

## Nonalcoholic fatty liver disease and the renin-angiotensin system: Implications for treatment

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is the commonest liver disease in Western countries. Treatment of NAFLD is currently based on lifestyle measures and no effective pharmacologic treatment is available so far. Emerging evidence, mainly from animal studies, suggests that the renin-angiotensin-aldosterone system may be of major importance in the pathogenesis of NAFLD and indicates that angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) as a potentially useful therapeutic approach. However, data from human studies are limited and contradictory. In addition, there are few randomized controlled trials (RCTs) on the effects of ACE-I or ARB in patients with NAFLD and most data are from retrospective studies, pilot prospective studies and post hoc analyses of clinical trials. Accordingly, more and larger RCTs are needed to directly assess the effectiveness of ACE-I and ARBs in NAFLD.

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**Key words:** Nonalcoholic fatty liver disease; Non alcoholic steatohepatitis; Renin-angiotensin-aldosterone system; Angiotensin-converting enzyme inhibitors; An-

giotensin receptor blockers; Fibrosis

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### EDITORIAL

Nonalcoholic fatty liver disease (NAFLD) is the commonest liver disease in Western countries with an estimated prevalence in the general population of 20%-30%<sup>[1]</sup>. Treatment of NAFLD is currently based on lifestyle measures and no effective pharmacologic treatment is available so far. Emerging evidence, mainly from animal studies, suggests that the renin-angiotensin-aldosterone system (RAAS) may be of major importance in the pathogenesis of NAFLD and indicates that angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) as a potentially useful therapeutic approach.

Within the circulating RAAS, the first step in the production of angiotensin II (Ang II) is the cleavage of angiotensinogen, produced in the liver, to Ang I by renin, which is released from the juxtaglomerular cells of the kidney. Then, the ACE converts Ang I into the physiologically active product of RAAS, Ang II. Actions of Ang II are mediated by the activation of the AT1 and the AT2 receptors (AT1R and AT2R). AT1R is in abundance in adult tissues whereas AT2 receptor is mainly expressed during fetal development and is up-regulated in pathologic conditions. AT1R mediates all the major Ang II-induced biological effects, such as the regulation of blood pressure, salt and water retention,

hormone secretion, renal function, as well as the autocrine and paracrine effects of Ang II on cell proliferation and migration and extracellular matrix formation. AT2R is generally reported to mediate effects opposing and counterbalancing those mediated by AT1R *in vitro* as well as *in vivo*<sup>[2]</sup>. Ang II is further metabolized by a variety of enzymes to the bioactive angiotensin fragments Ang III (Ang2-8), Ang IV (Ang 3-8) and Ang (1-7). Ang III (Ang 2-8) is formed by cleavage of Ang II by aminopeptidase A and shares similar actions with Ang II *via* AT1R and AT2R. Ang III can be further metabolized by aminopeptidase M into Ang IV. Actions of Ang IV are mediated by AT4/(insulin-regulated aminopeptidase) receptor and include regulation of blood flow, inhibition of renal tubular sodium reabsorption, cardiac hypertrophy, angiogenesis and stimulation of endothelial cell expression of platelet activator inhibitor 1 (PAI-1)<sup>[3]</sup>. Angiotensin (1-7) is generated either from Ang I by endopeptidases or from Ang II by ACE2. ACE2 also hydrolyzes Ang I to Ang-(1-9) which can be further metabolized to Ang-(1-7) by ACE. The effects of Ang-(1-7) are mainly mediated through the mas receptor and appear to counterbalance those of Ang II. In particular, the ACE2-angiotensin-(1-7)-Mas axis appears to promote vasodilatation and to exert anti-proliferative, anti-inflammatory, antifibrotic and anti-thrombotic actions<sup>[3,4]</sup>.

Apart from the circulating RAAS, local RAAS have been identified in most organs and tissues, with diverse physiological effects exerted through autocrine and paracrine actions. These local RAAS have been implicated in multiple functions including cell growth, differentiation, proliferation and apoptosis, reactive oxygen species (ROS) generation, tissue inflammation, fibrogenesis and hormonal secretion<sup>[5]</sup>. The systemic and local RAAS are considered to interact and operate in a complementary and integrated way<sup>[6]</sup>. Experimental studies have demonstrated the presence of key elements of RAAS in normal liver and their up-regulation and redistribution in liver injury<sup>[7,8]</sup>. The AT1R, which is localized in hepatocytes, bile duct cells, hepatic stellate cells (HSCs), myofibroblasts, Kupffer cells and vascular endothelial cells, mediates most of the actions of Ang II in the liver<sup>[4]</sup>. However, some studies also reported AT2R gene expression in liver tissue, suggesting that AT2R might have anti-fibrogenic effects in the liver<sup>[7,9]</sup>.

Insulin resistance (IR) plays a central role in the pathophysiology of NAFLD and evidence from experimental studies underlines the crosstalk between RAAS and insulin signaling, resulting in the worsening of IR. Ang II stimulates phosphorylation of serine residues in the insulin receptor beta-subunit and the p85 regulatory subunit of PI3-kinase, inhibiting the interactions between these components of the insulin signaling pathway<sup>[10]</sup>. Ang II also induces generation of ROS mainly by activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and regulates the production of pro-inflammatory mediators, including tumor necrosis factor  $\alpha$ , interleukin-6 (IL-6) and PAI-1, result-

ing in impairment of insulin signaling<sup>[11,12]</sup>.

*In vitro* experiments and animal studies suggest that the effects of RAAS inhibition on glucose metabolism are due to vasodilation. In particular, ACE-I and ARBs-induced vasodilation increases the delivery of glucose and insulin to insulin-sensitive tissues and improves blood flow in pancreas, promoting insulin secretion. Preliminary data indicate enhanced insulin signaling, modulation of muscle fiber composition, decreased sympathetic activity and improved ionic balance as additional potential mechanisms implicated in the improvement of insulin sensitivity and secretion by RAAS-blocking agents. The beneficial effects of ARBs on IR could also be related to the selective stimulation of peroxisome proliferator-activated receptors (PPAR)- $\gamma$ <sup>[13,14]</sup>. Furthermore, clinical trials have showed the ability of RAAS inhibition to prevent new-onset of diabetes mellitus. A recent meta-analysis including 100 848 patients showed a 20% reduction in the incidence of new onset diabetes with the use of ACE-Is or ARBs<sup>[15]</sup>. However, most studies included in this meta-analysis were post-hoc analyses and several were open label trials. In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication study, treatment with ramipril of patients with impaired fasting glucose levels or impaired glucose tolerance did not reduce the incidence of diabetes but increased regression to normoglycemia<sup>[16]</sup>. In the more recent Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial, treatment with valsartan of patients with impaired glucose tolerance was associated with a relative reduction of 14% in the incidence of diabetes<sup>[17]</sup>.

Accumulating data suggest that the RAAS might play a role in the pathogenesis of hepatic fibrosis. Bataller demonstrated that activated HSCs express renin and ACE and synthesize Ang II<sup>[7]</sup>. Ang II activates HSC, promoting their differentiation into myofibroblasts and stimulates cellular proliferation contraction, through the release of intracellular calcium. Moreover, Ang II up-regulates tissue inhibitor of metalloproteinases-1 (TIMP-1) mRNA expression and increases collagen and protein deposition in the extracellular matrix. The profibrogenic effect of Ang II is also mediated *via* NADPH oxidase, which produces ROS. AT1R activation also increases the expression of vascular endothelial growth factor, promoting neoangiogenesis. Ang II also exerts proinflammatory effects by up-regulating the synthesis of the pro-inflammatory cytokines IL-1 and IL-6 and the expression of the transcription factor nuclear factor kappa B. In addition, Ang II stimulates the production of growth factors including transforming growth factor (TGF)- $\beta$ 1 and connective tissue growth factor. Moreover, Ang II stimulates cell migration and concentration of activated HSCs at the site of hepatic injury<sup>[4,18,19]</sup>.

Several studies in a variety of established animal models of hepatic fibrosis support the role of RAAS in liver fibrosis and the antifibrotic effects of RAAS inhibition. Treatment with ACE-I and ARBs in these models attenu-

ated steatosis and prevented the development of lobular inflammation and hepatic fibrosis. These effects appear to be due to the attenuation of oxidative stress and HSC activation and the down-regulation of pro-inflammatory and profibrotic cytokines<sup>[4,20]</sup>. Other potential mechanisms include suppression of growth factors and TIMP-1, increase in circulating adiponectin levels and reduction of macrophage infiltration<sup>[21-23]</sup>.

Despite the supportive evidence of *in vitro* and *in vivo* studies, human data on the effects of RAAS inhibition on liver fibrosis are scarce. This can be attributed to the need for multiple liver biopsies and the slow progression of fibrosis necessitating studies with long-term follow-up. Regarding ARBs, a pilot study reported that prolonged administration of losartan (50 mg/d) for 18 mo was associated with downregulation of hepatic expression of fibrogenic genes in patients with hepatitis C<sup>[24]</sup>. Administration of losartan (50 mg/d) for 6 mo in patients with hepatitis C improved fibrosis stage compared with control patients<sup>[25]</sup>. Another study evaluated the efficacy of telmisartan (40 mg/d) and olmesartan (20 mg/d) in patients with NAFLD or chronic hepatitis C. Both drugs improved IR, measured by homeostasis model assessment of IR, and serum alanine aminotransferase levels but the benefit appeared to be greater with telmisartan<sup>[26]</sup>. In a controlled study, 30 patients with chronic hepatitis C were randomized to losartan (50 mg/d) and ursodeoxycholic acid (UDCA) or UDCA alone. Serum type IV collagen and plasma TGF-1 concentrations were significantly decreased in losartan group but there was no effect on fibrosis score<sup>[27]</sup>.

Several studies compared both ACE-I and ARBs with other antihypertensive agents in patients with hepatitis C. In a retrospective study in liver-transplant recipients with hepatitis C recurrence, patients treated with ACE-I or ARBs showed reduced risk for cirrhosis and less liver fibrosis progression compared with patients who did not receive these agents<sup>[28]</sup>. In a more recent study in a similar population, administration of ARBs was associated with less progression of inflammation, but not fibrosis, whereas ACE-I had no effect on liver histology<sup>[29]</sup>. Another retrospective study showed that hypertensive patients with hepatitis C receiving ACE-I or ARBs had less fibrosis than hypertensive patients who received other antihypertensive agents<sup>[30]</sup>. In contrast to the previous studies, the Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial demonstrated no benefit of RAAS blockers in hepatic fibrosis<sup>[31]</sup>. In this study, patients with chronic hepatitis C and advanced hepatic fibrosis, who had failed to achieve a sustained virologic response after previous treatment, underwent serial liver biopsies at baseline, 1.5 years, and 3.5 years after randomization to maintenance therapy with peginterferon alfa-2a or to no treatment for 42 mo<sup>[31]</sup>. The trial showed no association between baseline use of RAAS inhibitors and liver fibrosis stage at baseline and use of ACE-I or ARBs did not slow progression of liver fibrosis during follow-up<sup>[31]</sup>.

As far as patients with NAFLD or nonalcoholic ste-

atohepatitis (NASH) are concerned, there are no studies that evaluated the effects of ACE-I in this population. Regarding ARBs, a preliminary study in 12 patients with NASH showed that losartan (50 mg/d) can improve biochemical parameters, liver steatosis and inflammation but had no effect on fibrosis<sup>[32]</sup>. In another pilot prospective study, the administration of losartan (50 mg/d) for 48 wk in 7 patients with NASH reduced circulating markers of hepatic fibrosis, plasma TGF- $\beta$ 1 levels, transaminase levels and improved hepatic necroinflammation and fibrosis<sup>[33]</sup>. In a larger study, 54 hypertensive patients with NASH were randomly assigned to either telmisartan (20 mg/d) or valsartan (80 mg/d). Both ARBs reduced transaminase levels and improved IR but this improvement was more profound in the telmisartan group, which also showed a significant decrease of NASH activity score and fibrosis. Valsartan did not improve liver histology except steatosis<sup>[34]</sup>. These differences on the effects on IR, transaminase levels and liver histology between ARBs could be attributed to the PPAR- $\gamma$ -activating properties of telmisartan<sup>[35]</sup>. In addition, experimental studies demonstrated that telmisartan acts as a liver-specific partial PPAR- $\alpha$  agonist, has anti-inflammatory effects and modulates adipokine levels, by upregulating adiponectin levels and downregulating resistin levels<sup>[32,36]</sup>. Furthermore, structural differences between ARBs result in differences in their physicochemical properties and subsequently in their binding affinity to the Ang II receptor<sup>[32]</sup>. On the other hand, a recent 12-mo randomized open-label study in 137 patients with NASH showed no additional benefit on liver histology with combination therapy of rosiglitazone and losartan (50 mg/d) compared with rosiglitazone alone<sup>[37]</sup>.

Although there are no studies comparing ACE-I with ARBs in NAFLD, preliminary evidence indicates that treatment with ARBs result in greater improvement in insulin sensitivity and larger reduction in the risk for new onset diabetes mellitus. A meta-analysis showed that the number needed to treat to prevent one case of new onset diabetes is 100 and 50 with ACE-I and ARBs, respectively<sup>[15]</sup>. One possible explanation could be the inhibitory action of ACE-I on both AT1 and AT2 receptors, resulting in suppression of the counterbalancing effects of AT2 on the actions of AT1. Moreover, accumulating evidence suggests a beneficial role of ACE2/Ang-(1-7)/mas receptor axis since it appears to counterbalance the actions of Ang II. Apart from ACE-I and ARBs which have been shown to up-regulate this pathway, new drugs that mimic the effect of Ang-(1-7) might represent a novel treatment of liver fibrosis<sup>[4]</sup>.

In conclusion, the established role of both circulating and local RAAS on the pathogenesis of NAFLD and NASH created considerable interest on the effect of RAAS inhibitors since they are widely used, reasonably inexpensive, and with excellent safety profile. However, and despite the encouraging evidence from animal studies, data from human studies are limited and contradictory. In addition, there are few randomized controlled trials (RCTs)



on the effects of ACE-I or ARB in patients with NAFLD and most data are from retrospective studies, pilot prospective studies and post hoc analyses of clinical trials. Accordingly, more and larger RCTs are needed to directly assess the effectiveness of ACE-I and ARBs in NAFLD.

## REFERENCES

- 1 **Bedogni G**, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology* 2005; **42**: 44-52
- 2 **de Gasparo M**, Catt KJ, Inagami T, Wright JW, Unger T. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev* 2000; **52**: 415-472
- 3 **Fyhrquist F**, Saijonmaa O. Renin-angiotensin system revisited. *J Intern Med* 2008; **264**: 224-236
- 4 **Warner FJ**, Lubel JS, McCaughan GW, Angus PW. Liver fibrosis: a balance of ACEs? *Clin Sci (Lond)* 2007; **113**: 109-118
- 5 **Leung PS**. The physiology of a local renin-angiotensin system in the pancreas. *J Physiol* 2007; **580**: 31-37
- 6 **Paul M**, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; **86**: 747-803
- 7 **Bataller R**, Sancho-Bru P, Ginès P, Lora JM, Al-Garawi A, Solé M, Colmenero J, Nicolás JM, Jiménez W, Weich N, Gutiérrez-Ramos JC, Arroyo V, Rodés J. Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. *Gastroenterology* 2003; **125**: 117-125
- 8 **Paizis G**, Cooper ME, Schembri JM, Tikellis C, Burrell LM, Angus PW. Up-regulation of components of the renin-angiotensin system in the bile duct-ligated rat liver. *Gastroenterology* 2002; **123**: 1667-1676
- 9 **Nabeshima Y**, Tazuma S, Kanno K, Hyogo H, Iwai M, Horiuchi M, Chayama K. Anti-fibrogenic function of angiotensin II type 2 receptor in CCl4-induced liver fibrosis. *Biochem Biophys Res Commun* 2006; **346**: 658-664
- 10 **Folli F**, Saad MJ, Velloso L, Hansen H, Carandente O, Feener EP, Kahn CR. Crosstalk between insulin and angiotensin II signalling systems. *Exp Clin Endocrinol Diabetes* 1999; **107**: 133-139
- 11 **Wei Y**, Sowers JR, Nistala R, Gong H, Uptergrove GM, Clark SE, Morris EM, Szary N, Manrique C, Stump CS. Angiotensin II-induced NADPH oxidase activation impairs insulin signaling in skeletal muscle cells. *J Biol Chem* 2006; **281**: 35137-35146
- 12 **Liu Z**. The renin-angiotensin system and insulin resistance. *Curr Diab Rep* 2007; **7**: 34-42
- 13 **Scheen AJ**. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 2. Overview of physiological and biochemical mechanisms. *Diabetes Metab* 2004; **30**: 498-505
- 14 **Rong X**, Li Y, Ebihara K, Zhao M, Naowaboot J, Kusakabe T, Kuwahara K, Murray M, Nakao K. Angiotensin II type 1 receptor-independent beneficial effects of telmisartan on dietary-induced obesity, insulin resistance and fatty liver in mice. *Diabetologia* 2010 Apr 15; Epub ahead of print
- 15 **Al-Mallah M**, Khawaja O, Sinno M, Alzohaili O, Samra AB. Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis. *Cardiol J* 2010; **17**: 448-456
- 16 **Bosch J**, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, Diaz R, Avezum A, Lanan F, Probstfield J, Fodor G, Holman RR. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; **355**: 1551-1562
- 17 **McMurray JJ**, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang FT, Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GE, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamás G, Tognoni G, Tuomilehto J, Villamil AS, Vozár J, Califf RM. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362**: 1477-1490
- 18 **Lubel JS**, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol* 2008; **23**: 1327-1338
- 19 **Lugo-Baruqui A**, Muñoz-Valle JF, Arévalo-Gallegos S, Armendáriz-Borunda J. Role of angiotensin II in liver fibrosis-induced portal hypertension and therapeutic implications. *Hepatol Res* 2010; **40**: 95-104
- 20 **Hirose A**, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, Takahashi M, Akisawa N, Iwasaki S, Oben JA, Onishi S. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. *Hepatology* 2007; **45**: 1375-1381
- 21 **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**: 988-996
- 22 **Yoshiji H**, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Yanase K, Namisaki T, Yamazaki M, Tsujinoue H, Imazu H, Fukui H. Angiotensin-II induces the tissue inhibitor of metalloproteinases-1 through the protein kinase-C signaling pathway in rat liver fibrosis development. *Hepatol Res* 2003; **27**: 51-56
- 23 **Yu F**, Takahashi T, Moriya J, Kawaura K, Yamakawa J, Kusaka K, Itoh T, Sumino H, Morimoto S, Kanda T. Angiotensin-II receptor antagonist alleviates non-alcoholic fatty liver in KKAY obese mice with type 2 diabetes. *J Int Med Res* 2006; **34**: 297-302
- 24 **Colmenero J**, Bataller R, Sancho-Bru P, Domínguez M, Moreno M, Forns X, Bruguera M, Arroyo V, Brenner DA, Ginès P. Effects of losartan on hepatic expression of nonphagocytic NADPH oxidase and fibrogenic genes in patients with chronic hepatitis C. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**: G726-G734
- 25 **Sookoian S**, Fernández MA, Castaño G. Effects of six months losartan administration on liver fibrosis in chronic hepatitis C patients: a pilot study. *World J Gastroenterol* 2005; **11**: 7560-7563
- 26 **Enjoji M**, Kotoh K, Kato M, Higuchi N, Kohjima M, Nakashima M, Nakamuta M. Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: a pilot study. *Int J Mol Med* 2008; **22**: 521-527
- 27 **Terui Y**, Saito T, Watanabe H, Togashi H, Kawata S, Kamada Y, Sakuta S. Effect of angiotensin receptor antagonist on liver fibrosis in early stages of chronic hepatitis C. *Hepatology* 2002; **36**: 1022
- 28 **Rimola A**, Londoño MC, Guevara G, Bruguera M, Navasa M, Forns X, García-Retortillo M, García-Valdecasas JC, Rodes J. Beneficial effect of angiotensin-blocking agents on graft fibrosis in hepatitis C recurrence after liver transplantation. *Transplantation* 2004; **78**: 686-691
- 29 **Cholongitas E**, Vibhakorn S, Lodato F, Burroughs AK. Angiotensin II antagonists in patients with recurrent hepatitis C virus infection after liver transplantation. *Liver Int* 2010; **30**: 334-335
- 30 **Corey KE**, Shah N, Misraji J, Abu Dayyeh BK, Zheng H, Bhan AK, Chung RT. The effect of angiotensin-blocking agents on liver fibrosis in patients with hepatitis C. *Liver Int* 2009; **29**: 748-753
- 31 **Abu Dayyeh BK**, Yang M, Dienstag JL, Chung RT. The ef-

- fects of angiotensin blocking agents on the progression of liver fibrosis in the HALT-C Trial cohort. *Dig Dis Sci* 2011; **56**: 564-568
- 32 **Georgescu EF**, Georgescu M. Therapeutic options in non-alcoholic steatohepatitis (NASH). Are all agents alike? Results of a preliminary study. *J Gastrointestin Liver Dis* 2007; **16**: 39-46
- 33 **Yokohama S**, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, Hasegawa T, Tokusashi Y, Miyokawa N, Nakamura K. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology* 2004; **40**: 1222-1225
- 34 **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**: 942-954
- 35 **Schupp M**, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation* 2004; **109**: 2054-2057
- 36 **Clemenz M**, Frost N, Schupp M, Caron S, Foryst-Ludwig A, Böhm C, Hartge M, Gust R, Staels B, Unger T, Kintscher U. Liver-specific peroxisome proliferator-activated receptor alpha target gene regulation by the angiotensin type 1 receptor blocker telmisartan. *Diabetes* 2008; **57**: 1405-1413
- 37 **Torres DM**, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of non-alcoholic steatohepatitis in humans: a 12-month randomized, prospective, open-label trial. *Hepatology* 2011; **54**: 1631-1639

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