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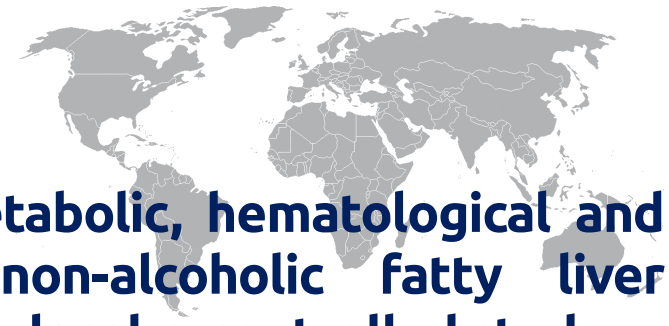

Telmisartan improves the metabolic, hematological and inflammasome indices in non-alcoholic fatty liver infiltration: A pilot open-label placebo-controlled study

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ABSTRACT

Objective: This study aimed to investigate the pleotropic effects of telmisartan against the metabolic derangement, and the maturation of the inflammasome (interleukins 1β and 18) that associated with NAFLD.

Methods: This open label clinical trial was carried in the Department of Pharmacology, College of Medicine at University of Sulaimani in cooperation with the Shar Hospital in the Sulaimani-Iraq. A total number of 51 NAFLD patients were recruited and grouped randomly into Group I (n=25) treated with placebo and Group II (n=26) treated with telmisartan (20 mg single oral dose, daily) for 8 weeks. Anthropometric measurements, fasting lipid profile and glucose levels, hematological indices, hepatic-fibrosis assessment, and inflammatory (including interleukins 1β and -18) markers were determined.

Results: Telmisartan significantly reduced the waist circumference, blood pressure, triglyceride-glucose index, and aspartate transaminase enzyme. A significant high value of hepatic fibrosis in Group I patients compared with Group II patients was observed. Telmisartan significantly reduced the inflammasome markers, granulocyte number and without producing a significant effect against platelet count.

Conclusions: Short-term therapy with low dose telmisartan can suppresses the maturation of inflammasome manifested by significant low levels of serum IL-1β and IL-18. This effect associated with improvement of the metabolic derangement and decreasing the liver fibrosis in NAFLD.

Keywords: non-alcoholic fatty liver disease, telmisartan, inflammasome markers

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is commonly associated with the features of metabolic syndrome including obesity, diabetes mellitus and dyslipidemia. It characterized by fatty infiltration detected by abdomen ultrasonography and high serum level of alanine transaminase (1). Proinflammatory cytokines played a significant role in the development of the liver cirrhosis and hepatocellular carcinoma in NAFLD patients (2). Healthy individuals who have high serum levels of proinflammatory markers are susceptible to NAFLD in the future (3). Interleukin (IL)-1β and-18 are proinflammatory cytokines that available as an inactive form in the inflammasome. Activation of the inflammasome by a number of triggers leads to maturation and secretion of IL-1β and IL-18. IL-1β played a role in the pathogenesis of alcoholic and non-alcoholic fatty liver disease by inducing fatty infiltration, inflammation, hepatocyte injury, and liver fibrosis (4-6). Moreover, IL-1β can induce inflammation in the adipose tissue, and played a role in the development of the insulin resistant (7, 8). Interleukin-18, which is also known as an interferon-γ producing proinflammatory does not involve in the inflammation, and it acts as endogenous cytokine against insulin resistant and dyslipidemia. For that reason, the serum IL-18 is significantly high in T2D and metabolic syndrome as a protective defense mechanism (9). Therefore, exogenous IL-18 is of benefit in management of alcohol-fatty liver disease, NAFLD, dyslipidemia and obesity.

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Telmisartan is angiotensin-II receptor blocker that clinically used in management of hypertension. Telmisartan has multiple and complex extra-vascular effects which collectively termed as pleotropic effects. Experimental studies found that telmisartan promotes the glucose uptake and sensitize the adipocyte to the insulin (10). It improves the glycemic index in the diabetic patient by inhibiting the peroxisome proliferator-activated receptor-γ, and it exerts an anti-inflammatory effect by reducing the levels of C-reactive protein and tumor necrosis factor-α (TNF-α) (11). In the experimental animal model of traumatic brain injury, telmisartan reduced the cerebral edema by blocking the maturation of the IL-1β and IL-18 in the inflammasome due to inactivation of the caspase-1 (12). It suppressed the expressions of C-reactive protein (CRP) IL-1β, IL-6, and TNF-α in the experimental animal model of acute colitis and acute myocardial infarction (13, 14). Telmisartan reduced the fibrosis liver score in rats fed with high fat diet for three months, which represented an animal model of NAFLD, by suppressing the expression of leptin in the liver (15). In the murine NASH model, telmisartan delay the progression of steatohepatitis by complex mechanisms including anti-inflammatory (as it suppressed macrophage infiltration into the liver), and anti-adiposity like effect (16). Telmisartan (40/80 mg single oral dose daily for 12 months can reduce the histological findings of NAFLD (including steatosis, inflammation, and fibrosis), alanine transaminase (ALT) enzyme, insulin index, and the liver fibrosis score (17).

Recent review documents that telmisartan is useful in the management of NAFLD because it improves glycemic index, lipid profile, and reducing the hepatic inflammation and fibrosis by activating angiotensin converting enzyme (ACE)/angiotensin Mas-17 (18). Therefore, any suppression of the inflammatory process may be of benefit to halt or reduce the progress of the disease which can achieve by using telmisartan. This open-label clinical study aimed to investigate the effect of telmisartan on the serum levels of IL-1β and IL-18, the markers of the inflammasome, and to relate this effect to the metabolic and hepatic indexes that commonly used in the assessment of NAFLD.

PATIENTS AND METHODS

The Institute Ethical Scientific Committee at the University of Sulaimani approved this study according to the ethical guidelines that stated by the University. Any drug or instrument that used in this study should be harmless without serious adverse reactions, and the patients were free to withdraw from the study at any time. Patients who willing to enroll in this study signed a consent form.

This open-labelled clinical study was performed in the Department of Pharmacology, College of Medicine at the University of Sulaimani in cooperation with Shar hospital in the Sulaimani city from January 2018 to June 2018. The patients were recruited from the Shar hospital under the supervision of the consultant gastroenterologists. The patients were attended the Consultant Clinics at Shar Hospital for clinical complaint suggestive hepatic cause and according to the eligibility, the patients recruited randomly by using randomized tables. Eligible patients were both genders of whatever age who were not alcoholic. Patients with high serum liver enzymes including alanine (ALT) and aspartate transaminase (AST) and the characteristic ultrasonography features of fatty liver infiltration were included. Patients with current or previous liver diseases, inflammatory disorders, connective tissue diseases, pregnancy and lactated nursing, and patients treated with steroidal and non-steroidal anti-inflammatory drugs were excluded from the study. Participants presented with co-morbidities illnesses e.g. diabetes, dyslipidemia, hypothyroidism and hypertension were on the recommended medicines for their illnesses, and none of them used angiotensin-receptors blockers.

The Institutional Scientific Committee restricted us to use a large sample size because telmisartan is still unproved by United State–Food and Drug Administration. Therefore, we designed this study as preliminary or pilot study. The mean, standard deviations, and the difference between the means of NAFLD patients and subjects with risk factors were calculated. The power of the study 1- β is fixed at 80% (0.8), and the significance level (α), is fixed at 5% , where α is type I error, and β is type II error. Sample size is equal to = 1 + 2C (Standard deviation divided by the difference between means), where C represents the Constant value that derived from the statistical tables and it equals to 7.85 when the 1-β =0.8 and α=0.05.

A total number of 51 patients (22 male and 29 female), their ages ranged from 29 to 68 years were included. The patients allocated randomly and grouped into two groups:

Group I (n=25): Patients treated with a dummy tablet (one tablet orally per day) for eight weeks, and served as a placebo-treated group.

Group II (n=26): Patients treated with 20 mg/day once oral dose telmisartan tablet for eight weeks and served as a drug or telmisartan-treated group.

Clinical Assessment

Each patient was assessed clinically, and the following measurements were done:

Ultrasonography: The examination was done by a consultant radiologists using a 2-5 MHz convex transducer. Diagnosis of NAFLD was suspected when the liver echogenicity exceeds that of renal cortex and spleen due to fatty infiltration. The grading classification of fatty liver infiltration was used as described by others (19, 20).

Anthropometric Measurements

These measurements included body weight (kg), height (m), and waist circumference (cm). Body weight (kg) divided by square height (m) was equal to the body mass index (kg/m^2). The waist (cm) to height (cm) ratio was calculated, and any value is ≥ 0.5 indicated the patient is at risk of cardiovascular event (21).

Blood Pressure

Blood pressure (mmHg) was measured by electronic sphygmomanometer at sitting position after 3 minutes rest. The mean ± SD of three readings was considered in this study. Pulse pressure is equal to the systolic *minus* diastolic blood pressure. Mean arterial pressure is equal to diastolic blood pressure *plus* 1/3 pulse pressure.

Laboratory Investigations

A 12-hour overnight fasting venous blood was drawn from each patient and collected into two series of test tubes, the first portion with anticoagulant (EDTA) test tubes for determination of hematological indices using automated hematological analyzer (Coulter machine). The second portion without anticoagulant by which the sera separated by centrifugation (3000 rpm, for 15 minutes) for determination of fasting serum lipid profile (total cholesterol, triglyceride, high density lipoprotein-cholesterol) fasting serum glucose, hepatocellular enzymes ALT, AST, and alkaline phosphatase). Serum IL-1β and IL-18 were determined by using the technique of enzyme linked immunosorbent assay (ELISA) according to the instruction of the manufacturer.

The following indexes were calculated:

Non-high density lipoprotein-cholesterol (non-HDL-c) (mg/dl) = Total cholesterol *minus* high density lipoprotein-cholesterol

Triglyceride-glucose index (22) = Ln $\frac{Serum\ (\frac{mg}{dl})Glucose \times Triglyceride}{2}$ tacking a cutoff value of insulin resistance is ≥4.68.

Fibrosis-4 (Fib-4) score = $\frac{Age\ (year) \times AST\ level\ (U/L)}{Platelet\ count\ (10^9/L) \times \sqrt{ALT\ (U/L)}}$

Any value < 1.45 indicates no evidence of advance fibrosis (23).

Non-alcoholic fibrosis score (NFS) = -1.675 + 0.037 × age (year) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × (AST/ALT ratio) - 0.013 × platelet count (×10^9/L) (24).

Serum ALT level/platelet count ratio (APR) (25) = $\frac{\boldsymbol{Serum\ ALT\ level}}{\boldsymbol{absolute\ number\ of\ platelet}}$

Neutrophil to lymphocyte ratio (NLR) = $\frac{absolute\ number\ of\ neutrophil}{absolute\ number\ of\ lymphocyte}$

Platelet to lymphocyte ratio (PLR) = $\frac{absolute\ number\ of\ lymphocyte}{absolute\ number\ of\ blood\ platelet}$

Follow-up of the Patients

All the patients managed with a diet modifying regimen i.e., meals with low refined sugar and fat (rich with saturated fatty acids). The authors follow-up each patient for eight weeks, and at the end of the trial the anthropometric, blood pressure, hematological, biochemical and inflammatory values were measured. Two patients of Group II were missed, this means that the total number of patients completed the study was 24 patients.

Statistical Analysis

The results are expressed as number, percentage, and mean ± SD. Difference between means of two groups were analyzed using two-tailed independent two sample t-test. Paired t-test was used to analyze the effectiveness of treatment in each Group. P value of ≤ 0.05 is the cutoff level of significance. Excel software (2010) was used for data analyses.

Table 1: *Characteristics of the participants enrolled in the study*

Variables	Group I (n=25)	Group II (n=26)	P-value
Gender (male : female ratio	7:18	15:11	0.032
Age (year)	44.0±9.7	43.3±9.0	0.781
Residency			
Rural	3 (12.0)	3 (11.5)	0.959
Urban	22 (88.0)	23 (88.5)	
Smoking			
Current	2 (8)	3 (11.5)	0.928
Ex-smokers	3 (12)	5 (19.2)	
Concomitant illness			
Diabetes mellitus	7(28.0)	1(3.8)	
Hypothyroidism	3(12.0)	3 (11.5)	
Hypertension	13(42.0)	5 (19.2)	0.0652
Dyslipidemia	1(4.0)	2 (7.7)	
others	1(4.0)	2 (7.7)	
No concomitant illness	8(32.0)	15 (57.7)	
Ultrasonography grades			
Mild	15	19	
Mild-moderate	1	2	
Moderate	8	5	
Moderate-severe	0	0	0.479
Severe	1	0	

The results expressed as number (%) and mean ± SD. Two tailed independent two sample t-test for continuous data and Chi-square test for category data used to calculate the significant difference

RESULTS

Table 1 shows the characteristic features of the patients enrolled in this study. Non- significant difference between Group I and Group II in the distribution of gender while the mean age, status of smoking, and frequency of the concomitant illnesses were observed. Ultrasonography grading of fatty liver infiltration of the Group I did not differ significantly from corresponding grades of Group II (**Table 1**). Telmisartan significantly (p=0.009) decreased the mean value of waist circumference by 1.3 cm, and this reflected on a significant (p=0.010) decrease of a waist to height ratio by 0.009 while its effect against the body mass index did not reach to a significant level (**Table 2**). Group I patients did not show significant changes in the anthropometric measurements including body mass index, wait circumference, and waist to height ratio (**Table 2**). Telmisartan significantly reduced the systolic, diastolic, pulse, and mean arterial pressures while the patients treated with the placebo showed non-significant changes in the blood pressure (**Table 2**). Placebo significantly reduced the serum total cholesterol (6.7%) and a non-high density lipoprotein cholesterol (9.3%) levels (**Table 2**). Telmisartan treatment did not produce significant changes of the fasting serum profile levels (**Table 2**). Fasting serum glucose and serum uric acid levels did not significantly change with placebo (Group I) or telmisartan (Group II) treatments (**Table 2**). Telmisartan significantly reduced the triglyceride-glucose index compared with placebo treatment, which reached to 48.5% of the pretreatment value (**Table 2**). Patients treated with the placebo had significant low serum levels of ALT, AST, and a significant increase of non-alcoholic fatty liver score (**Table 3**). Telmisartan significantly decreased the serum levels of ALT, AST, and alkaline phosphatase, and a non-significant effect against the non-alcoholic fatty liver disease score (**Table 3**). Neither the placebo nor the telmisartan produced significant effects against the scores of fibrosis-4 or to the ratio of aspartate transaminase to platelet count (**Table 3**). The patients treated with placebo (Group I) showed a significant increase of the lymphocyte count which reflected on a significant low platelet to lymphocyte ratio (**Table 4**). The placebo did not change significantly the serum levels of inflammasome markers including the serum IL-1β and IL-18. Telmisartan (Group II) significantly increased the granulocyte count, and significantly decreased the serum IL-1β and IL-18 levels (**Table 4**). None of our participants reported any significant adverse reactions.

Table 2: *Effects of telmisartan versus placebo-treatment against risk factors that associated with non-alcoholic fatty liver disease*

Variables	Group I (n=25)			Group II (n=26)		
	Before treatment	After treatment	P-value	Before treatment	After treatment	P-value
Body mass index (kg/m^2)	33.9±7.4	33.9±7.2	0.447	31.8±3.4	31.7±3.4	0.275
Waist circumference(cm)	107.7±12.7	106.8±13.2	0.349	105.0±7.4	103.7±7.6	0.009
Waist to height ratio	0.661±0.084	0.656±0.09	0.355	0.636±0.056	0.627±0.060	0.010
Blood pressure (mmHg)						
Systolic	134.4±20.0	131.3±19.5	0.203	146.3±12.4	132.2±17.8	<0.001
Diastolic	83.9±13.3	80.5±11.3	0.073	91.2±9.7	83.9±8.5	0.002
Pulse	50.5±11.0	50.8±12.4	0.874	55.1±9.9	48.3±14.5	0.031
Mean arterial	100.7±15.0	97.4±13.2	0.085	109.5±9.6	100.0±10.3	<0.001
Fasting lipid profile (mg/dl)						
Total cholesterol	185.4±31.8	172.9±31.5	0.003	189.3±27.6	180.5±30.0	0.110
Triglyceride	173.6±90.2	153.5±80.1	0.077	167.2±93.9	162.9±75.3	0.782
HDL-c	42.4±11.3	43.2±10.2	0.534	38.6±10.3	37.9±10.9	0.656
Non-HDL-c	143.0±27.7	129.7±29.8	0.001	150.7±26.1	142.6±30.3	0.142
Fasting serum glucose (mg/dl)	120.9±36.4	118.1±39.3	0.263	112.1±20.7	109.7±17.8	0.481
Serum uric acid (mg/dl)	5.1±1.5	5.2±1.2	0.581	5.4±1.2	5.2±1.0	0.115
Triglyceride Glucose Index	9.09±0.67	8.96±0.62	0.141	9.245±0.208	4.845±0.218	<0.001

The result are presented as mean ± SD. P-value calculated using two tail paired samples t-test

Table 3: *Effects of telmisartan versus placebo-treatment against liver indices in patients with non-alcoholic fatty liver disease*

Variables	Group I			Group II		
	Before treatment	After treatment	P-value	Before treatment	After treatment	P-value
Alanine transaminase (U/L)	41.4±21.8	35.2±18.2	0.013	43.4±16.8	38.6±21.8	0.160
Aspartate tranaminase (U/L)	25.9±11.6	21.8±6.6	0.035	29.3±10.6	23.8±11.2	0.015
Alkaline phosphatase (K.A.U)	108.1±39.3	94.9±25.5	0.102	103.0±56.7	81.2±19.2	0.045
Alanine to aspartate transaminase ratio	1.70±0.64	1.61±0.67	0.509	1.61±0.61	1.66±0.72	0.701
Aspartate to alanine transaminase ratio	0.67±0.24	0.77±0.48	0.296	0.74±0.33	0.71±0.28	0.549
Fibeosis-4 score	0.815±0.453	0.812±0.331	0.959	0.887±0.405	0.807±0.356	0.226
Non-alcoholic fatty liver score	-3159.6±9.36.1	-2903.1±714.2	0.024	-2983.6±509.3	-2879.1±543.4	0.220
Alanine transaminase to platelet count ratio	0.12±0.07	0.10±0.04	0.118	0.13±0.05	0.113±0.08	0.201

The results are presented as mean ± SD. P-value calculated using two-tailed paired samples t-test

Table 4: *Effects of placebo and telmisartan on the inflammasomes markers and hematological-proinflammatory markers*

Variables	Group I			Group II		
	Before treatment	After treatment	p-value	Before treatment	After treatment	P-value
White cell count /mm^3	7402±1848	7205.6±2225.1	0.627	7127±2010	6540±1419	0.186
Platelet count x10^3/mm^3	243.36±72.00	223.64±54.960	0.024	229.8±39.2	221.8±41.8	0.220
Granulocyte number./mm^3	4602.1±1333.5	4528.0±703.1	0.652	4326±1764	3930±1196	<0.001
Lymphocyte number./ mm^3	2010.4±508.6	2267.2±543.8	0.004	2258±544	2220±569	0.761
Neutrophil-lymphocyte ratio	2.42±1.42	2.06±0.92	0.216	2.10±1.26	2.01±0.50	0.610
Platelet-lymphocyte ratio	127.2±50.4	103.0±30.2	<0.001	108.7±22.4	120.1±37.0	0.894
Interleukin-1β (pg/ml)	23.2±7.1	23.3±6.6	0.908	24.1±8.7	20.3±8.9	<0.001
Interleukin-18 (pg/ml)	298.8±48.2	296.8±49.6	0.709	314.3±54.7	281.5±54.4	<0.001

The results are presented as mean ± SD. P-value calculated using two tail paired samples t-test. Group I: treated with placebo, Group II: treated with telmisartan

DISCUSSION

The results of this study show that short-term therapy with telmisartan can ameliorate the insulin resistance (represented by a significant decrease of triglyceride-glucose index), the maturation of the inflammasome (represented by a significant decrease of IL-1β and IL-18) and preventing the progression of liver fibrosis (represented by a non-significant changes in the scoring of non-alcoholic liver fibrosis).

The baseline data did not show a significant difference between Group I and Group II indicating that there is no bias in the results that obtained by telmisartan compared with placebo. A significant difference in the gender distribution

between Group I and II does not bias the effect of telmisartan. The pharmacological actions of telmisartan did not influence by the gender (26). The possible explanation of the effect of telmisartan on the waist circumference is telmisartan induced changes in the fat distribution, and thereby it reduced the visceral obesity (27). Placebo-treated patients showed a significant improvement in the lipid profile, which can be attributed to the diet modifying regimen. This finding did not observe in the telmisartan-treated group indicating that telmisartan adversely affected the lipid profile. Previous studies suggested to use a combination of a lipid lowering agent *plus* telmisartan in the management of the NAFLD (28). Telmisartan improves the insulin resistance at the muscle by reducing significantly the triglyceride-glucose index. Previous studies explored a significant improvement of insulin resistance in NAFLD by determination the homeostasis model of assessment-insulin resistance (HOMA-IR) (29). This study adds another index of assessment of insulin resistance in the NAFLD. Telmisartan reduced the fasting serum glucose, which agreed other studies. A non-significant decrease of fasting serum glucose can attribute to the small sample size (30). The non-significant effect of telmisartan on the serum level of ALT is due to a short period of time. Previous studies observed that long term therapy of telmisartion induced a significant reduction of ALT in NAFLD patients (31). Neither placebo nor telmisartan was significantly altered the severity of fatty liver infiltration by the evidences that the mean ± SD of ALT/AST ratio did not change with any treatment (32). On the other hand, we assessed the liver fibrosis by using three indices: AST/ALT ratio, Fib-4 score and NFS. We observed non-significant changes in the mean values of AST/ALT ratio, and Fib-4 score. The mean value of NFS was significantly increased in Group I while it remained stable in Group II, which indicated that telmisartan prevented the progression of liver fibrosis. This observation confirmed previous studies that showed telmisartan had antifibrotic effect (15, 33, 34). The antifibrotic effect of telmisartan is associated with suppression of inflammasome maturation by evidence of a significant decrease of serum levels of IL-1β and Il-18. Recent reviews focus on the activation of caspase-1 (i.e. maturation of inflammasome) and the function of the NLRP3 inflammasome in the progression of NAFLD (35, 36). This study showed a simultaneous increase of the serum levels of IL-1β and IL-18. The mean ±SD of serum uric acid did not significantly alter in Group I or Group II indicating that uric acid as a trigger of inflammasome maturation has no role. It is possible to link the antifibrotic effect of telmisartan to its anti-inflammatory effect. This study showed that the anti-inflammatory effect of telmisartan extended to suppression of the inflammasome cytokines. Small sample size is a critical limitation of the study which cannot avoided because this study was carried in one center, and the ethical committee did not allow to use this medication on the large sample size.

We conclude that telmisartan improves metabolic derangement, prevents the progression of the liver fibrosis, and suppresses the maturation of the inflammasome in NAFLD.

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REFERENCES

1. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2018; pii: S2213-8587(18)30154-2. https://doi.org/10.1016/S2213-8587(18)30154-2
2. Wang JK, Feng ZW, Li YC, Li QY, Tao XY. Association of tumor necrosis factor-α gene promoter polymorphism at sites -308 and -238 with non-alcoholic fatty liver disease: A meta-analysis. J Gastroenterol Hepatol 2012;27(4):670–6. https://doi.org/10.1111/j.1440-1746.2011.06978.x
3. Seo YY, Cho YK, Bae JC, Seo MH, Park SE, Rhee EJ, Park CY, Oh KW, Park SW, Lee WY. Tumor necrosis factor-α as a predictor for the development of nonalcoholic fatty liver disease: A 4-year follow-up study. Endocrinol Metab (Seoul) 2013;28(1):41–5. https://doi.org/10.3803/EnM.2013.28.1.41
4. Tilg H, Moschen AR, Szabo G. Interleukin-1 and inflammasomes in alcoholic liver disease/acute alcoholic hepatitis and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Hepatology 2016;64(3):955-65. https://doi.org/10.1002/hep.28456
5. Szabo G, Petrasek J. Inflammasome activation and function in liver disease. Nat Rev Gastroenterol Hepatol 2015;12(7): 387-400. https://doi.org/10.1038/nrgastro.2015.94
6. Gieling RG, Wallace K, Han YP. Interleukin-1 participates in the progression from liver injury to fibrosis. Am J Physiol Gastrointest Liver Physiol 2009;296(6): G1324-31. https://doi.org/10.1152/ajpgi.90564.2008

7. Tack CJ, Stienstra R, Joosten LA, Netea MG. Inflammation links excess fat to insulin resistance: the role of the interleukin-1 family. Immunol Rev2012;249(1):239-52. https://doi.org/10.1111/j.1600-065X.2012.01145.x
8. Negrin KA, Roth Flach RJ, DiStefano MT, Matevossian A, Friedline RH, Jung D, Kim JK, Czech MP. IL-1 signaling in obesity-induced hepatic lipogenesis and steatosis. PLoS One 2014;9(9):e107265. https://doi.org/10.1371/journal.pone.0107265
9. Yamaoka-Tojo M, Tojo T, Wakaume K, Kameda R, Nemoto S, Takahira N, Masuda T, Izumi T. Circulating interleukin-18: a specific biomarker for atherosclerosis-prone patients with metabolic syndrome. Nutr Metab (Lond) 2011;8:3. https://doi.org/10.1186/1743-7075-8-3
10. Fang T, Di Y, Li G, Cui X, Shen N, Li Y, et al. Effects of telmisartan on TNFα induced PPARγ phosphorylation and insulin resistance in adipocytes. Biochem Biophys Res Commun 2018;503(4):3044-9. https://doi.org/10.1016/j.bbrc.2018.08.091
11. Chen T, Xing J, Liu Y. Effects of telmisartan on vascular endothelial function, inflammation and insulin resistance in patients with coronary heart disease and diabetes mellitus. Exp Ther Med 2018;15(1):909-13. https://doi.org/10.3892/etm.2017.5451
12. Wei X, Hu CC, Zhang YL, Yao SL, Mao WK. Telmisartan reduced cerebral edema by inhibiting NLRP3 inflammasome in mice with cold brain injury. J Huazhong Univ Sci Technolog Med Sci 2016; 36(4):576-83. https://doi.org/10.1007/s11596-016-1628-1
13. Arumugam S, Sreedhar R, Thandavarayan RA, Giridharan VV, Karuppagounder V, Pitchaimani V, Afrin R, Harima M, Nakamura T, Ueno K, Nakamura M, Suzuki K, Watanabe K. Telmisartan treatment targets inflammatory cytokines to suppress the pathogenesis of acute colitis induced by dextran sulphate sodium. Cytokine 2015;74(2):305-12. https://doi.org/10.1016/j.cyto.2015.03.017
14. Song Z, Bai J, Zhang L, Sun X, Zhang M, Zheng H, Zhang J. Effects of telmisartan on inflammation and fibrosis after acute myocardial infarction in rats]. Zhonghua Yi Xue Za Zhi 2014; 94(33):2628-33.
15. Zhang QZ, Liu YL, Wang YR, Fu LN, Zhang J, Wang XR, Wang BM. Effects of telmisartan on improving leptin resistance and inhibiting hepatic fibrosis in rats with non-alcoholic fatty liver disease. Exp Ther Med 2017;14(3):2689-94. https://doi.org/10.3892/etm.2017.4809
16. Kudo H, Yata Y, Takahara T, Kawai K, Nakayama Y, Kanayama M, Oya T, Morita S, Sasahara M, Mann DA, Sugiyama T. Telmisartan attenuates progression of steatohepatitis in mice: role of hepatic macrophage infiltration and effects on adipose tissue. Liver Int 2009; 29(7):988-96. https://doi.org/10.1111/j.1478-3231.2009.02006.x
17. Alam S, Kabir J, Mustafa G, Gupta U, Hasan SK, Alam AK. Effect of telmisartan on histological activity and fibrosis of non-alcoholic steatohepatitis: A 1-year randomized control trial. Saudi J Gastroenterol 2016;22(1):69-76. https://doi.org/10.4103/1319-3767.173762
18. Borém LMA, Neto JFR, Brandi IV, Lelis DF, Santos SHS. The role of the angiotensin II type I receptor blocker telmisartan in the treatment of non-alcoholic fatty liver disease: a brief review. Hypertens Res 2018;41(6):394-405. https://doi.org/10.1038/s41440-018-0040-6
19. Joseph AE, Saverymuttu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991;43(1):26-31. https://doi.org/10.1016/S0009-9260(05)80350-2
20. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123(3):745-50. https://doi.org/10.1053/gast.2002.35354
21. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. Nutr Res Rev 2010;23(2): 247–69. https://doi.org/10.1017/S0954422410000144
22. Mazidi M, Kengne AP, Katsiki N, Mikhailidis DP, Banach M. Lipid accumulation product and triglycerides/glucose index are useful predictors of insulin resistance. J Diabetes Complications 2018;32(3):266-70. https://doi.org/10.1016/j.jdiacomp.2017.10.007
23. Sterling RK, Lissen E, Clumeck N, , Sola R, Correa MC, Montaner J, et al.. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43(6):1317-25. https://doi.org/10.1002/hep.21178

24. Rotundo L, Persaud A, Feurdean M, Ahlawat S, Kim HS. The Association of leptin with severity of non-alcoholic fatty liver disease: A population-based study. Clin Mol Hepatol. 2018 Aug 2. https://doi.org/10.3350/cmh.2018.0011
25. Fallatah HI, Akbar HO, Fallatah AM. Fibroscan compared to FIB-4, APRI, and AST/ALT Ratio for assessment of liver fibrosis in Saudi patients with nonalcoholic fatty liver disease. Hepat Mon 2016;16(7):e38346. https://doi.org/10.5812/hepatmon.38346
26. Zhu D, Bays H, Gao P, Mattheus M, Voelker B, Ruilope LM. Efficacy and tolerability of a single-pill combination of telmisartan 80 mg and hydrochlorothiazide 25 mg according to age, gender, race, hypertension severity, and previous antihypertensive use: planned analyses of a randomized trial. Integr Blood Press Control 2013; 6:1-14. https://doi.org/10.2147/IBPC.S33104
27. Choi GJ, Kim HM, Kang H, Kim J. Effects of telmisartan on fat distribution: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2016; 32(7):1303-9. https://doi.org/10.1185/03007995.2016.1171204
28. Bochar OM. Combined effect of appointment telmisartan and atorvastatin on hemodynamic indicators and the indicators of lipid profile in patients with arterial hypertension combined with obesity and steatohepatitis. Wiad Lek. 2014;67(2 Pt 2):157-60.
29. Wang Y, Qiao S, Han DW, Rong XR, Wang YX, Xue JJ, Yang J. Telmisartan improves insulin resistance: A meta-analysis. Am J Ther 2018 Mar 16. https://doi.org/10.1097/MJT.0000000000000733
30. Mahmood IH, Abed MN, Merkhan MM. Effects of blocking of angiotensin system on the prevalence of metabolic syndrome in type 2 diabetic patients. Pak J Med Sci 2013;29(1):140-3. https://doi.org/10.12669/pjms.291.2782
31. Georgescu EF, Ionescu R, Niculescu M, Mogoanta L, Vancica L. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. World J Gastroenterol 2009;15(8):942-54. https://doi.org/10.3748/wjg.15.942
32. Nanji AA, French SW, Freeman JB. Serum alanine aminotransferase to aspartate aminotransferase ratio and degree of fatty liver in morbidly obese patients. Enzyme 1986;36(4):266-9. https://doi.org/10.1159/000469304
33. Ionică FE, Mogoantă L, Negreş S, Bejenaru LE, Cristea OM, Badea O, Bejenaru C.. Comparing the antifibrotic effect on the liver of telmisartan and pentoxifylline, in a Wistar rat experimental model. Rom J Morphol Embryol 2017;58(4):1237-48.
34. Ionică FE, Mogoantă L, Nicola GC, ChiriŢă C, Negreş S, Bejenaru C, Turculeanu A, Badea O, Popescu NL, Bejenaru LE. Antifibrotic action of telmisartan in experimental carbon tetrachloride-induced liver fibrosis in Wistar rats. Rom J Morphol Embryol 2016;57(4):1261-72.
35. Kanda T, Matsuoka S, Yamazaki M, Shibata T, Nirei K, Takahashi H, Kaneko T, Fujisawa M, Higuchi T, Nakamura H, Matsumoto N, Yamagami H, Ogawa M, Imazu H, Kuroda K, Moriyama M. Apoptosis and non-alcoholic fatty liver diseases. World J Gastroenterol 2018; 24(25):2661-72. https://doi.org/10.3748/wjg.v24.i25.2661
36. Del Campo JA, Gallego P, Grande L. Role of inflammatory response in liver diseases: Therapeutic strategies. World J Hepatol. 2018;10(1):1-7. https://doi.org/10.4254/wjh.v10.i1.1

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