Pioglitazone on nonalcoholic steatohepatitis: A systematic review and meta-analysis of 15 RCTs

Yan Zhao, Mastera,b, Wenli Zhao, PhDb,c,d, Hongwu Wang, PhDb, Ye Zhao, PhDb, Huaien Bu, PhDb, Hirokazu Takahashi, PhDb,*

Abstract: Nonalcoholic steatohepatitis is regarded as a risk factor of many liver diseases.

Methods: Relevant studies were searched from The National Library of Medicine, Cochrane Library, Elsevier, China National Knowledge Infrastructure, Web of Science and WANFANG databases. A total of 15 eligible studies were analyzed in the Reviewer Manager 5.3 software, including 7 English articles and 8 Chinese articles.

Results: Fifteen studies are selected for this meta-analysis, which includes totally 623 patients in the treatment group and 594 patients in the control group. As a result, 8 studies show that the total effective rate of the treatment group is higher than that of the control group \( Z = 3.64, 95\% \text{ confidence intervals (CI)}: 1.78 (1.31–2.43), P = .0003 \); eleven studies show that fasting plasma glucose levels of the experimental group are lower than that of the control group \( Z = 4.38, 95\% \text{ CI:} −0.95 (−1.38 to −0.53), P < .0001 \); ten studies show that glutamic-pyruvic transaminase levels of the experimental group are lower than that of the control group \( Z = 3.69, 95\% \text{ CI:} −11.16 (−18.01 to −5.51), P = .0002 \); 6 studies show that glutamic oxalacetic transaminase levels of the experimental group are lower than that of the control group \( Z = 2.43, 95\% \text{ CI:} −23.77 (−42.98 to −4.57), P = .02 \); 9 studies show that triglyceride levels of the experimental group are lower than that of the control group \( Z = 3.06, 95\% \text{ CI:} −0.62 (−1.01 to −0.22), P = .002 \); 6 studies show that the homeostasis model assessment of insulin resistance of the experimental group is lower than that of the control group \( Z = 4.50, 95\% \text{ CI:} −1.90 (−2.72 to −1.07), P < .0001 \); five studies show that the fasting insulin of the experimental group is lower than that of the control group \( Z = 3.22, 95\% \text{ CI:} −2.33 (−3.75 to −0.91), P = .001 \); 6 studies show that the glycated hemoglobin A1c of the experimental group is lower than that of the control group \( Z = 3.42, 95\% \text{ CI:} −2.25 (−3.53 to −0.96), P = .0006 \).

Conclusion: Pioglitazone intake is effective in nonalcoholic steatohepatitis management.

Abbreviations: ALT = glutamic-pyruvic transaminase, AST = glutamic oxalacetic transaminase, BMI = body mass index, CI = confidence intervals, FFA = free fatty acids, FNS = fasting insulin, FPG = fasting plasma glucose, GGT = gamma-glutamyl transpeptidase, HbA1c = glycated hemoglobin A1c, HOMA-IR = homeostasis model assessment of insulin resistance, NAFLD = nonalcoholic fatty liver disease, NASH = Nonalcoholic steatohepatitis, PPAR-γ = peroxisome proliferator activated receptor, SMD = standardized mean difference, TG = triglyceride.

Keywords: meta-analysis, nonalcoholic steatohepatitis, pioglitazone, randomized controlled trial, systematic review

1. Introduction

Nonalcoholic steatohepatitis (NASH) affects about 3% to 6% of adults and its prevalence is increasing.\(^1\) NASH is a major cause of chronic liver disease. It is closely related to obesity, dyslipidemia, diabetes and metabolic syndrome. In a small number of patients with NASH, the disease may progress and eventually lead to advanced fibrosis, cirrhosis and hepatocellular carcinoma.\(^2\) Most NASH patients have no symptom or nonspecific symptom, most commonly, patients with NASH were identified after tom, most commonly, patients with NASH were identified after
There are also many statements about its treatment. At present, there is no recognized drug therapy, and the progress of treatment is slow. Dietary and lifestyle changes are now the primary treatment for patients with NASH. Mediterranean diet can effectively reduce liver fat, even if it does not lose weight, is the most recommended diet. It is characterized by a reduction in carbohydrate intake, especially sugar and refined carbohydrates, and an increase in monounsaturated fatty acids and omega-3 fatty acids. Experimental studies show that a diet rich in omega-3 polyunsaturated fatty acids can improve insulin sensitivity; it can reduce the content of triglyceride in liver and improve steatohepatitis. Monounsaturated fatty acids have a good effect on blood lipid level. Exercise also has recognized benefits in improving overall cardiovascular health, which is the leading cause of death in NALFD patients. These benefits, including improved liver and peripheral insulin resistance, may not be associated with weight loss. One study shows that the group with high exercise intensity (>250 min/wk) has favorable changes in metabolic parameters and a significant decrease in liver fat content compared with those less than 250 min/wk. Bariatric surgery is suitable for patients with severe or morbid obesity, and a variety of operations have been performed. Most patients undergoing bariatric surgery also have NALFD. It is well known that weight loss can improve insulin sensitivity and play a beneficial role in reducing visceral fat. A new study reports that bariatric surgery can improve body mass index (BMI), insulin resistance index and other markers significantly, and NASH disappeared in 85% of patients.

Although the above general treatments have obvious effect, there is no FDA approval for specific drugs for NASH. However, the pioglitazone, a thiazolidinedione insulin sensitizer through peroxisome proliferator activated receptor (PPAR-γ), has shown some benefit in some randomized controlled trials. Studies show that the pioglitazone can improve insulin and glucose parameters, increase lipid storage in the subcutaneous adipose tissue, increase the adiponectin, and reduce the lipid toxicity of liver. However, there are still some problems worthy of attention in the clinical application of pioglitazone. Increased risk of prostate or pancreatic cancer, weight gain, fluid retention, female fracture and increased cardiovascular events.

Therefore, pioglitazone in the treatment of NASH is still controversial, which needs to be further clarified. We performed a meta-analysis to investigate the relationship between pioglitazone and NASH.

2. Methods

2.1. Research strategy

The National Library of Medicine, Cochrane Library, Elsevier, China National Knowledge Infrastructure, Web of Science and WANFANG databases were searched from their earliest records to November 2021 using the following key words: NASH and pioglitazone. The search was performed by combining the search terms with the subject words.

2.2. Inclusive criteria

The inclusion criteria are randomized controlled clinical trials. The treatment group is treated with pioglitazone alone or on the basis of conventional treatments, while the control group is treated with placebo or conventional treatment (including diet, exercise, etc.) for NASH. Trials investigating the impact of pioglitazone on at least one outcome of glutamic-pyruvic transaminase (ALT), glutamic oxalacetic transaminase (AST), BMI, weight, fasting plasma glucose (FPG), gamma-glutamyl transpeptidase (GGT), homeostasis model assessment of insulin resistance (HOMA-IR), glycated hemoglobin A1c (HbA1c), fasting insulin (FINS), fibrosis and histological improvements are considered for inclusion.
2.3. Exclusion criteria
We exclude repetitive articles; nonintervention studies such as case-control studies, case reports and experiences, theoretical studies and reviews; and nonclinical trials, such as animal tests.

2.4. Quality evaluation and data extraction
The methodological quality of the included studies is evaluated based on the quality assessment criteria recommended in the Cochrane systematic review manual. The main evaluation criteria include the following: a randomly assigned method, allocation concealment, use of blinding, data integrity, selectively reported results, and the presence of bias (“low risk” indicates a low risk of bias; “high risk” indicates a high risk of bias; and “unclear risk” indicates that the literature does not provide sufficient information for bias assessment). The data quality was evaluated by 2 independent researchers. Inconsistent opinions were resolved via a discussion or by soliciting the advice of a third party regarding the inclusion of a particular study.

2.5. Statistical analysis
All statistical analyses were performed using Review Manager (version.5.3). The risk ratio is used for count data, while the standardized mean difference (SMD) is adopted for continuous variables as effect size. Respectively, both are demonstrated with the effect size and 95% confidence intervals (CI). If there is no heterogeneity among the studies, that is, a P-value greater than .10 or I² less than 50%. It is explained that the heterogeneity of the research is small, and the fixed effect model is used to analyze. A P-value less than .10 or I² greater than 50% suggested that there is obvious heterogeneity among the included studies, and the random effect model is used to combine the effect volume. The bias of the study is analyzed by funnel plot.

3. Results
3.1. Study selection
A total of 1822 articles are searched from English and Chinese databases. 1135 of which are duplicated and 1120 are generally excluded based on the inclusion criteria. Finally, 15 eligible articles are included in the meta-analysis. The study selection procedure is outlined in Figure 1.

3.2. Study characteristics and quality
The study information is shown in Table 1, and the quality of the study evaluation is shown in Table 2.

3.3. Meta-analysis of outcome
3.3.1. Total effective rate. In general, 8 studies use the total effective rate as an indicator of the effectiveness of pioglitazone-guided interventions. The results are shown in Figure 2. A total of 462 patients with NASH are included in this evaluation (284 in the experimental group and 178 in the control group). The heterogeneity test shows that the heterogeneity is large (I² = 0.89), so the random effect model is used. The results show that the difference is significant, the effective rate of the experimental group is 78% higher than that of the control group [risk ratio = 1.78, 95% CI: (1.31–2.43)].

3.3.2. Weight. Five studies use the weight as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 420 patients with NASH are included in this evaluation (215 in the experimental group and 205 in the control group), according to the results of meta-analysis (P = .37, I² = 0%). No heterogeneity is found between the studies, so why the fixed effect model is used to calculate. There is no significant difference in changes in weight between the experimental group and the control group. The results are shown in Figure 3.

3.3.3. Body mass index. Seven studies use BMI as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 606 patients with NASH are included in this evaluation (310 in the experimental group and 296 in the control group). The heterogeneity was large (P = .002, I² = 0.71), so the random effect model is used. Changes in BMI between the experimental group and the control group are no significant, as shown in Figure 4.

3.3.4. FPG level. Eleven studies use the FPG level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 972 patients with NASH are included in this evaluation (494 in the experimental group and 478 in the control group). The heterogeneity is large (P < .00001, I² = 0.90). So, the random effect model is used. The meta-analysis shows that the FPG level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [SMD = −0.95, 95% CI: (−1.38 to −0.53)], as shown in Figure 5.

3.3.5. ALT level. Ten studies use the ALT level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 851 patients with NASH are included in this evaluation (431 in the experimental group and 420 in the control group). The heterogeneity is large (P < .00001, I² = 0.89). So, the random effect model is used. Changes in the ALT level between the experimental group and the control group are significant. The ALT level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [Z = 3.69, P = .0002, MD = −11.76, 95% CI: (−18.01 to −5.51)], as shown in Figure 6.

3.3.6. AST level. Six studies use the AST level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 627 patients with NASH are included in this evaluation (317 in the experimental group and 310 in the control group). The heterogeneity is small (P = .16, I² = 0.37). So, the fixed effect model is used. The meta-analysis shows that the AST level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [Z = 7.40, P < .0001, MD = −3.01, 95% CI: (−4.57 to −1.44)], as shown in Figure 7.

3.3.7. GGT level. Six studies use the GGT level as an indicator of the effectiveness of pioglutazone-guided interventions. A total of 580 patients with NASH are included in this evaluation (291 in the experimental group and 289 in the control group). The heterogeneity is large (P = .0002, I² = 0.79). So, the random effect model is used. Changes in the GGT level between the experimental group and the control group are significant. The GGT level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [Z = 2.43, P = .02, MD = −23.77, 95% CI: (−42.98 to −4.57)], as shown in Figure 8.

3.3.8. TG level. Nine studies use the TG level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 743 patients with NASH are included in this evaluation (380 in the experimental group and 363 in the control group). The heterogeneity is large (P < .00001, I² = 0.85). So, the random effect model is used. The meta-analysis shows that the TG level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [Z = 3.06,
3.3.9. HOMA-IR. Six studies use the HOMA-IR as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 467 patients with NASH are included in this evaluation (239 in the experimental group and 228 in the control group). The heterogeneity is large ($P < .00001$, $I^2 = 0.99$). So, the random effect model is used. Changes in the HOMA-IR between the experimental group and the control group are significant. The HOMA-IR level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [$Z = 3.22$, $P = .001$, MD = $-2.33$, 95% CI: $(-3.75$ to $-0.91)$], as shown in Figure 10.

3.3.10. HbA1c level. Six studies use the HbA1c level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 432 patients with NASH are included in this evaluation (226 in the experimental group and 206 in the control group). The heterogeneity is large ($P < .00001$, $F = 1.00$). So, the random effect model is used. Changes in the HbA1c level between the experimental group and the control group are significant. The HbA1c level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [$Z = 4.50$, $P < .00001$, MD = $-1.90$, 95% CI: $(-2.72$ to $-1.07)$], as shown in Figure 11.

3.3.11. FNS level. Five studies use the FNS level as an indicator of the effectiveness of pioglitazone-guided interventions. A total of 406 patients with NASH are included in this evaluation (208 in the experimental group and 198 in the control group). The heterogeneity is large ($P < .00001$, $F = 0.96$). So, the random effect model is used. Changes in the FNS level between the experimental group and the control group are significant. The FNS level of NASH patients treated with pioglitazone are lower than those received the placebo or conventional treatments [$Z = 3.42$, $P = .0006$, SMD = $-2.25$, 95% CI: $(-3.53$ to $-0.96)$], as shown in Figure 12.
3.3.12. Adverse reactions. No major adverse reactions are reported in all studies, although some patients had adverse events (21 cases of lower extremity edema, 1 case of right upper abdominal pain, 1 case of right upper abdominal pain, 1 case of vertigo, 1 case of diarrhea, 1 case of headache, 3 cases of mild liver enzyme elevation). After symptomatic medication, the symptoms disappeared automatically, which did not affect the follow-up study. However, its safety is still worthy of further study.

3.3.13. Publication bias. As shown in Figure 13, based on the FPG level, funnel plot is applied to evaluate the publication biases of all 15 studies. The results show no publication bias.

4. Discussion

4.1. Analysis of pioglitazone efficacy

In this meta-analysis, pioglitazone has a certain effect on patients with NASH. It can effectively improve the degree of NASH, liver function and blood glucose. Also, there is no major adverse events in the study. The change of each index comes from different mechanism. As demonstrated in the meta-analysis, the total effective rate of the experimental group for NASH patients rose by about 78% compared with that of the control group. The main reason may be that pioglitazone can improve the sensitivity of target tissue to insulin, reduce insulin resistance and regulate blood lipid.[43] Most other parameters are lower in the experimental group than those in the control group. But there is no
significant changing difference in weight or BMI. The main reason for the decline of FPG level may be that pioglitazone regulates the genes’ transcription related to insulin, so it may control the generation, transportation and utilization of the blood glucose. Pioglitazone downgrades fasting glucose by enhancing insulin-induced suppression of gluconeogenesis and glycogenolysis rather than by altering insulin resistance.
than by glucagon reduction.[44] The main reason for the decline of HbA1c and TG level may be that pioglitazone can also increase uncoupling protein 1 expression in adipocytes and promote the energy consumption.[45] Moreover, pioglitazone can significantly reduce ALT, AST, and GGT. All results indicate that pioglitazone can control the liver enzyme spectrum caused by fatty liver.

Considering the mechanism on reducing the steatosis and inflammation of liver, pioglitazone can promote the

| Figure 6. The experimental group compared with the control group in ALT changes after treatment. ALT = glutamic-pyruvic transaminase. |
| Figure 7. The experimental group compared with the control group in AST changes after treatment. AST = glutamic oxalacetic transaminase. |
| Figure 8. The experimental group compared with the control group in GGT changes after treatment. GGT = gamma-glutamyl transpeptidase. |
| Figure 9. The experimental group compared with the control group in TG changes after treatment. TG = triglyceride. |
differentiation of white adipocytes, increase the number of small adipocytes and reduce the number of large adipocytes after activating PPARγ in the body. Small adipocytes are more sensitive to insulin, which can promote glucose uptake, promote energy consumption and reduce the storage of excess energy in adipose tissue.[46] A declining of FNS and HOMA-IR indicates that pioglitazone does not promote the secretion of islet β cells, however, it can increase the tissues’ insulin sensitivity. The main reason for the decline of FNS and HOMA-IR level may be that pioglitazone can down regulate the expression of tumor necrosis factor-α, leptin and resistin genes, and these cytokines are closely related to insulin resistance, which may be 1 of the mechanisms of pioglitazone enhancing insulin sensitivity.[47]

4.2. Limitations

Although the 15 articles included in this meta-analysis prove that pioglitazone is useful, there are still some limitations: Firstly, there are some differences in the condition and basic treatments of NASH among the studies, which is also the reason for the heterogeneity of some indicators. Secondly, only Chinese and English literatures are included, and other languages are not involved. Language restrictions may lead to inappropriate results. Thirdly, all clinical studies have small sample size which may affect the reliability of the analysis results. Finally, the RCTs included in this study are biased in research design, methodology and result reporting. The details provided, such as randomization method, allocation concealment and blind method, are insufficient. Therefore, the evidence strength of the results is affected.

4.3. Applications prospects

In recent years, NASH becomes a serious public health problem. Its symptoms and related complications seriously affect the quality of patients’ lives.[48] Pioglitazone is an insulin sensitizer that selectively activates PPAR-γ.[49] PPARs are the main regulators of genes related to the glucose metabolism and the fat metabolism.[50] Pioglitazone can promote the uptake and up-regulate the expression of the insulin receptor substrate-1.[51] It can reduce the level of serum fatty acids and improve the insulin sensitivity of liver, muscle and adipose tissue. So, pioglitazone can achieve the purpose of treating NASH.[52] The liver damage caused by NASH is mainly manifested by the abnormal biochemical indexes of liver function. ALT, AST and GGT are commonly used in clinical practice to reflect the liver function.[53] Among them, ALT mainly exists in mitochondria of hepatocytes, and the intracellular concentration is 1000 to 3000 times higher than that of serum.[54] The concentration of AST in normal human serum is very low.
GGT mainly exists in the intrahepatic bile duct epithelium and the cytoplasm of hepatocytes. When the intrahepatic and extrahepatic bile duct obstruction can lead to the increase of GGT in serum. When the liver lesions are serious, a large number of hepatocytes and serious damage, GGT will increase. In this meta-analysis, liver function indexes are significantly different before and after the pioglitazone treatment. ALT, AST and GGT are significantly decreased. However, some studies have shown that weight gain is common in patients taking thiazolidine 2 ketone drugs, which can cause fluid retention and congestive heart failure. In addition, studies on the effect of pioglitazone withdrawal also show a significant rebound in the ALT.

5. Conclusion
Pioglitazone intake is effective in NASH management, including the total effective rate and other related clinical indexes. The treatment of NASH needs to be further verified.

Acknowledgments
The authors thank Dr Bin Wang for assistance with data extraction.

Author contributions
All authors contributed to the design and concept, performed the literature searches, wrote the manuscript and critiqued the successive versions, and approved the final manuscript. YZ coordinated the effort and integrated the sections and comments.

Conceptualization: Wenli Zhao, Huaien Bu.
Data curation: Yan Zhao.
Formal analysis: Yan Zhao, Ye Zhao.
Funding acquisition: Hongwu Wang.
Investigation: Yan Zhao, Ye Zhao.
Methodology: Wenli Zhao, Hongwu Wang, Ye Zhao, Hirokazu Takahashi.
Project administration: Hirokazu Takahashi.
Resources: Huaien Bu, Hirokazu Takahashi.
Software: Wenli Zhao.
Supervision: Huaien Bu, Hirokazu Takahashi.

Validation: Hirokazu Takahashi.
Writing – original draft: Huaien Bu.
Writing – review & editing: Huaien Bu.

References
[1] Sheka AC, Adeyi O, Thompson J, et al. Nonalcoholic steatohepatitis: a review. JAMA. 2020;323:1175–83.
[2] Caligiuri A, Gentilini A, Marra F. Molecular pathogenesis of NASH. Int J Mol Sci. 2016;17:1575–609.
[3] Marra F, Lotersztajn S. Pathophysiology of NASH: perspectives for a targeted treatment. Curr Pharm Des. 2013;19:5250–69.
[4] Marchesini G, Potta S, Dalle Grave R, Dutt, weight loss, and liver health in nonalcoholic fatty liver disease: pathophysiology, evidence, and practice. Hepatology. 2016;63:2032–43.
[5] Bujanese E, Moscardiello S, Ciarpavella MF, et al. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des. 2010;16:1941–51.
[6] Guilherme A, Virbasius JV, Puri V, et al. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008;9:367–77.
[7] Machado MV, Diehl AM. Pathogenesis of nonalcoholic steatohepatitis. Gastroenterology. 2016;150:1769–77.
[8] Cusi K. Role of insulin resistance and lipotoxicity in non-alcoholic steatohepatitis. Clin Liver Dis. 2009;13:543–63.
[9] Jian T, Yu C, Ding X, et al. Hepatoprotective effect of seed coat of curvyle ferox extract in non-alcoholic fatty liver disease induced by high-fat diet in mice by increasing IRS-1 and inhibiting CYP2E1. J Oleo Sci. 2019;68:581–9.
[10] Puri P, Mirshahi F, Cheung O, et al. Activation and dysregulation of the unfolded protein response in nonalcoholic fatty liver disease. Gastroenterology. 2008;134:568–76.
[11] Malli H, Kaufman RJ. Endoplasmic reticulum stress in liver disease. J Hepatol. 2011;54:795–809.
[12] Tilg H, Adolph TE, Moschen AR. Multiple parallel hits hypothesis in NAFLD - Revisited after a decade. Hepatology. 2021;73:833–42.
[13] Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell. 2010;140:909–17.
[14] Farhadi A, Gundlappalli S, Shahk M, et al. Susceptibility to gut leakiness: a possible mechanism for endotoxaemia in non-alcoholic steatohepatitis. Liver Int. 2008;28:1026–33.
[15] Schuster S, Cabrera D, Arrese M, et al. Triggering and resolution of inflammation in NASH. Nat Rev Gastroenterol Hepatol. 2018;15:349–64.
[16] Schneider KM, Bieghs V, Heymann F, et al. CX3CR1 is a gatekeeper for intestinal barrier integrity in mice: limiting steatohepatitis by maintaining intestinal homeostasis. Hepatology. 2015;62:1405–16.
He D, Li J, Liu T, et al. The effect of pioglitazone on serum adiponectin levels in patients with impaired glucose tolerance with non-alcoholic fatty liver disease. LiaoCheng Second People’s Hospital of Shandong Province. Central Plains Med J. 2008;35:5–7.

Jin H, Zhou Y, Ming K. Efficacy of pioglitazone in treatment of 60 patients with nonalcoholic steatohepatitis. Pharm Care Res. 2010; 10:221–232.

Li H, Jiang T, Kang K. Efficacy of pioglitazone and metformin in the treatment of newly diagnosed type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Chin J Gerontol. 2014;34:4454–6.

Xiang X, Zhang H, Liu X, et al. Effect of pioglitazone on plasma hormone levels in patients with type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Clin Focus. 2009;24:1349–50.

Xie L, Liang B, Li J, et al. Therapeutic efficacy of pioglitazone combined with non-drug treatment on nonalcoholic fatty liver disease. J Guangdong Med College. 2014;32:776–80.

Al-Majed A, Bakhiet AH, Abdel Aziz HA, et al. Pioglitazone. Prof Drug Subs Esc Rel Methodol. 2016;41:379–438.

Basu R, Shah P, Basu A, et al. Comparison of the effects of pioglitazone and metformin on hepatic and extra-hepatic insulin action in people with type 2 diabetes. Diabetes. 2008;57:24–31.

Kubota N, Terauch Y, Kubota T, et al. Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. J Biol Chem. 2006;281:8748–55.

Zhao W, Payne V, Tommasi E, et al. Administration of the peroxisomal proliferator-activated receptor gamma agonist pioglitazone during fractionated brain irradiation prevents radiation-induced cognitive impairment. Int J Radiat Oncol Biol Phys. 2007;67:6–9.

Tahara N, Matsui T, Yamagishi S. Change in serum PEDF level after pioglitazone treatment is independently correlated with that in HOMA-IR. Int J Cardiol. 2014;172:244–6.

Wan X, Xu C, Yu C, et al. Role of NLRP3 inflammasome in the progression of NAFLD to NASH. Can J Gastroenterol. 2016;2016:6489012.

Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nonniglyceride fatty acid metabolites. Hepatology. 2010;52:774–88.

Sacks D, Baxter B, Campbell BCV, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int Stroke J. 2018;13:612–22.

Kodama Y, Taura K, Miura K, et al. Antiapoptotic effect of c-Jun N-terminal Kinase-1 through Mcl-1 stabilization in TNF-induced hepatocyte apoptosis. Gastroenterology. 2009;136:1423–34.

Promrat K, Lutchman G, Uwaifo GI, et al. pilot study of pioglitazone treatment options for non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol. 2016;1:56–67.

Basu R, Shah P, Basu A, et al. Comparison of the effects of pioglitazone and metformin on hepatic and extra-hepatic insulin action in people with type 2 diabetes. Diabetes. 2008;57:24–31.

Mager DR, Ilieiu SB, Cilmour S, et al. The effect of a low fructose and low glycemic index/load (FRAGILE) dietary intervention on indices of liver function, cardiometabolic risk factors, and body composition in children and adolescents with nonalcoholic fatty liver disease (NAFLD). J Parenter Enteral Nutr. 2015;39:73–84.

Yang H, Li D, Song X, et al. Joint associations of serum uric acid and ALT with NAFLD in elderly men and women: a Chinese cross-sectional study. J Transl Med. 2018;16:285.

Nier A, Brandt A, Conzelmann IB, et al. Non-alcoholic fatty liver disease in overweight children: role of fructose intake and dietary pattern. Nutrients. 2018;10:1329.

Hossain IA, Rahman Shah MM, Rahman MK, et al. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: association of GGT and HOMA-IR with NAFLD. Diabetes Metab Syndr. 2016;10(1 Suppl 1):S25–29.

Wong VW, Chitturi S, Wong GL, et al. Pathogenesis and novel treatment options for non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol. 2016;1:56–67.

Lutchman G, Modii A, Kleinier DE, et al. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. Hepatology. 2007;46:424–9.