

A sleep apneic's gene: perspectives for development of diabetes

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Obstructive sleep apnea (OSA) is a prevalent sleep breathing disorder with major cardiometabolic sequelae.¹ Several longitudinal studies have demonstrated an association between OSA and incident type 2 diabetes.^{2,3} In a recent population-based longitudinal study of more than 36 000 individuals and up to 25 years of follow-up, Strausz et al⁴ showed that OSA is an independent risk factor for diabetes and diabetic kidney disease. OSA increased the risk for development of diabetes by 48% and the risk for development of diabetic kidney disease in the diabetic population by 75%. Importantly, the presence of comorbidities such as diabetes increases the mortality risk for patients with OSA.^{5,6} All-cause mortality was increased by OSA in diabetic individuals by 35%.⁴ Together, these studies suggest that diabetes prevention in OSA population would have profound clinical implications. Towards this goal, it would be important to risk stratify patients with OSA such that individuals in whom diabetes is more likely to develop may be readily identified.

OSA is a complex heterogeneous disorder resulting from culmination of various anatomical, neuromuscular, and environmental factors. In recent years, emerging evidence from familial aggregation of OSA along with genetic linkage and genetic association studies have suggested a strong genetic predisposition to develop OSA.⁷ Notably, obesity is a common underlying denominator for both OSA and diabetes, which has a strong underlying genetic component as well. Since not all patients with sleep apnea develop diabetes, it is likely that OSA provides a unique environment (intermittent hypoxic conditions and sleep fragmentation), precluding the development of diabetes in only some genetically predisposed individuals.

In this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Bielicki et al⁸ presented their findings from a targeted association-based approach to identify genetic risk for diabetes in patients with OSA. This study is the first to examine genetic basis for

diabetes in a well-defined OSA population. Five candidate genes were selected based on prior evidence linking to the development of diabetes and obesity. A single nucleotide polymorphism in these genes was determined by specific TaqMan genotyping assays using DNA samples obtained from 600 patients with OSA. Importantly, in this cross-sectional study, the diagnosis of OSA was based on polysomnographic evidence and the presence or absence of diabetes was confirmed by HbA_{1c}, fasting glucose, or oral glucose tolerance test. Despite the small population and limited gene polymorphisms being investigated, the authors identified APOA5 rs3135506 GG homozygotes as associated with a lower incidence of type 2 diabetes in patients with OSA. In other words, the presence of APOA5 rs3135506 CG heterozygotes was associated with an increased risk for diabetes by more than 2.5 fold. Importantly, the polymorphism in APOA5 has been previously demonstrated to be associated with circulating triglyceride levels, body mass index, diabetes, hypertension, and ischemic stroke.^{9,10} Of note, APOA5 polymorphisms include several variants that were not included in the above study, such as rs662799.⁹ Moreover, ethnic and sex differences in APOA5 gene polymorphisms have been shown, which suggests that additional studies need to be undertaken in a more diverse population to understand the importance of this gene to OSA pathology.⁹ Interestingly, in the study population, patients with OSA and diabetes showed higher levels of triglycerides even in the presence of lower levels of total cholesterol. These findings suggest an important role for lipid metabolism in the development of diabetes in the OSA population. If confirmed, this may be exploited to improve long-term clinical outcomes in the OSA population.

An important limitation related to gene association studies in human populations is that they cannot demonstrate causality. Therefore, animal studies examining the importance of the genetic

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variations of *APOA5* in conditions of intermittent hypoxia and/or sleep fragmentation need to be undertaken to demonstrate direct effects on glucose homeostasis. These studies would also be important to identify drugs which may be more useful in mitigating the risk associated with specific gene variations. Lastly, the study population was limited by the sample size, which prevented the examination of the differential effects of the gene polymorphisms in men versus women. Global combined efforts should be engineered to undertake the study of the *APOA5* gene polymorphisms in large, diverse, and a well-defined OSA population.

Nevertheless, the findings provide a strong basis for future studies examining genetic predisposition to the development of diabetes and other comorbidities in patients with OSA. Designing studies using unbiased approaches to identify gene polymorphisms which may associate with cardiometabolic dysfunctions would be critical to prevent bias related to the targeted gene approach. It would also allow identification of novel genes or targets that may underlie OSA pathophysiology. Longitudinal prospective studies examining the ability of gene polymorphisms to predict the development of diabetes and other cardiometabolic disorders in patients with OSA would be of clinical importance as well. The goal would be to identify the contribution of relevant single nucleotide polymorphisms to provide an overall individualized composite score to determine diabetes, cardiovascular, and mortality risk in OSA. Using genetic markers for risk stratification in patients with OSA would enable development of personalized interventions to prevent diabetes and other comorbidities, thereby decreasing the overall cardiometabolic burden and reduce mortality risk. Indeed, studies investigating the role of genetic variations including the *APOA1/C3/A4/A5* gene cluster and lipid response to lipid-lowering drugs, such as fenofibrate, have been undertaken.¹¹

Irrespective of OSA, diabetes is a major global health concern associated with increased morbidity, mortality, as well as high economic burden.¹² Furthermore, the relationship between OSA and diabetes is bidirectional.^{2,13} Individuals with diabetes have been shown to have a higher risk of sleep apnea. The relationship of incident OSA in a diabetic population may be more profound in patients using insulin compared with individuals without diabetes.¹³ Therefore, future studies examining the genetic factors predisposing diabetic individuals to OSA will be of interest, so that optimal therapeutic interventions may be used to reduce the risk of OSA and associated cardiovascular diseases.

To summarize, the use of gene polymorphisms to identify high-risk patients in OSA and diabetic populations presents as an exciting opportunity that may provide important clues to the development of individualized treatment strategies to reduce cardiovascular burden and mortality risk.

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