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Lipolyse Enzyms Levels in Patients with Obstructive Sleep Apnea Syndrome; Especially Perilipin-1

Obstrüktif Uyku Apne Sendromlu Hastalarda Lipoliz Enzim Düzeyleri; Özellikle Perilipin-1

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ABSTRACT

Objective: Since obesity is an important risk factor in obstructive sleep apnea syndrome (OSAS), it will be important to determine the relationship between intracellular and intravascular lipolysis enzymes and OSAS. In this study we investigated the levels of lipolysis enzymes Perilipin-1 (Plin-1), adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL) and lipoprotein lipase (LPL) in patients with OSAS and the relationship between these enzymes and OSAS.

Material and Method: 51 OSAS patients with obstructive sleep apnea syndrome and 25 volunteers diagnosed with simple snoring as a control group were included in the study. Polysomnographic evaluation, age, gender, and body mass index of each participant were recorded. Blood was taken from the participants on the same day to analyse enzymes.

Results: Between the OSAS group (n:51) and the control group (n:25), age (mean: 45.3±10 vs 40.9±9.1, p value: 0.065), gender (female/male in the patient and control group, respectively: 5/46, 3/22, p value: 0.76) and BMI (min-max 23.3-40.1 vs 24-44.1kg/m², p value: 0.21, respectively) were similar. For ATGL, HSL, LPL, no significant difference was detected between the groups (median values: 65.9 vs 68.3ng/ml, 7.30 vs 7.33ng/ml, 484.2 vs 485.3pg/ml, p values: 0.33, 0.69, 0.33, respectively). Plin-1 level was found to be significantly higher in the OSAS group (median value: 5.34 vs 4.87 ng/ml, p:0.038). It was determined that Plin-1 had a positive correlation with WASO (wake after sleep onset) and a negative correlation with total sleep time (p value: 0.003, 0.006, r value: 0.41, -0.38, respectively). In the linear regression analysis performed for the OSAS group, WASO was detected as a risk factor for Plin-1 elevation (p: 0.003, B: 0.012).

Conclusion: We found that Plin-1 levels increased secondary to sleep disruptions in patients with OSAS, independent of obesity.

Keywords: *Obstructive Sleep Apnea Syndrome, Perilipin-1, Lipolysis*

ÖZET

Giriş: Obstrüktif uyku apne sendromunda (OSAS) obezite önemli bir risk faktörü olduğundan, hücre içi ve damar içi lipoliz enzimleri ile OSAS arasındaki ilişkiyi belirlemek önemli olacaktır. Bu çalışmada OSAS'lı hastalarda lipoliz enzimleri Perilipin-1 (Plin-1), yağ trigliserit lipaz (ATGL), hormon duyarlı lipaz (HSL) ve lipoprotein lipaz (LPL) düzeylerini ve bu enzimlerle OSAS arasındaki ilişkiyi araştırdık.

Materyal ve Metot: Obstrüktif uyku apne sendromu olan 51 OSAS hastası ve kontrol grubu olarak basit horlama tanısı almış 25 gönüllü çalışma ya dahil edildi. Her katılımcının polisomnografik değerlendirmesi, yaşı, cinsiyeti ve vücut kitle indeksi kaydedildi. Enzimleri analiz etmek için katılımcılardan aynı gün kan alındı.

Bulgular: OSAS grubu (n: 51) ile kontrol grubu (n: 25) arasında yaş (ortalama: 45,3 ± 10 vs 40,9 ± 9,1, p değeri: 0,065), cinsiyet (hasta ve kontrol grubunda kadın/ erkek, sırasıyla: 5/46, 3/22, p değeri: 0,76) ve VKİ (sırasıyla min-maks 23,3-40,1 vs 24-44,1 kg/m², p değeri: 0,21) benzerdi. ATGL, HSL, LPL için gruplar arası anlamlı fark saptanmadı (sırasıyla medyan değerler: 65,9 vs 68,3 ng/ml, 7,30 vs 7,33 ng/ml, 484,2 vs 485,3 pg/ml, p değerleri: 0,33, 0,69, 0,33). Plin-1 düzeyinin OSAS grubunda anlamlı olarak daha yüksek olduğu bulundu (ortanca değer: 5,34'e karşı 4,87 ng/ml, p: 0,038). Plin-1'in WASO (uyku başlangıcından sonra uyanma) ile pozitif korelasyon ve toplam uyku süresi ile negatif korelasyona sahip olduğu belirlendi (sırasıyla p değeri: 0,003, 0,006, r değeri: 0,41, -0,38). OSAS grubu için yapılan doğrusal regresyon analizinde, WASO'nun Plin-1 yükselmesi için bir risk faktörü olduğu tespit edildi (p: 0,003, B: 0,012).

Sonuç: Obstrüktif Uyku Apnesi Sendromu'na sahip hastalarda Plin-1 düzeylerinin obeziteye bağlı olmaksızın uyku bozukluklarına bağlı olarak arttığını bulduk.

Anahtar kelimeler: *Obstrüktif Uyku Apnesi Sendromu, Perilipin-1, Lipoliz*

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a chronic respiratory disorder caused by recurrent partial upper airway obstruction and diagnosed by detecting hypopnea-apnea during sleep (Strollo and Rogers, 1996). It is an important sleep disorder that affects 2-4% of the general population and its prevalence is increasing due to obesity (Young et al., 1993; Peppard et al., 2013). Its prevalence is 17% in women and 34% in men between the ages of 30-70 (Peppard et al., 2013). Nowadays it is well known that; there is an independent association between OSAS and metabolic dysfunction, especially insulin resistance and dyslipidemia (Drager et al., 2015; Kent et al., 2015; Gileles-Hilles et al., 2017). The most important epidemiological risk factors for OSAS are obesity and male gender (Davies, 1990; Reichmuth et al., 2005).

Lipolysis enzymes, which carry out lipid metabolism, play an important role in obesity. Clinical and epidemiological evidence suggests that OSAS is associated with dysregulation of lipoprotein metabolism (Newman et al., 2001; Trzepizur et al., 2013). Energy storage as fat and energy consumption through lipolysis have a complex mechanism that occurs intravascularly and intracellularly. In intravascular lipolysis, in the fed state, circulating fatty acids obtained from dietary sources are transported by lipoproteins in an esterified form as triacylglycerol. Fatty acids are released from triacylglycerols associated with lipoproteins by lipoprotein lipase (LPL) to deliver fatty acids to target tissues (Hundahl et al., 2021).

In intracellular lipolysis, fat droplets in white adipose tissue are hydrolyzed into fatty acid and glycerol to be used or released by cells. Triglyceride storage and hydrolysis in adipose tissue is extremely important for the body's metabolic homeostasis. Excess energy nutrients are stored as triglycerides in fat drops in adipocytes. On the other hand, in cases of hunger and stress, triglycerides are hydrolyzed into fatty acids and glycerol and released into the blood. This balance affects adipocyte volume. Increased lipid stores and bypassing lipolysis are the main pathophysiological mechanisms in obesity (Londos et al., 2005). Perilipin, adipose triglyceride lipase, hormone sensitive lipase and monoacylglycerol lipase play a role in intracellular lipolysis.

Perilipin is one of the gene family associated with obesity risk (Maghroun et al., 2021). Perilipin-1 (Plin-1) is a predominant protein of mature adipocytes and is the most abundant protein on the lipid droplet surface. In the basal state, Plin-1 blocks cytosolic lipases (hormone sensitive lipase (HSL), adipose triglyceride lipase (ATGL)) from reaching lipid droplets, thus facilitating the storage of triglycerides (Ding et al., 2020).

In the state of stress and starvation, Plin-1 is phosphorylated by protein kinase A to facilitate lipolysis. Plin-1 phosphorylation allows hormone-sensitive lipase to reach the lipid droplet and promotes adipose triglyceride lipase-dependent lipolysis (Zhang et al., 2003; Miyoshi et al., 2007).

Lipolysis, which consists of the hydrolysis of triglycerides into three fatty acids and glycerol respectively, is catalyzed by three different enzymes. In the first step of this process, triacylglycerol is hydrolyzed to diacylglycerol and a fatty acid molecule by a reaction catalyzed primarily by the enzyme adipose triglyceride lipase. Next, diacylglycerol is converted to monoacylglycerol and a second fatty acid by the action of hormone-sensitive lipase. Finally, monoacylglycerol is hydrolyzed to a final fatty acid and glycerol by monoacylglycerol lipase (Bolsoni-Lopes and Alonso-Vale, 2015).

ATGL (desnutrin), with a molecular weight of 54 kDa, is found mostly in brown-white adipose tissue and to a lesser extent in testicles, pancreatic islets, cardiac muscle and skeletal muscle. ATGL is the main enzyme responsible for triacylglycerol hydrolysis and is found in lipid droplets in adipocytes. Therefore, its hydrolytic activity on triacylglycerol occurs independently of the protein barrier containing lipid droplets, making lipase crucial in basal lipolysis (Bolsoni-Lopes and Alonso-Vale, 2015). The main phenotypic consequence of ATGL reduction is the accumulation of large amounts of triacylglycerol in adipocytes and other tissues, the development of obesity and other metabolic complications (Haemmerle et al., 2006). Overexpression of ATGL is associated with increased fatty acid oxidation, basal and stimulated lipolysis, and decreases adipocyte size and triacylglycerol stores (Smirnova et al., 2006; Bézaire and Langin, 2009).

Various hormones and peptides mediate interactions between metabolism and obesity in OSAS, but the relationship between lipolysis enzymes in OSAS has not been fully clarified. Since obesity is an important risk factor in OSAS, it will be important to determine the relationship between intracellular and intravascular lipolysis enzymes and OSAS.

In this study, we investigated serum Plin-1, ATGL, HSL and LPL levels and the relationship between these enzymes and OSAS.

MATERIAL and METHOD

This study was planned as observational and cross-sectional. It was conducted in the Chest Diseases Department of Van Yüzüncü Yıl University Dursun Odabaş Medical Center. Ethical approval for the study was received from Van Yüzüncü Yıl University Clinical Research Ethics Committee on 21.11.2017 (No:01).

The study was conducted on 76 adults over the age of 18 who applied to the sleep laboratory with complaints of snoring and shortness of breath, excessive daytime sleepiness, fatigue and headaches. 51 OSAS patients with obstructive sleep apnea syndrome and 25 volunteers diagnosed with simple snoring were included in the study. The data cannot be shared openly to protect study participant privacy.

Those who have any other chronic disease other than OSAS or snoring, such as diabetes, cancer, heart failure, chronic obstructive pulmonary disease, hepatic or renal failure, those who receive systemic steroid or hormone replacement therapy, those who receive surgical or medical treatment for an anatomical anomaly affecting the respiratory tract, or sleep disorders and pregnant women were not included in the study.

Polysomnographic evaluation (PSG): Each participant underwent standard overnight PSG using a digital PSG system. A ≥90% decrease in airflow compared to baseline values for ≥10 seconds with an effort to continue breathing was considered apnea. Oxygen desaturation of ≥3% or a decrease in airflow of ≥30% for ≥10 seconds with awakening from sleep was considered hypopnea.

Apnea-Hypopnea index (AHI): Calculated by dividing the total number of apnea and hypopnea episodes by sleep duration (per hour). The diagnosis of OSAS was made by evaluating the symptoms and sleep tests together.

Polysomnographic evaluation was performed on every patient who applied to the sleep laboratory. The diagnoses of OSAS were drawn on the findings regarding overnight PSG that was conducted with a 16-channel digital recording system (Embla; MedcareFlaga, Reykjavik, Iceland). Patients with Apnea-Hypopnea Index (AHI) ≥ 5 were considered as the OSAS group and those with AHI < 5 were considered as the control group.

All participants' apnea hypopnea index (AHI), wake after sleep onset (WASO), total sleep time, oxygen desaturation index (ODI), mean desaturation index (MDI), apnea index (AI), hypopnea index (HI), AHI in REM sleep (REM AHI), AHI in non-REM sleep, AHI in the supine position, REM sleep duration, nonREM sleep duration, and desaturation duration were recorded.

Participants' weight and height were measured while wearing light clothing and without shoes. Body mass indexes were calculated and recorded by dividing their weight by the square of their height.

Fasting blood samples were taken between 08:00 and 10:00 in the morning the day after the sleep study. On the day of blood collection, glucose was measured on the Abbot architect i2000 immunoassay analyser (USA) and insulin on the Abbot architect c16000 chemistry analyzer (USA). For other parameters, blood samples were separated into serum by centrifugation at 3500 RPM for 10 minutes. Serum samples were stored at -20 °C until the day of study. Serum perilipin 1, adipose triglyceride lipase, hormone-sensitive lipase and lipoprotein lipase levels were studied by ELISA method using commercial kits. Measurement of lipoprotein lipase, ATGL, perilipin1, hormone-sensitive lipase activities were performed with a Biotek ELX-800 ELISA reader.

The homeostatic assessment for insulin resistance (HOMA-IR) was computed from fasting glucose and insulin concentrations and recorded.

After all analyzes were performed and recorded, the OSAS and control group comparison was made statistically. In addition, the OSAS group was grouped as mild, moderate and severe OSAS and appropriate statistical analysis was performed.

SPSS package program was used for statistical analysis (SPSS 20.9, SPSS Inc., Chicago, IL, USA). Results are given as mean ± standard deviation. Chi-square test was used for nonparametric data, student t test, One Way Anova test for normally distributed data, Mann Whithey U test and Kruskal Wallis test were used for non-normally distributed data to compare the groups. Multivariate linear regression analysis was also performed for risk analysis of the dependent variable. $P<0.05$ value was accepted as statistical significance.

RESULTS

Between the OSAS group (n:51) and the control group (n:25), age (mean: 45.3±10 vs 40.9±9.1, p value: 0.065), gender (female/male in the patient and control group, respectively: 5/46, 3/22, p value: 0.76) and BMI (min-max 23.3-40.1 vs 24-44.1kg/m², p value: 0.21, respectively) were similar (Table 1).

Table 1. Demographic analyse for OSAS and control groups.

	Gender*			Age**			Body Mass Index*** (kg/m²)		
	Male (n)	Female (n)	P value	Mean	Standard deviation	P value	Minimum	Maximum	P value
Patient	46	5	0.76	45.3	10	0.065	23.3	40.1	0.21
Control	22	3		40.9	9.1		24	44.1	

*Chi square test. ** Independent T test. ***Mann Whitney U test

The mean and standard deviation values of WASO, total sleep time, supine AHI, REM sleep time, non-REM sleep time parameters of the OSAS group were 111.6±80.2, 306.39±86.7min, 48.8±37.8min, 9.4±7.8, 90.6±7.8min, respectively. The minimum and maximum values of apnea index, AHI, ODI, desaturation time, REM AHI, hypopnea index data were 0-90.7, 5 -135.4, 0.5-133.6, 0-137, 0-99.3, 0-85.4, respectively.

Plin-1 level was found to be significantly higher in the OSAS group (median value: 5.34 vs 4.87ng/ml, p:0.038). No significant difference was detected between the groups for ATGL, HSL, and LPL (median values: 65.9 vs 68.3ng/ml, 7.30 vs 7.33ng/ml, 484.2 vs 485.3pg/ml, respectively, p values: 0.33, 0.69, 0.33, respectively) (Table 2).

Table 2. Plin-1, ATGL, HSL, LPL analyses; Mann Whitney U test

	Plin-1* (ng/ml)		ATGL** (ng/ml)		HSL*** (ng/ml)		LPL**** (pg/ml)	
	MeanRank	P value	MeanRank	P value	MeanRank	P value	MeanRank	P value
Patient	42.1	0.038	36.7	0.33	37.8	0.69	36.7	0.33
Control	31		42		39.9		42	

*: Perilipin-1, **: Adipous triglyceride lipase, ***: Hormone sensitive lipase, ****: Lipoproteine lipase

Plin-1, ATGL, HSL, LPL levels were similar between mild (n:11), moderate (n:12) and severe OSAS groups (n:28) (p values: 0.13, 0.17, 0.44, 0.083, respectively).

In the correlation analysis, a significant positive relationship was detected between BMI and WASO, ODI, AHI, HI and desaturation time in the OSAS group, and a significant negative relationship with total sleep time and REM sleep time (p; 0.01, 0.006, 0.02, 0.026, 0.00, 0.048, 0.029, r:0.35, 0.37, 0.32, 0.31, 0.48, -0.27, -0.3, respectively) (Table 3).

Table 3. BMI and total sleep time, REM* sleep time, WASO**, ODI***, AHI****, HI*****, Desaturation time correlationanalyse.

		Total sleep time	REM sleep time	WASO	ODI	AHI	HI	Desaturation time
BMI	**r**	-0.27	-0.3	0.35	0.37	0.32	0.31	0.48
	P	0.048	0.029	0.01	0.006	0.02	0.026	0.00

*Rapid eye movement sleep time, **Wake after sleep onset, ***Oxygen desaturation index, ****Apnea hypopnea index, *****Hypopnea index

A positive correlation of Plin-1 with ATGL, LPL, HSL and WASO and a negative correlation with total sleep time was detected (p value: 0.00, 0.01, 0.00, 0.003, 0.006, r value: 0.79, 0.35, 0.62, 0.41, -0.38, respectively) (Table 4).

Table 4. Plin-1and total sleep time, WASO, ATGL, HSL, LPL correlation analyze

		Total sleep time	WASO	ATGL	HSL	LPL
Plin-1	**r**	-0.38	0.41	0.79	0.62	0.35
	p	0.006	0.003	0.00	0.00	0.01

In the linear regression analysis performed for the OSAS group, WASO was detected as a risk factor for Plin-1 elevation (p: 0.003, B: 0.012) (Table 5)

Table 5. WASO linear regression analysis with Plin-1 dependent variable in the OSAS group.

	Unstandardized Coefficients		t	p	%95 Confidence Interval	
B		**Std. Error**			**lower**	**upper**
WASO	,012	,004	3,163	,003	,004	,020
			Model Summary			
R: 0,412		R2: 0,170		Adjusted R2: 0,153		Anova-p: 0,003

DISCUSSION

We compared the serum perilipin-1 (Plin 1), adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL), lipoprotein lipase (LPL) levels of OSAS patients with similar body mass index and a healthy control group, except for simple snoring, and we investigated the relationship of these enzymes with OSAS. When compared to the simple snoring group with similar body mass index, only Plin-1 level was found to be significantly higher in patients with OSAS. Plin-1 showed a positive correlation with wake after sleep onset (WASO) and a negative correlation with total sleep time. No correlation was detected between Plin-1 and hypoxia parameters. Only WASO was identified as a risk factor for Plin-1 elevation. It was statistically calculated that each minute of sleep interruption caused a 0.012 ng/ml increase in Plin-1 level.

In some studies, perilipin presentation on the lipid cells surface was found to be significantly lower in obese individuals compared to non-obese individuals (Smith and Ordovás, 2012; Luglio et al., 2015). In experimental studies, it was reported that perilipin knockout mice were lean and resistant to the adipogenic effects of a high-fat diet (Tansey et al., 2001; Martinez-Botas et al., 2000). There is also a study showing higher levels of perilipin expression in obese individuals than in nonobese individuals (Kern et al., 2004). This study was interpreted as perilipin levels being high in obese people due to excess fat accumulation and increased body fat ratio increasing perilipin gene expression. Supporting this finding, in a study conducted by Maghroun et al. with healthy volunteers, a decrease in Plin-1 was observed in the entire group, including adults, after weight loss (Maghroun et al., 2021). In our study, the average BMI of the OSAS patients was 30.7±4.7kg/m² and Plin-1 was found to be significantly higher ($p = 0.038$) compared to the control group with similar BMI (p: 0.21).

In addition to obesity, hypoxia may be another factor affecting fat metabolism in OSAS. In experimental studies with 3T3-L1 adipocytes, increased glycerol release as a sign of lipolysis in short-term hypoxia has been reported (Yin et al., 2009; Regazzetti et al., 2009). However, it has also been reported that continuous hypoxia increases intracellular lipid stores and lipid droplet sizes (Weiszenstein et al., 2016).

We found a significant increase in Plin-1 in OSAS patients compared to the control group. However, we did not detect a relationship between this finding and any hypoxia parameters. Again, no significant difference was detected in Plin-1 levels between mild, moderate and severe OSAS patients. A significant relationship was found only between WASO, a parameter of sleep fragmentation, and Plin-1 level.

Obesity is considered a significant risk factor for the development and progression of OSAS, and it is estimated that at least 30% of the adult population is obese and 60 to 90% of OSAS patients are overweight (Sun et al., 2021). The relationship between OSAS and obesity has been explained by various mechanisms. Sleep fragmentation due to OSAS may contribute to accelerated weight gain (Öztürk et al., 2022). Sleep disruptions, which indicate the amount of brief awakenings that occur throughout the night, are an important indicator of sleep disturbance (Smurra et al., 2001). Sleep disruptions can be evaluated objectively by PSG and various parameters as well as wake after sleep onset (WASO) measurement (Lutsey et al., 2015). It has been shown that mice exposed to long-term sleep disruptions experience an increase in weight and fat mass, as well as differentiation and mobilization of adipocyte precursors and inflammation in adipose tissue (Khalyfa et al., 2014; Zhang et al, 2014; Poroyko et al., 2016; Gozal et al, 2017). Studies have shown that sleep disruptions lead to obesity in mice and that this relationship also exists in humans (Wang et al., 2014; Koolhaas et al., 2019; Zhao et al., 2021a). In the study of Zhao and his group, it was shown that bad sleep efficiency and WASO were significantly associated with the prevalence of hypertension (Zhao, 2021b). It has also been shown that sleep disruptions are associated with low physical activity, insulin resistance, obesity and increased inflammation (Van den Berg et al., 2008; Hursel et al., 2011; Cox et al., 2019; Yan et al., 2020). Sleep disturbance ultimately affects life expectancy (Cappuccio et al., 2010). Our study is the first study showing that sleep disruptions, which are associated with all these pathologies, cause Plin-1 elevation and may shed light on one of the pathogenetic pathways.

It has been stated that ATGL is induced by fasting and suppressed in the nutritional state in mice and has a possible role in the development of obesity (Villena et al., 2004).

In a clinical study, HSL activity was also shown to be lower in obese patients compared to healthy controls (Costabile et al., 2011). In a study conducted on rats, it was reported that the ATGL level of rats exposed to long-term hypoxia decreased, but the HSL level did not change, compared to control rats not exposed to hypoxia (Hashimoto et al., 2013).

Catecholamines stimulate lipolysis. Short- and long-term hypoxia reduces catecholamine-induced lipolysis, which in turn reduces the expression of proteins associated with lipid droplets, such as ATGL and HSL (Hashimoto et al., 2013). In the current study, although there was no significant difference in ATGL and HSL levels between the two groups, which could be called the effect of hypoxia, both enzymes tended to be lower than the control ($p = 0.33$, 0.69, respectively) (Table 2). No relationship was found between these two enzymes with either sleep fragmentation or hypoxia parameters.

Serum levels of LPL, a key enzyme in intravascular lipolysis, have been shown to be reduced in patients with OSAS compared to healthy controls (Iesato et al., 2007). In another study, it was reported that the serum LPL level decreased in patients with OSAS, was correlated with the severity of OSAS, and that the LPL level increased significantly after 6 months of Continuous Positive Airway Pressure device treatment (Li et al., 2014). It has been reported that serum LPL levels in rats exposed to chronic intermittent hypoxia were significantly lower compared to the control group (Drager et al., 2012).

It has been reported that sustained hypoxia upregulates angiopoietin-like protein 4, a potent LPL inhibitor, in human pulmonary artery endothelial cells, cardiomyocytes, and adipocytes (Wang et al., 2007). In our study, serum LPL level was lower in the OSAS group compared to the control group, but this decrease was not significant and we did not detect any relationship with hypoxia ($p = 0.33$).

Our study is the first to detect a relationship between sleep disruption and lipolysis enzymes, especially Plin-1 levels, in patients with OSAS. However, there are limiting aspects in the study. First, the sample size is small. Further studies with larger sample numbers should be conducted. Secondly, this study was designed as a cross-sectional study, so a full definition of causality is impossible. Therefore, our findings should be confirmed by long-term prospective studies.

As a result, we found that Plin-1 levels increased secondary to sleep disruptions in patients with OSAS, independent of obesity. PSG is an important and costly method for diagnosing OSAS. Additionally, it may be difficult for patients to access this modality. Before this modality, Plin-1 levels may be measured in patients for screening purposes.

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Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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