Sleep Apnea and Ectopic Fat Deposition

To the Editor:

We read the recently published article in CHEST (March 2014) by Minville et al1 with a great interest. The authors demonstrated that OSA and, more specifically, severity of nocturnal hypoxia were significantly associated with ectopic fat deposition in the liver.

Indeed, as pointed out by the authors, OSA is linked to a multitude of derangements of metabolism, including diabetes mellitus, hyperlipidemia, and others. It is essential to understand whether OSA-targeted therapy will prevent or halt the development of associated cardiometabolic conditions. One potential way to do this is to detect populations at risk at early stages, when the impact of OSA therapy on the development and/or progression of comorbid conditions may be the greatest. Recent research data suggest that ectopic fat deposition in the pancreas precedes a similar process in the liver.2 Nonalcoholic fatty pancreatic disease (NAFPD) is strongly linked to metabolic abnormalities, similar to nonalcoholic fatty liver disease.3 Given the possibility that NAFPD may be an earlier manifestation of excessive metabolic risk, it might be useful to study whether OSA is more common in this group than in people without NAFPD.4 If this is found to be true, further research should focus on whether OSA treatment would lead to resolution of NAFPD and, more importantly, beneficially impact the metabolic profile.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.14-0627

References

Response

To the Editor:

We thank Drs Mirrakhimov and Mirrakhimov for their interest in our recent article in CHEST.1 They mainly raise the question of a potential role for nonalcoholic fatty pancreatic disease (NAFPD) as an underlying mechanism for the association between OSA and type 2 diabetes.

Rapidly accumulating data from both epidemiologic and clinical studies have suggested that OSA is independently associated with alterations in glucose metabolism as well as with an increased risk of developing type 2 diabetes. Multiple mechanistic pathways contribute to the deteriorated plasma glucose/insulin homeostasis in OSA, the primary one being sympathetic overactivity, due to sleep fragmentation and intermittent hypoxia. Independent of autonomic nervous system activation, intermittent hypoxia in rodent models contributes to decreased glucose use in oxidative muscle fibers. Intermittent hypoxia also seems to be responsible for increased β-cell proliferation and cell death, the latter being due to oxidative stress.

OSA is also commonly associated with obesity and independently participates in the development of visceral obesity. Adipocytes exposed to hypoxia exhibit a dysregulated production of adipocytokines, which may contribute to insulin resistance and metabolic syndrome in patients with OSA. We have demonstrated in morbid obesity that chronic intermittent hypoxia is strongly associated with nonalcoholic fatty liver disease (NAFLD) and more severe fibrotic or inflammatory liver injuries.2 There are different aspects of lipid storage that

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are not systematically detrimental. For example, lipid droplets can act as a defense mechanism to compensate for dysregulated lipolysis in liver. Whether this phenomenon exists in the pancreas is unknown.

Drs Mirrakhimov and Mirrakhimov correctly underline the lack of data regarding NAFPD in patients with OSA. A high-fat diet in rodents induces fat accumulation, inflammatory cell infiltration, and fibrosis in the pancreas with secondary insulin resistance and features of both NAFLD and NAFPD. Recently, both diabetes and NAFLD have been demonstrated as associated factors of fatty pancreas, independent of age, sex, adiposity, and other cardiometabolic risk factors. Further studies in rodent models exposed to intermittent hypoxia and in OSA cohorts need to address this issue.

Effective treatment of OSA has been proposed as an important target for improving cardiometabolic risk and reducing ectopic fat. Recent literature shows that it is not realistic to expect a clinically relevant decrease in abdominal and liver fat with CPAP therapy. The range of response, if any, is not equivalent to lipid-lowering drugs or weight-loss programs. However, men with OSA at baseline had a smaller reduction in body weight and fewer metabolic improvements associated with lifestyle intervention than men without OSA. Also, after bariatric surgery, epicardial fat volume loss, another feature of ectopic fat, was limited in patients with obesity.

Intermittent hypoxia may induce a high level of fibrosis in different ectopic adipose tissues, which can initiate resistance to weight loss or CPAP intervention efficacy.

In conclusion, all the features of ectopic fat deposits (ie, abdominal, hepatic, pancreatic, and epicardial) need to be better documented in OSA cohorts. The mechanisms by which OSA induces a resistance to classic intervention addressing ectopic fat syndrome are promising research avenues.

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References