Check for updates

CORRESPONDENCE

Fibromax-based nonalcoholic fatty liver disease in chronic obstructive pulmonary disease patients with obstructive sleep apnea: Methodological considerations [version 1; referees: 2 approved]

Denis Monneret 🆔

Department of Metabolic Biochemistry, La Pitié Salpêtrière-Charles Foix University Hospital (AP-HP), Paris, F-75013, France

Abstract

The relationship between nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA) has been well demonstrated, but remains to be evidenced in chronic obstructive pulmonary disease (COPD). Recently, Viglino *et al.* (Eur Respir J, 2017) attempted to determine the prevalence of liver fibrosis, steatosis and nonalcoholic steatohepatitis (NASH) in COPD patients, some of whom had OSA, basing the NAFLD diagnostic on three circulating biomarker-based liver scores: the FibroTest, SteatoTest and NashTest, from the Fibromax® panel. Among the main findings, the absence of OSA treatment emerged as independently associated with liver fibrosis and steatosis, when compared to effective treatment. However, besides the low number of treated patients, no polysomnographic respiratory data was provided, making it difficult to differentiate the impact of OSA from that of COPD in NAFLD prevalence. Furthermore, NAFLD diagnosis relied exclusively on circulating biomarker-based liver scores, without histological, imagery or other liver exploratory methods. Therefore, in this article, some methodological points are reminded and discussed, including the choice of OSA measurements, and the significance of ActiTest and AshTest scores from Fibromax® in this pathophysiological context.

Open Peer Review

Referee Status: ✔ ✔

	Invited Referees	
	1	**2**
version 1 published 08 Sep 2017	✔ report	✔ report

1 **Valentina Giorgio** 🆔 , Università Cattolica Sacro Cuore, Institute of Pediatrics, Italy

2 **Omar A Mesarwi**, UC San Diego Department of Medicine, USA

Discuss this article

Comments (0)

The relationship between nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA) has been well demonstrated[1–3], but remains to be evidenced in chronic obstructive pulmonary disease (COPD). To this end, using biomarker-based Fibromax® scores, Viglino *et al.* recently attempted to determine the prevalence of liver fibrosis, steatosis and nonalcoholic steatohepatitis (NASH) in COPD patients, which they found at nearly 61%, 41%, and 37%, respectively[4]. Interestingly, the absence of OSA treatment emerged as independently associated with liver fibrosis and steatosis, when compared to effective treatment. However, the number of treated patients was low (10 *versus* 38 untreated), and no polysomnographic respiratory data was provided, making it difficult to differentiate the impact of OSA from that of COPD in NAFLD prevalence. Furthermore, NAFLD diagnosis relied exclusively on circulating biomarker-based liver scores, without histological, imagery or other liver exploratory methods. It is, therefore, the opportunity to remind and discuss some methodological points, especially concerning the choice of OSA measurements, and the significance of ActiTest and AshTest scores from Fibromax® in this pathophysiological context.

1) Impact of OSA on NAFLD in COPD patients

Recently, Pépin's team showed a prevalence of liver steatosis of about 40–45% in moderate-to-severe OSA patients, with nearly 40–60% of patients displaying borderline NASH[5]. They also showed in obese OSA patients that fibrosis and NAFLD-related lesions, like hepatocyte ballooning and lobular inflammation, were more severe in those with the highest nocturnal oxygen desaturation[6]. Accordingly, nocturnal time spent at <90% oxygen saturation was independently associated with liver fibrosis in patients with suspicion of OSA[7]. In the Viglino *et al.* study, the absence of OSA treatment emerged as an independent factor of liver fibrosis and steatosis, as compared to treatment. Including the absence *versus* effective OSA treatment in the multivariate model is not the most appropriate criterion, since the authors recently showed that 6–12 weeks of CPAP treatment did not reduce steatosis, NASH or liver fibrosis[5]. This is in addition to the very low number of treated patients (10 *vs* 38 untreated). Instead, and according to the increasingly obvious hypothesis of chronic intermittent hypoxia (CIH) on NAFLD, the authors could have chosen the oxygen desaturation index as a criterion (e.g. with a cut-off < or ≥15 events/h), which they elsewhere claimed to be "*a good marker of CIH*"[6]. Studies displaying detailed results for both OSA and liver scores are few to date, and do not allow an in-depth analysis of their relationships. Therefore, in such NAFLD/COPD/OSA-related studies, polysomnographic respiratory profiles should be provided, including oxygen desaturation measurements, along with liver scores and detailed biology, for the overall COPD group and for OSA patients (all, treated and untreated), in order to strengthen conclusions and enable comparison with further studies.

2) Fibromax® scores

Viglino *et al.* focused on the three most appropriate NAFLD scores (i.e. FibroTest, SteatoTest, and NashTest). However, they did not provide ActiTest, another Fibromax® score proposed for the estimation of liver necroinflammatory activity in chronic hepatitis C and B[8], which is based on the measurement of the five Fibrotest® parameters *plus* alanine aminotransferase. Interestingly, ActiTest has been shown as highly accurate for the diagnosis of NASH and steatosis in patients with severe obesity, with notably an excellent negative predictive value for NASH at 96% using a cut-off at 0.29[9]. In another study on patients with suspected NAFLD, ActiTest showed a significant diagnostic value for NASH, which was not shown for FibroTest[10]. The informative value of ActiTest on the inflammatory component of NAFLD in COPD patients with or without OSA remains questionable; it could therefore be provided and discussed with regards to other inflammatory biomarkers (tumour necrosis factor-α and leptin in the Viglino *et al.* study).

Furthermore, alcohol consumption at ≥20g/day (women) and ≥30g/day (men) was chosen by the authors as exclusion criteria to discard potential alcoholic steatohepatitis (ASH). However, alcohol consumption may vary over time, even in abstainers or occasional drinkers, and may thus introduce a misclassification bias[11]. Self-reported alcohol consumption remains subjective and should ideally be evaluated using a reliable and objective measure. In this way, the AshTest score –the fifth of Fibromax® – is proposed for the detection of alcoholic steatohepatitis[12], and thus could be provided as a control for non-excessive alcohol consumption in such pathophysiological contexts.

3) Statistical consideration

Depending on the score, age, sex and/or weight and height are included in the Fibromax® calculation formulas. Therefore, the multivariate analyses from Viglino *et al*, which included age, sex and/or BMI as independent variables in addition to the Fibromax® score as a dependent variable may induce multicollinearity, and thus cause imprecise estimates of coefficient values or introduce large prediction errors in the case of extrapolation. Consequently, multicollinearity must be tested in such models, and controlled as much as possible.

4) Biomarker standardization

Viglino *et al.* did not provide any information about the methods used for Fibromax® parameters. Analytically, standardization allows the reduction of inter-laboratory variability. It is of particular importance for gamma-glutamyl transferase, known for its high inter-method variability, as well as for transaminases, which are measurable with or without pyridoxal 5-posphate as a coenzyme activator[13]. Fibromax® proteins also need standardization given their weight in score calculation, especially α2-macroglobulin[14]. Comparison with peer and method groups – through programs of quality control – allows inter-laboratory variation assessment; it is an analytical requirement of the ISO15189 standard for accreditation of medical laboratories, which is a strong guarantee of result reliability[15,16]. If ISO15189 certified methods are used for Fibromax® assays, it must be mentioned, along with methods and analyzers, in order to strengthen the biomarker component, to make it sufficiently informative to be compared with further studies.

To conclude, in such studies evaluating NAFLD, based exclusively on combined-biomarker scores without clinical, histological, imagery or other liver exploratory methods, information on assay methods, analyzers, and guarantees of analytical performance are

required, which requires a strong collaboration between clinicians and lab practitioners.

Competing interests

No competing interests were disclosed.

References

1. Musso G, Cassader M, Olivetti C, *et al.*: **Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis.** *Obes Rev.* 2013; **14**(5): 417–31.
   PubMed Abstract | Publisher Full Text

2. Polotsky VY, Patil SP, Savransky V, *et al.*: **Obstructive sleep apnea, insulin resistance, and steatohepatitis in severe obesity.** *Am J Respir Crit Care Med.* 2009; **179**(3): 228–34.
   PubMed Abstract | Publisher Full Text | Free Full Text

3. Nobili V, Cutrera R, Liccardo D, *et al.*: **Obstructive sleep apnea syndrome affects liver histology and inflammatory cell activation in pediatric nonalcoholic fatty liver disease, regardless of obesity/insulin resistance.** *Am J Respir Crit Care Med.* 2014; **189**(1): 66–76.
   PubMed Abstract | Publisher Full Text

4. Viglino D, Jullian-Desayes I, Minoves M, *et al.*: **Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease.** *Eur Respir J.* 2017; **49**(6): pii: 1601923.
   PubMed Abstract | Publisher Full Text

5. Jullian-Desayes I, Tamisier R, Zarski JP, *et al.*: **Impact of effective versus sham continuous positive airway pressure on liver injury in obstructive sleep apnoea: Data from randomized trials.** *Respirology.* 2016; **21**(2): 378–85.
   PubMed Abstract | Publisher Full Text

6. Aron-Wisnewsky J, Minville C, Tordjman J, *et al.*: **Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese.** *J Hepatol.* 2012; **56**(1): 225–33.
   PubMed Abstract | Publisher Full Text

7. Minville C, Hilleret MN, Tamisier R, *et al.*: **Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea.** *Chest.* 2014; **145**(3): 525–33.
   PubMed Abstract | Publisher Full Text

8. Morra R, Munteanu M, Imbert-Bismut F, *et al.*: **FibroMAX: towards a new universal biomarker of liver disease?** *Expert Rev Mol Diagn.* 2007; **7**(5): 481–90.
   PubMed Abstract | Publisher Full Text

9. Poynard T, Lassailly G, Diaz E, *et al.*: **Performance of biomarkers FibroTest, ActiTest, SteatoTest, and NashTest in patients with severe obesity: meta analysis of individual patient data.** *PLoS One.* 2012; **7**(3): e30325.
   PubMed Abstract | Publisher Full Text | Free Full Text

10. Ratziu V, Massard J, Charlotte F, *et al.*: **Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease.** *BMC Gastroenterol.* 2006; **6**: 6.
    PubMed Abstract | Publisher Full Text | Free Full Text

11. Rehm J, Irving H, Ye Y, *et al.*: **Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstention.** *Am J Epidemiol.* 2008; **168**(8): 866–71.
    PubMed Abstract | Publisher Full Text | Free Full Text

12. Thabut D, Naveau S, Charlotte F, *et al.*: **The diagnostic value of biomarkers (AshTest) for the prediction of alcoholic steato-hepatitis in patients with chronic alcoholic liver disease.** *J Hepatol.* 2006; **44**(6): 1175–85.
    PubMed Abstract | Publisher Full Text

13. Halfon P, Imbert-Bismut F, Messous D, *et al.*: **A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease.** *Comp Hepatol.* 2002; **1**(1): 3.
    PubMed Abstract | Publisher Full Text | Free Full Text

14. Rosenthal-Allieri MA, Peritore ML, Tran A, *et al.*: **Analytical variability of the Fibrotest proteins.** *Clin Biochem.* 2005; **38**(5): 473–8.
    PubMed Abstract | Publisher Full Text

15. Guzel O, Guner EI: **ISO 15189 accreditation: Requirements for quality and competence of medical laboratories, experience of a laboratory I.** *Clin Biochem.* 2009; **42**(4–5): 274–8.
    PubMed Abstract | Publisher Full Text

16. AbdelWareth LO, Pallinalakam F, Ibrahim F, *et al.*: **Fast Track to Accreditation: An Implementation Review of College of American Pathologists and International Organization for Standardization 15189 Accreditation.** *Arch Pathol Lab Med.* 2017.
    PubMed Abstract | Publisher Full Text

Open Peer Review

Current Referee Status: ✔ ✔

Version 1

Referee Report 27 November 2017

✔ **Omar A Mesarwi**

Division of Pulmonary, Critical Care, and Sleep Medicine, UC San Diego Department of Medicine, La Jolla, CA, USA

This article, by Dr. Monneret, presents many very salient points in reference to the article by Viglino et al. I would like to make a minor remark:

In section 1, I think the article may benefit from a very brief mention of the biological differences between intermittent and sustained hypoxia - experimentally these exposures yield very different metabolic outcomes, and the mechanisms which underlie these effects (sympathetic activation, oxidative stress, tissue oxygen profiles, etc.) may be quite different in sustained hypoxia as in COPD, versus chronic intermittent hypoxia, as in OSA.

Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 27 November 2017

✔

Valentina Giorgio iD

Fondazione Policlinico Universitario A. Gemelli, Università Cattolica Sacro Cuore, Institute of Pediatrics, Rome, Italy

This letter is interesting, written in good and fluent English, clearly addressing the limits of a paper attempting to find a link between obstructive sleep apnea (OSA) and Non alcoholic Fatty Liver, in patients with chronic obstructive pulmonory disease (COPD). I agree with Monneret that one of the main limit of this paper, among others, is that it is quite difficult to differentiate the impact of OSA from that of COPD in fatty liver prevalence, because of the common respiratory nature of OSA and COPD and the common negative effect in oxygen saturation. Therefore, although the paper has the merit of pointing out that non alcoholic fatty liver disease can be present -and maybe more often present- in patients with COPD, more polysomnographic respiratory profiles should be provided, including oxygen desaturation measurements.

Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.