlistat and fenofibrate, alone or in combination, on small dense LDL and lipoprotein-associated phospholipase A2 in obese patients with metabolic syndrome. *Atherosclerosis* 2007; **193**: 428-437 [PMID: 16911813 DOI: 10.1016/j.atherosclerosis.2006.07.010]
- 48 **Hermans MP**. Impact of Fenofibrate on Type 2 Diabetes Patients with Features of the Metabolic Syndrome: Subgroup Analysis From FIELD. *Curr Cardiol Rev* 2010; **6**: 112-118 [PMID: 21532777 DOI: 10.2174/157340310791162686]
- 49 **Staels B**, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998; **98**: 2088-2093 [PMID: 9808609 DOI: 10.1161/01.CIR.98.19.2088]
- 50 **Tailleux A**, Wouters K, Staels B. Roles of PPARs in NAFLD: potential therapeutic targets. *Biochim Biophys Acta* 2012; **1821**: 809-818 [PMID: 22056763 DOI: 10.1016/j.bbali.2011.10.016]
- 51 **Staels B**, Koenig W, Habib A, Merval R, Lebret M, Torra IP, Delerive P, Fadel A, Chinetti G, Fruchart JC, Najib J, Maclouf J, Tedgui A. Activation of human aortic smooth-muscle cells is inhibited by PPAR $\alpha$  but not by PPAR $\gamma$  activators. *Nature* 1998; **393**: 790-793 [PMID: 9655393 DOI: 10.1038/31701]
- 52 **Kleemann R**, Gervois PP, Verschuren L, Staels B, Princen HM, Kooistra T. Fibrates down-regulate IL-1-stimulated C-reactive protein gene expression in hepatocytes by reducing nuclear p50-NF $\kappa$ B-C/EBP $\beta$  complex formation. *Blood* 2003; **101**: 545-551 [PMID: 12393563 DOI: 10.1182/blood-2002-06-1762]
- 53 **Ip E**, Farrell GC, Robertson G, Hall P, Kirsch R, Leclercq I. Central role of PPAR $\alpha$ -dependent hepatic lipid turnover in dietary steatohepatitis in mice. *Hepatology* 2003; **38**: 123-132 [PMID: 12829994 DOI: 10.1053/jhep.2003.50307]
- 54 **Abdelmegeed MA**, Yoo SH, Henderson LE, Gonzalez FJ, Woodcroft KJ, Song BJ. PPAR $\alpha$  expression protects male mice from high fat-induced nonalcoholic fatty liver. *J Nutr* 2011; **141**: 603-610 [PMID: 21346097 DOI: 10.3945/jn.110.135210]
- 55 **Stienstra R**, Mandard S, Patsouris D, Maass C, Kersten S, Müller M. Peroxisome proliferator-activated receptor  $\alpha$  protects against obesity-induced hepatic inflammation. *Endocrinology* 2007; **148**: 2753-2763 [PMID: 17347305 DOI: 10.1210/en.2007-0014]
- 56 **Ip E**, Farrell G, Hall P, Robertson G, Leclercq I. Administration of the potent PPAR $\alpha$  agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice. *Hepatology* 2004; **39**: 1286-1296 [PMID: 15122757 DOI: 10.1002/hep.20170]
- 57 **Agouridis AP**, Kostapanos MS, Tsimihodimos V, Kostara C, Mikhailidis DP, Bairaktari ET, Tselepis AD, Elisaf MS. Effect of rosuvastatin monotherapy or in combination with fenofibrate or  $\omega$ -3 fatty acids on lipoprotein subfraction profile in patients with mixed dyslipidaemia and metabolic syndrome. *Int J Clin Pract* 2012; **66**: 843-853 [PMID: 22897461 DOI: 10.1111/j.1742-1241.2012.02972.x]
- 58 **Filippatos TD**. A review of time courses and predictors of lipid changes with fenofibrin acid-statin combination. *Cardiovasc Drugs Ther* 2012; **26**: 245-255 [PMID: 22592524 DOI: 10.1007/s10557-012-6394-0]
- 59 **Filippatos TD**, Tsimihodimos V, Kostapanos M, Kostara C, Bairaktari ET, Kiortsis DN, Elisaf MS. Analysis of 6-month effect of orlistat administration, alone or in combination with fenofibrate, on triglyceride-rich lipoprotein metabolism in overweight and obese patients with metabolic syndrome. *J Clin Lipidol* 2008; **2**: 279-284 [PMID: 21291744 DOI: 10.1016/j.jacl.2008.06.001]
- 60 **Rosenson RS**. Effect of fenofibrate on adiponectin and inflammatory biomarkers in metabolic syndrome patients.

- Obesity* (Silver Spring) 2009; **17**: 504-509 [PMID: 19023279 DOI: 10.1038/oby.2008.530]
- 61 **Belfort R**, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. *J Clin Endocrinol Metab* 2010; **95**: 829-836 [PMID: 20061429 DOI: 10.1210/jc.2009-1487]
- 62 **Hamilton SJ**, Chew GT, Davis TM, Watts GF. Fenofibrate improves endothelial function in the brachial artery and forearm resistance arterioles of statin-treated Type 2 diabetic patients. *Clin Sci (Lond)* 2010; **118**: 607-615 [PMID: 20047560 DOI: 10.1042/CS20090568]
- 63 **Genest J**, Nguyen NH, Theroux P, Davignon J, Cohn JS. Effect of micronized fenofibrate on plasma lipoprotein levels and hemostatic parameters of hypertriglyceridemic patients with low levels of high-density lipoprotein cholesterol in the fed and fasted state. *J Cardiovasc Pharmacol* 2000; **35**: 164-172 [PMID: 10630748 DOI: 10.1097/00005344-200001000-00022]
- 64 **Keech A**, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366**: 1849-1861 [PMID: 16310551 DOI: 10.1016/S0140-6736(05)67667-2]
- 65 **Gerstein HC**, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]
- 66 **Buldak L**, Dulawa-Buldak A, Labuzek K, Okopien B. Effects of 90-day hypolipidemic treatment on insulin resistance, adipokines and proinflammatory cytokines in patients with mixed hyperlipidemia and impaired fasting glucose. *Int J Clin Pharmacol Ther* 2012; **50**: 805-813 [PMID: 22943927 DOI: 10.5414/CP201735]
- 67 **Koh KK**, Quon MJ, Shin KC, Lim S, Lee Y, Sakuma I, Lee K, Han SH, Shin EK. Significant differential effects of omega-3 fatty acids and fenofibrate in patients with hypertriglyceridemia. *Atherosclerosis* 2012; **220**: 537-544 [PMID: 22153696 DOI: 10.1016/j.atherosclerosis.2011.11.018]
- 68 **Li XM**, Li Y, Zhang NN, Xie YH, Shi YQ. Combination therapy with metformin and fenofibrate for insulin resistance in obesity. *J Int Med Res* 2011; **39**: 1876-1882 [PMID: 22117989 DOI: 10.1177/147323001103900531]
- 69 **Shin SJ**, Lim JH, Chung S, Youn DY, Chung HW, Kim HW, Lee JH, Chang YS, Park CW. Peroxisome proliferator-activated receptor-alpha activator fenofibrate prevents high-fat diet-induced renal lipotoxicity in spontaneously hypertensive rats. *Hypertens Res* 2009; **32**: 835-845 [PMID: 19644507 DOI: 10.1038/hr.2009.107]
- 70 **Krysiak R**, Labuzek K, Okopien B. Effect of atorvastatin and fenofibric acid on adipokine release from visceral and subcutaneous adipose tissue of patients with mixed dyslipidemia and normolipidemic subjects. *Pharmacol Rep* 2009; **61**: 1134-1145 [PMID: 20081249 DOI: 10.1016/j.regpep.2009.03.008]
- 71 **Koh KK**, Quon MJ, Lim S, Lee Y, Sakuma I, Lee YH, Han SH, Shin EK. Effects of fenofibrate therapy on circulating adipocytokines in patients with primary hypertriglyceridemia. *Atherosclerosis* 2011; **214**: 144-147 [PMID: 21075373 DOI: 10.1016/j.atherosclerosis.2010.10.023]
- 72 **Fatani S**, Itua I, Clark P, Wong C, Naderali EK. The effects of diet-induced obesity on hepatocyte insulin signaling pathways and induction of non-alcoholic liver damage. *Int J Gen Med* 2011; **4**: 211-219 [PMID: 21475632 DOI: 10.2147/IJGM.S17376]
- 73 **Hong XZ**, Li LD, Wu LM. Effects of fenofibrate and xuezhikang on high-fat diet-induced non-alcoholic fatty liver disease. *Clin Exp Pharmacol Physiol* 2007; **34**: 27-35 [PMID: 17201732 DOI: 10.1111/j.1440-1681.2007.04547.x]
- 74 **Shiri-Sverdlov R**, Wouters K, van Gorp PJ, Gijbels MJ, Noel B, Buffat L, Staels B, Maeda N, van Bilsen M, Hofker MH. Early diet-induced non-alcoholic steatohepatitis in APOE2 knock-in mice and its prevention by fibrates. *J Hepatol* 2006; **44**: 732-741 [PMID: 16466828 DOI: 10.1016/j.jhep.2005.10.033]
- 75 **Lalloyer F**, Wouters K, Baron M, Caron S, Vallez E, Vanhoutte J, Baugé E, Shiri-Sverdlov R, Hofker M, Staels B, Tailleux A. Peroxisome proliferator-activated receptor-alpha gene level differently affects lipid metabolism and inflammation in apolipoprotein E2 knock-in mice. *Arterioscler Thromb Vasc Biol* 2011; **31**: 1573-1579 [PMID: 21474829 DOI: 10.1161/ATVBAHA.110.220525]
- 76 **Seo YS**, Kim JH, Jo NY, Choi KM, Baik SH, Park JJ, Kim JS, Byun KS, Bak YT, Lee CH, Kim A, Yeon JE. PPAR agonists treatment is effective in a nonalcoholic fatty liver disease animal model by modulating fatty-acid metabolic enzymes. *J Gastroenterol Hepatol* 2008; **23**: 102-109 [PMID: 18171348 DOI: 10.1155/2012/757803]
- 77 **Cong WN**, Tao RY, Tian JY, Liu GT, Ye F. The establishment of a novel non-alcoholic steatohepatitis model accompanied with obesity and insulin resistance in mice. *Life Sci* 2008; **82**: 983-990 [PMID: 18417155 DOI: 10.1016/j.lfs.2008.01.022]
- 78 **Harano Y**, Yasui K, Toyama T, Nakajima T, Mitsuyoshi H, Mimani M, Hirasawa T, Itoh Y, Okanou T. Fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, reduces hepatic steatosis and lipid peroxidation in fatty liver Shionogi mice with hereditary fatty liver. *Liver Int* 2006; **26**: 613-620 [PMID: 16762007 DOI: 10.1111/j.1478-3231.2006.01265.x]
- 79 **Chan SM**, Sun RQ, Zeng XY, Choong ZH, Wang H, Watt MJ, Ye JM. Activation of PPAR $\alpha$  ameliorates hepatic insulin resistance and steatosis in high fructose-fed mice despite increased endoplasmic reticulum stress. *Diabetes* 2013; **62**: 2095-2105 [PMID: 23349482 DOI: 10.2337/db12-1397]
- 80 **Hiukka A**, Maranghi M, Matikainen N, Taskinen MR. PPAR $\alpha$ : an emerging therapeutic target in diabetic microvascular damage. *Nat Rev Endocrinol* 2010; **6**: 454-463 [PMID: 20567246 DOI: 10.1038/nrendo.2010.89]
- 81 **Davis TM**, Ting R, Best JD, Donoghoe MW, Drury PL, Sullivan DR, Jenkins AJ, O'Connell RL, Whiting MJ, Glasziou PP, Simes RJ, Kesäniemi YA, GebSKI VJ, Scott RS, Keech AC. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011; **54**: 280-290 [PMID: 21052978 DOI: 10.1007/s00125-010-1951-1]
- 82 **Ginsberg HN**, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563-1574 [PMID: 20228404 DOI: 10.1056/NEJMoa1001282]
- 83 **Kondo K**, Sugioka T, Tsukada K, Aizawa M, Takizawa M, Shimizu K, Morimoto M, Suematsu M, Goda N. Fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, improves hepatic microcirculatory patency and oxygen availability in a high-fat-diet-induced fatty liver in mice. *Adv Exp Med Biol* 2010; **662**: 77-82 [PMID: 20204774 DOI: 10.1007/978-1-4419-1241-1\_10]
- 84 **Baron M**, Leroyer AS, Majd Z, Lalloyer F, Vallez E, Bantubungi K, Chinetti-Gbaguidi G, Delerive P, Boulanger CM, Staels B, Tailleux A. PPAR $\alpha$  activation differently affects microparticle content in atherosclerotic lesions and liver of a mouse model of atherosclerosis and NASH. *Atherosclerosis* 2011; **218**: 69-76 [PMID: 21529810 DOI: 10.1016/j.atherosclerosis.2011.03.009]
- 85 **Villarreal-Molina MT**, Antuna-Puente B. Adiponectin: anti-inflammatory and cardioprotective effects. *Biochi-*

- mie 2012; **94**: 2143-2149 [PMID: 22796520 DOI: 10.1016/j.biochi.2012.06.030]
- 86 **Ouchi N**, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 2003; **14**: 561-566 [PMID: 14624132 DOI: 10.1097/00041433-200312000-00003]
- 87 **Matsuzawa Y**, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004; **24**: 29-33 [PMID: 14551151 DOI: 10.1161/01.ATV.0000099786.99623.EF]
- 88 **Pagano C**, Soardo G, Esposito W, Fallo F, Basan L, Donnini D, Federspil G, Sechi LA, Vettor R. Plasma adiponectin is decreased in nonalcoholic fatty liver disease. *Eur J Endocrinol* 2005; **152**: 113-118 [PMID: 15762194 DOI: 10.1530/eje.1.01821]
- 89 **Tsochatzis E**, Papatheodoridis GV, Archimandritis AJ. The evolving role of leptin and adiponectin in chronic liver diseases. *Am J Gastroenterol* 2006; **101**: 2629-2640 [PMID: 16952281 DOI: 10.1111/j.1572-0241.2006.00848.x]
- 90 **Xu A**, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest* 2003; **112**: 91-100 [PMID: 12840063 DOI: 10.1172/JCI17797]
- 91 **Neumeier M**, Weigert J, Schäffler A, Weiss TS, Schmidl C, Büttner R, Bollheimer C, Aslanidis C, Schölmerich J, Buechler C. Aldehyde oxidase 1 is highly abundant in hepatic steatosis and is downregulated by adiponectin and fenofibric acid in hepatocytes in vitro. *Biochem Biophys Res Commun* 2006; **350**: 731-735 [PMID: 17022944 DOI: 10.1016/j.bbrc.2006.09.101]
- 92 **Walter R**, Wanninger J, Bauer S, Eisinger K, Neumeier M, Weiss TS, Amann T, Hellerbrand C, Schäffler A, Schölmerich J, Buechler C. Adiponectin reduces connective tissue growth factor in human hepatocytes which is already induced in non-fibrotic non-alcoholic steatohepatitis. *Exp Mol Pathol* 2011; **91**: 740-744 [PMID: 21946149 DOI: 10.1016/j.yexmp.2011.09.006]
- 93 **Christou GA**, Tellis KC, Elisaf MC, Tselepis AD, Kiortsis DN. High density lipoprotein is positively correlated with the changes in circulating total adiponectin and high molecular weight adiponectin during dietary and fenofibrate treatment. *Hormones (Athens)* 2012; **11**: 178-188 [PMID: 22801564 DOI: 10.1194/jlr.M029934]
- 94 **Li P**, Shibata R, Maruyama S, Kondo M, Ohashi K, Ouchi N, Murohara T. Fenofibrate promotes ischemia-induced revascularization through the adiponectin-dependent pathway. *Am J Physiol Endocrinol Metab* 2010; **299**: E560-E566 [PMID: 20663986 DOI: 10.1152/ajpendo.00284.2010]
- 95 **Kaser S**, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F, Ebenbichler CF, Patsch JR, Tilg H. Adiponectin and its receptors in non-alcoholic steatohepatitis. *Gut* 2005; **54**: 117-121 [PMID: 15591515 DOI: 10.1136/gut.2003.037010]
- 96 **Ma H**, Gomez V, Lu L, Yang X, Wu X, Xiao SY. Expression of adiponectin and its receptors in livers of morbidly obese patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2009; **24**: 233-237 [PMID: 18713296 DOI: 10.1111/j.1440-1746.2008.05548.x]
- 97 **Yamauchi T**, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007; **13**: 332-339 [PMID: 17268472 DOI: 10.1038/nm1557]
- 98 **Rahman SM**, Qadri I, Janssen RC, Friedman JE. Fenofibrate and PBA prevent fatty acid-induced loss of adiponectin receptor and pAMPK in human hepatoma cells and in hepatitis C virus-induced steatosis. *J Lipid Res* 2009; **50**: 2193-2202 [PMID: 19502591 DOI: 10.1194/jlr.M800633-JLR200]
- 99 **Athyros VG**, Mikhailidis DP, Didangelos TP, Giouleme OL, Liberopoulos EN, Karagiannis A, Kakafika AI, Tziomalos K, Burroughs AK, Elisaf MS. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study. *Curr Med Res Opin* 2006; **22**: 873-883 [PMID: 16709309 DOI: 10.1185/030079906X104696]
- 100 **Bajaj M**, Suraamornkul S, Hardies LJ, Glass L, Musi N, DeFronzo RA. Effects of peroxisome proliferator-activated receptor (PPAR)-alpha and PPAR-gamma agonists on glucose and lipid metabolism in patients with type 2 diabetes mellitus. *Diabetologia* 2007; **50**: 1723-1731 [PMID: 17520238 DOI: 10.1007/s00125-007-0698-9]
- 101 **Fernández-Miranda C**, Pérez-Carreras M, Colina F, López-Alonso G, Vargas C, Solís-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 200-205 [PMID: 18261709 DOI: 10.1016/j.dld.2007.10.002]
- 102 **Balfour JA**, McTavish D, Heel RC. Fenofibrate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. *Drugs* 1990; **40**: 260-290 [PMID: 2226216 DOI: 10.2165/00003495-199040020-00007]
- 103 **Thulin P**, Rafter I, Stockling K, Tomkiewicz C, Norjavaara E, Aggerbeck M, Hellmold H, Ehrenborg E, Andersson U, Cotgreave I, Glinghammar B. PPARalpha regulates the hepatotoxic biomarker alanine aminotransferase (ALT1) gene expression in human hepatocytes. *Toxicol Appl Pharmacol* 2008; **231**: 1-9 [PMID: 18455211 DOI: 10.1016/j.taap.2008.03.007]
- 104 **Kobayashi A**, Suzuki Y, Kuno H, Sugai S, Sakakibara H, Shimoi K. Effects of fenofibrate on plasma and hepatic transaminase activities and hepatic transaminase gene expression in rats. *J Toxicol Sci* 2009; **34**: 377-387 [PMID: 19652460 DOI: 10.2131/jts.34.377]

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