Hitting two birds with one stone: the potential role of serum hypoxia-inducible factor-1α protein levels in obstructive sleep apnea–related cardiovascular disease

To the editor We have read with great interest the study by Gabryelska et al,[1] suggesting that serum hypoxia-inducible factor-1α (HIF-1α) protein might serve as a promising diagnostic marker in obstructive sleep apnea (OSA), after exclusion of some chronic hypoxia disorders. The marker showed an area under the curve (AUC) of 0.841 for a cutoff value of 1055.6 pg/ml, with high sensitivity, specificity, and positive predictive value. In addition, no circadian fluctuation was demonstrated.[1]

A previous meta-analysis of prospective studies showed that moderate and severe OSA is associated with a significant increase in the risk of major adverse cardiovascular events, irrespective of the presence of comorbidities, as well as coronary artery disease, while severe OSA also increases the risk of stroke and cardiovascular and all-cause mortality.[2]

Serum HIF-1α levels have been previously shown to correlate with the coronary artery calcification (CAC) score in a cohort of 405 asymptomatic patients with type 2 diabetes (r = 0.36, P <0.001), with an AUC of 0.775, a sensitivity of 61.1%, and a specificity of 87.6% for predicting the extent of CAC (cutoff value, 236.5 pg/ml).[3] These findings might imply that the serum HIF-1α level is an independent risk factor for CAC in patients with type 2 diabetes, a frequent comorbidity in OSA.[3]

Another observational study including 296 patients with acute decompensated heart failure demonstrated that serum HIF-1α levels were higher in these patients compared with healthy controls (P <0.001), while they were also significantly higher in patients with heart failure with reduced ejection fraction, compared with patients with heart failure with preserved ejection fraction.[4] Of note, serum HIF-1α levels were higher in patients who died during follow-up as compared with survivors (P <0.001).[4] In addition, investigators documented that serum HIF-1α levels positively correlated with the concentrations of N-terminal fragment of the prohormone brain natriuretic peptide (r = 0.337, P <0.001) and cardiac troponin T (r = 0.357, P <0.001), while they negatively correlated with left ventricular ejection fraction (r = –0.332, P <0.001) and systolic blood pressure (r = –0.145, P = 0.013). However, no association between serum HIF-1α levels and in-hospital mortality was observed in the fully adjusted Cox regression model. Finally, the AUC of serum HIF-1α in predicting the type of acute decompensated heart failure was shown to be 0.73, with a sensitivity of 35.2% and a specificity of 90%, for the cutoff value of 3.62 ng/ml.[4]

To sum up, serum HIF-1α levels might have significant diagnostic and even prognostic value in patients with either asymptomatic or symptomatic cardiovascular disease (CVD). It would be interesting if Gabryelska et al[1] could perform a subgroup analysis assessing whether there is a difference in serum HIF-1α levels among enrolled patients with OSA according to the CVD status at baseline. Of course, large-scale prospective studies are required to investigate whether this biomarker could provide prognostic information on the development of CVD and its manifestation in patients with OSA.

ARTICLE INFORMATION

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Authors' reply Patoulias et al[1] have made an interesting point, highlighting a possible impact of hypoxia-inducible factor-1α (HIF-1α) on the development and manifestation of cardiovascular diseases (CVDs), which are the main comorbidities in patients with obstructive sleep apnea (OSA).[2] This association has a strong pathophysiological basis, as HIF-1α is responsible for the activation of multiple genes involved in angiogenesis and vascular resistance, most notably vascular endothelial growth factor and endothelin 1.[3]

To assess whether individuals with a history of CVD had increased serum HIF-1α protein levels, we performed a supplementary analysis to evaluate a diagnostic value of this parameter in OSA.[4] Cardiovascular diseases included heart failure, myocardial infarction, cardiomyopathy, and cardiac arrythmias.

We found that the serum HIF-1α protein level was increased in individuals with CVD (n = 18), both in the evening (median, 1071.2 pg/ml [interquartile range [IQR], 640.4–1637 pg/ml] vs 1504.9 pg/ml [IQR, 899.2–2337.9 pg/ml]; $P = 0.049$) and in the morning (median, 1193 pg/ml [IQR, 622.5–1662.9 pg/ml] vs 1694.4 pg/ml [IQR, 1071.5–2022.5 pg/ml]; $P = 0.045$), as compared with patients without history of CVD (n = 42).

Furthermore, in the study group, evening and morning serum HIF-1α protein levels correlated with the apnea–hypopnea index (AHI; $r = 0.37$, $P = 0.001$ and $r = 0.362$, $P = 0.001$, respectively) and body mass index (BMI; $r = 0.259$, $P = 0.018$ and $r = 0.276$, $P = 0.011$, respectively).

To assess the effect of confounding variables, the analysis of covariance (ANCOVA) was performed with serum HIF-1α protein levels as a dependent factor, the presence of CVD as an independent factor, and AHI and BMI as covariates. In the applied ANCOVA model, only the presence of CVD differentiated serum HIF-1α protein levels in the evening and in the morning: F = 4.737, $P = 0.032$ and F = 5.477, $P = 0.022$, respectively. Covariates did not affect the observed differences in serum HIF-1α protein levels in the evening and in the morning, which remained significant ($P = 0.034$ and $P = 0.035$, respectively).

This additional analysis showed that OSA patients with CVD have increased serum HIF-1α protein levels, both in the evening and in the morning, independently of AHI and BMI. The results suggest the involvement of HIF-1α in the development and manifestation of CVD. However, as stated by Patoulias et al,[1] large prospective studies are needed to corroborate these findings. Our research can be perceived as a pilot study, especially that the diagnosis of CVD was based only on patient history and no additional examinations were performed to confirm it. Moreover, the effect of continuous positive air pressure treatment[5] should be assessed in relation to serum HIF-1α protein levels and comorbid CVD, including its severity, to show all aspects of this complex issue.

ARTICLE INFORMATION

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