February 01, 2016

Dear Editor,

We are pleased to learn the favorable comments from the reviewers about our article. We are in agreement with the reviewers recommendations up to some degree. According to the reviewers' suggestions, we made the following changes. We would like to submit the revised version of our manuscript for your consideration for publication.

Answers to Reviewer #02860797 Comments:

1-a- A paragraph "In addition, Vgontzas et al, include the production of inflammatory cytokines leading to oxidative stress in patients with chronic sleep apnea may be a possible mechanism contributing to the pathogenesis of NAFLD. This process may not only contribute to the increased insulin resistance seen in patients with NAFLD but also it may accelerate the process of liver fibrosis leading to the progression to steatohepatitis, cirrhosis and its complications[140,141]." was added to obstructive sleep apnea section.

140-**Vgontzas AN,** Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; **85:** 1151–1158. [PMID: 10720054]

141-**Musso G,** Olivetti C, Cassader M, Gambino R. Obstructive sleep apnea-hypopnea syndrome and nonalcoholic fatty liver disease: emerging evidence and mechanisms. Semin Liver Dis 2012; **32:** 49–64. [PMID: 22418888 DOI: 10.1055/s-0032-1306426]

b- A paragraph "The main results of their analysis are the following: (1) NAFLD was associated with an increased prevalence and incidence of CKD; (2) liver disease severity in NAFLD was associated with an increased risk and severity of CKD; (3) these associations remained statistically significant in diabetic and non-diabetic individuals, as well as in studies adjusting for traditional risk factors for CKD, and were independent of whole body/abdominal obesity and insulin resistance[144]. " was added to chronic kidney disease section.

144-**Musso G**, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J, Barrera F, Hafliðadóttir S, Björnsson ES, Armstrong MJ, Hopkins LJ, Gao X, Francque S, Verrijken A, Yilmaz Y, Lindor KD, Charlton M, Haring R, Lerch MM, Rettig R, Völzke H, Ryu S, Li G, Wong LL, Machado M, Cortez-Pinto H, Yasui K, Cassader M. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; **11:** e1001680 [PMID: 25050550 DOI:10.1371/journal.pmed.1001680]

c- A paragraph " Insulin resistance is also the proven risk factor of CVD by inducing the dyslipidemia and secreting proinflammatory cytokine, such as tumor necrosis factor-α and interleukin-6 accelerating the arteriosclerosis[131,132]. Under these effects of insulin resistance, arterial vascular elasticity and luminal width may be able to decrease to raise BP. In addition, sympathetic activation provoked by insulin resistance was likely to contribute to the development of hypertension. Previous studies showed that insulin resistance could raise BP through the sympathetic excitation[133,134]. Elevated insulin level related to insulin resistance was reported to induce the sympathetic overactivity by the direct and indirect action on central nervous system, and the enhanced uptake of noradrenaline in arterial wall by hyperinsulinemia increased the vascular sympathetic tone[135]. Accordingly, elevated sympathetic activation related to insulin resistance could play a significant role in the development of hypertension of NAFLD patients." was added to hypertension section.

131- **Kern PA,** Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 2003; **52**: 1779–1785. [PMID: 12829646 DOI: 10.2337/diabetes.52.7.1779]

132- **Targher G,** Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. *Atherosclerosis* 2007; **191**: 235–240. [PMID: 16970951 DOI: 10.1016/j.atherosclerosis.2006.08.021]

133-**Landsberg L,** Young JB. Insulin mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. *Int. J. Obes.* 1985; **9**: 63–68. [PMID: 3934092]

134-**Anderson EA,** Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J. Clin. Invest.* 1991; **87**: 2246–2252. [PMID: 2040704 DOI: 10.1172/JCI115260]

135-**Bhagat B,** Burke WJ, Dhalla NS. Insulin-induced enhancement of uptake of noradrenaline in atrial strips. *Br. J. Pharmacol.* 1981; **74**: 325–32. [PMID: 6274461 DOI: 10.1111/j.1476-5381.1981.tb09975.x]

2-We think that our review is well written and easily readable. It doesn't need a figure or table.

3-Some typos were corrected in this article.

Answers to Reviewer #02861277 Comments:

1-A paragraph "Elevated fatty acid β-oxidation as a result of increased lipolysis of adipose tissue in the NAFLD patients increases reactive oxygen species and activates oxidative stress[28]. The hepatic lipid accumulation and intracellular stresses activate the transcription and release of pro-inflammatory factors, such as interleukin-6, tumor necrosis factor-α and C-reactive protein[29,30]. A sedentary lifestyle in conjunction excessive energy intake promotes obesity and dysfunction of white

adipose tissue. White adipose tissue secretes more TNF-α and IL-6 and reduces the secretion of adiponectin[30]. The elevated circulating levels of pro-inflammatory cytokines and reduced anti-inflammatory factors cause a chronic low-grade inflammatory state that is recognized as an important pathogenic mechanism of NAFLD.'' was added to definition and pathogenesis section at page 5.

28- **Gentile CL,** Pagliassotti MJ. The role of fatty acids in the development and progression of nonalcoholic fatty liver disease. J Nutr Biochem 2008; **19:** 567–576. [PMID: 18430557 DOI: 10.1016/j.jnutbio.2007.10.001]

29- **Pirgon O,** Bilgin H, Cekmez F, Kurku H, Dundar BN. Association between insulin resistance and oxidative stress parameters in obese adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2013; **5:** 33–39. [PMID: 23367495 DOI: 10.4274/Jcrpe.825]

30- **Asrih M,** Jornayvaz FR. Inflammation as a potential link between nonalcoholic fatty liver disease and insulin resistance. J Endocrinol 2013; **218:** R25–36. [PMID: 23833274 DOI: 10.1530/JOE-13-0201]

2-''apnoea'' was corrected as ''apnea'' at page 7.

Answers to Reviewer #02860761 Comments:

We focused the relationship between pathogenesis of NAFLD and systemic diseases in this review. A separate review may be written in the genetic area. There are so much speculative data in this area. So, we aimed to give basic and well-proven genetic knowledge to readers in the pathogenetic section.

Answers to Reviewer #02861333 Comments:

We are thankful of reviewer's good comments.

Answers to Reviewer #02861252 Comments:

We are thankful of reviewer's good comments.

Answers to Reviewer # 02861131Comments:

We are thankful of reviewer's good comments. "Cardiovascular disease and NAFLD" section may be divided in the small different sections. But, we think that cardiovascular diseases have intense interaction with each other's. So, we didn't separate this section.

Answers to Reviewer # 02861262Comments:

1-"patientsubgroups" was separated as "patient subgroups" at page 3.

2-We aren't agree with reviewer's comment about objectives of this article is not definite. We focused on relationship between NAFLD and cardiovascular disease, hypertension, obstructive sleep apnea, chronic kidney disease.

3- a- A paragraph "In addition, Vgontzas et al, include the production of inflammatory cytokines leading to oxidative stress in patients with chronic sleep apnea may be a possible mechanism contributing to the pathogenesis of NAFLD. This process may not only contribute to the increased insulin resistance seen in patients with NAFLD but also it may accelerate the process of liver fibrosis leading to the progression to steatohepatitis, cirrhosis and its complications[140,141]." was added to obstructive sleep apnea section.

140-**Vgontzas AN,** Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to

visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; **85:** 1151–1158. [PMID: 10720054]

141-**Musso G,** Olivetti C, Cassader M, Gambino R. Obstructive sleep apnea-hypopnea syndrome and nonalcoholic fatty liver disease: emerging evidence and mechanisms. Semin Liver Dis 2012; **32:** 49–64. [PMID: 22418888 DOI: 10.1055/s-0032-1306426]

b- A paragraph "The main results of their analysis are the following: (1) NAFLD was associated with an increased prevalence and incidence of CKD; (2) liver disease severity in NAFLD was associated with an increased risk and severity of CKD; (3) these associations remained statistically significant in diabetic and non-diabetic individuals, as well as in studies adjusting for traditional risk factors for CKD, and were independent of whole body/abdominal obesity and insulin resistance[144]. " was added to chronic kidney disease section.

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4- We think that our review is well written and easily readable. It doesn't need a figure.

We hope that our revised manuscript is now satisfactory for publication in your journal. We would like to know if additional changes are necessary.

Best Regards,

Hakan Fotbolcu, MD.