Original article

Hyperuricemia in systemic lupus erythematosus: is it associated with the neuropsychiatric manifestations of the disease?

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ABSTRACT

Objectives: To assess the association between hyperuricemia and different neuropsychiatric manifestations and stroke risk factors in systematic lupus erythematosus (SLE) patients.

Methods: This study was conducted on 204 SLE patients who were admitted to a tertiary referral center. A standardized questionnaire was completed for all the participants and the medical records were reviewed regarding the occurrence of arterial or venous thrombotic events, stroke, seizure, depression, headache, psychosis, and peripheral neuropathy. In addition blood samples were drawn to obtain serum uric acid, triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol levels.

Results: Hyperuricemia (serum uric acid ≥6 mg/dl for women and ≥7 mg/dl for men) was detected in 16.1% of SLE patients and was significantly associated with the occurrence of stroke (OR, 2.38; 95%CI, 1.2–7.24), and peripheral neuropathy (OR, 3.49; 95% CI, 1.52–12.23), independent of hypertension and hyperlipidemia. Hyperuricemia was also significantly associated with hypertension (OR, 7.76; 95% CI, 2.72–15.76), hyperlipidemia (OR, 5.05; 95% CI, 1.59–11.32), and history of arterial thrombosis (OR, 4.95; 95% CI, 1.98–15.34), independent of age and body mass index.

Conclusions: Hyperuricemia in SLE patients is independently associated with the occurrence of stroke and peripheral neuropathy. It is also independently associated with hypertension, hyperlipidemia, and history of arterial thrombosis, which are the major stroke and myocardial infarction risk factors in SLE patients.

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Hiperuricemia no lúpus eritematoso sistêmico: está associada a manifestações neuropsiquiátricas da doença?

**Resumo**

Objetivos: Avaliar a associação entre a hiperuricemia e diferentes manifestações neuropsiquiátricas e os fatores de risco para AVE em pacientes com lúpus eritematoso sistêmico (LES).

Métodos: Este estudo foi realizado em 204 pacientes com LES que foram internados em um centro de referência de atenção terciária. Todos os participantes preencheram um questionário padronizado e os prontuários médicos foram analisados quanto à ocorrência de eventos trombóticos arteriais ou venosos, acidente vascular encefálico, convulsões, depressão, cefaleia, psicose e neuropatia periférica. Além disso, foram coletadas amostras de sangue para se mensurar os níveis de ácido úrico, triglicerídeos (TG), lipoproteínas de alta densidade (HDL), lipoproteínas de baixa densidade (LDL) e colesterol total de sangue.

Resultados: A hiperuricemia (ácido úrico sérico ≥6 mg/dl para mulheres e ≥7 mg/dl para homens) foi detectada em 16,1% dos pacientes com LES e esteve significativamente associada à ocorrência de AVE (OR, 2,38; IC 95%, 1,2–7,24) e neuropatia periférica (OR, 3,49; IC 95%, 1,5–12,23), independentemente da hipertensão arterial e da hiperlipidemia. A hiperuricemia também esteve significativamente associada à hipertensão arterial (OR, 7,76; IC 95%, 2,72–17,56), hiperlipidemia (OR, 5,05; IC 95%, 1,59–11,32) e história de trombose arterial (OR, 4,95; 95% CI, 1,98–15,34), independentemente da idade e índice de massa corporal.

Conclusões: A hiperuricemia em pacientes com LES está independentemente associada à ocorrência de acidente vascular encefálico e neuropatia periférica. Também está independentemente associada à hipertensão, hiperlipidemia e história de trombose arterial, que são os principais fatores de risco para acidente vascular encefálico e infarto agudo do miocárdio em pacientes com LES.

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Introduction

Uric acid, the final product of purine degradation, is formed in the liver from precursor proteins and is excreted by the kidneys and intestines. At physiologic concentrations, uric acid exhibits excellent antioxidant activity; however, when uric acid exceeds its physiologic levels, it can propagate oxidative damage. Furthermore, chronic elevation of uric acid constitutes a risk factor for many diseases, as it can promote inflammation and endothelial dysfunction.\(^1\)\(^2\)

Hyperuricemia is a risk factor for myocardial infarction and stroke.\(^3\) In addition higher serum urate levels after acute stroke is a predictor of poor outcome and higher rates of future vascular event.\(^4\) Hyperuricemia has been also associated with peripheral neuropathy in diabetes.\(^5\) Therefore some researchers recommended lowering plasma uric acid levels to reduce the risk of future vascular events in high risk populations.\(^6\)\(^6\)

Neurologic involvement and vascular events have a wide range of frequency (12–95%) in patients with systemic lupus erythematosus (SLE) and can be very common causing significant morbidity and mortality in SLE patients.\(^7\) Based on the studies that showed higher levels of uric acid in SLE patients,\(^8\)\(^9\) and the studies that documented the injurious effect of uric acid on the nervous system,\(^9\) we postulate that hyperuricemia in SLE patients might increase the risk of neurologic involvement and vascular events during the course of the disease. By our extensive search we could not find studies assessing the relation between serum uric acid levels and the different neuropsychiatric manifestations of SLE. Whether a high serum uric acid level in SLE patients constitutes a risk factor for future neurologic, psychiatric and vascular involvements, remains unknown. Identifying these associations is very important and might help in identifying a modifiable risk factor for the neurologic and vascular events in SLE patients.

We undertook this study to evaluate the effect of hyperuricemia on the different neurologic manifestations seen in SLE patients; we also attempted assessing the associations of serum uric acid levels with the patients’ blood pressure and lipid profile, and the occurrence of vascular and thrombotic events.

Materials and methods

**Study population and study design**

This study was conducted on SLE patients who were admitted at our center (a tertiary referral hospital) between March 2011 and February 2014. A total of 235 SLE patients who met the American College of Rheumatology (ACR) SLE criteria participated in the study,\(^10\) and 31 of these were excluded due to the following criteria: history of smoking; opiate or alcohol consumption; and history of infections, fever, or antibiotic use during the previous two weeks. After obtaining a written informed consent, a total of 204 SLE patients aged 18–54 years...
completed the study, which was approved by the ethics committee and the research deputy of our institute.

Data and specimen collection

Upon enrollment a standardized questionnaire was completed for every participant through interviews, medical records, and physical examinations. The questionnaire consisted of demographic, medical, and social histories, as well as inquiries about body mass index (BMI), disease duration, and the received treatments and their duration. Patients files were investigated and the following information were recorded: the occurrence of arterial or venous thrombotic events documented by imaging studies, occurrence of stroke documented by imaging studies, recent onset seizure demonstrated by an abnormal electroencephalography (EEG) that was not due to infection or metabolic disturbances, the presence of depression, headache, psychosis due to lupus as defined by the ACR and SLE disease activity index (SLEDAI), and peripheral neuropathy documented by electromyography (EMG) and nerve conduction velocity (NCV) studies. In addition upon enrollment blood samples were drawn to obtain serum uric acid, creatinine, blood urea nitrogen (BUN), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol levels. Uric acid levels were determined by the enzymatic colorimetric method, and all laboratory investigations were performed by one person who was blinded to the results of the questionnaires.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (version 18.0.0: PASW, Chicago, IL). The Chi-square analysis, Fisher’s exact test, independent samples t-test, one-way analysis of variance, and Pearson correlation analysis were used to analyze the correlations and relationships between the variables. Multivariate logistic regression was used to evaluate the dependency of the obtained results. Sample size was calculated for an alpha error of 0.05, a desired level of absolute precision (δ) of 0.05, and an estimated design effect (DEFF) of one. Estimated odds ratios (OR) with 95% confidence intervals (95% CI) and p values were used to evaluate the statistical significance of the associations and correlations between the variables.

Results

Descriptive statistics

A total of 235 SLE patients agreed to participate in the study; of these, 31 patients were excluded. Sixteen of the 31 excluded patients had a history of smoking and opiate or alcohol consumption, and 15 had infections or had used antibiotics during the previous two weeks. The remaining 204 SLE patients completed the study. At enrollment, the population characteristics expressed as mean ± standard deviation (SD) were as follows: patients’ age, 35.3 ± 11.4 years; disease duration, 6.4 ± 4 years; BMI, 25.6 ± 4; serum creatinine, 0.9 ± 0.4 mg/dl; BUN, 20.4 ± 9.2 mg/dl; and serum uric acid, 4.7 ± 1.5 mg/dl.

No significant differences were observed in the demographics of the SLE patients with and without hyperuricemia (Table 1). There were no significant differences between the drugs used by the participants in each group (Table 2).

Of the participants who completed the study, 40 (19.6%) were male, 69 (33.8%) had hypertension (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or being treated with hypertensive drugs), 43 (21%) had hyperlipidemia (defined as serum total cholesterol ≥240 mg/dl, LDL cholesterol ≥160 mg/dl, or TG ≥200 mg/dl).

<table>
<thead>
<tr>
<th>The characteristic</th>
<th>Hyperuricemia</th>
<th>No (n = 171)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (Mean ± SD)</td>
<td>37.6 ± 13.2</td>
<td>34.7 ± 10.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Disease Duration (years) (Mean ± SD)</td>
<td>6.3 ± 4</td>
<td>6 ± 4</td>
<td>0.8</td>
</tr>
<tr>
<td>BMI (Mean ± SD)</td>
<td>25.1 ± 5</td>
<td>25.7 ± 4.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Male Gender [Number (%)]</td>
<td>9 (23.6%)</td>
<td>31 (19.1%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Serum CRP (Mean ± SD)</td>
<td>8.7 ± 15</td>
<td>9 ± 31.7</td>
<td>0.9</td>
</tr>
<tr>
<td>ESR (Mean ± SD)</td>
<td>42 ± 36.7</td>
<td>28.8 ± 26.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Positive ANA [Number (%)]</td>
<td>26 (78.7%)</td>
<td>123 (71.9%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive Anti ds-DNA [Number (%)]</td>
<td>23 (69.6%)</td>
<td>97 (56.7%)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

SD, standard deviation; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; ANA, anti nuclear antibody; Anti ds-DNA, anti double strand DNA.

<table>
<thead>
<tr>
<th>The drug</th>
<th>Hyperuricemia</th>
<th>No (n = 171)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>33 (100%)</td>
<td>166 (97%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>16 (48.4%)</td>
<td>102 (59.6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cellcept</td>
<td>13 (39.3%)</td>
<td>57 (33.3%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>7 (21.2%)</td>
<td>48 (28%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3 (9%)</td>
<td>20 (11.6%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Statins</td>
<td>4 (12.1%)</td>
<td>26 (15.2%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Calcium</td>
<td>7 (21.2%)</td>
<td>64 (37.4%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 1 – Demographic characteristics and some laboratory markers of the participants with and without hyperuricemia.

Table 2 – The drugs used by the participants with and without hyperuricemia.
22 (10.7%) had experienced at least one seizure attack, 10 (4.9%) had psychosis, 23 (11.27%) had depression, 55 (26.9%) had a severe headache, 19 (9.3%) had experienced CVA, 12 (5.8%) had peripheral neuropathy, 50 (24.5%) had experienced at least one venous thrombosis formation, and 20 (9.8%) had experienced at least one arterial thrombus formation.

The association between hyperuricemia and the different neurologic manifestations of SLE

Hyperuricemia was defined as serum uric acid ≥6 mg/dl for women and serum uric acid ≥7 mg/dl for men. Hyperuricemia was detected in 33 SLE patients (16.1%) and was significantly associated with the occurrence of CVA (p = 0.001), psychosis (p = 0.03), peripheral neuropathy (p = 0.001), and headache (p = 0.003). There was no statistically significant association between hyperuricemia and seizures (p = 0.3) or depression (p = 0.4) (Table 3).

The associations between serum uric acid levels and the different known CVA risk factors

Based on the Pearson correlation coefficients, serum uric acid levels were significantly correlated with blood pressure (r = 0.5, p = 0.000), total cholesterol (r = 0.3, p = 0.000), TG (r = 0.03, p = 0.000), and LDL cholesterol (r = 0.2, p = 0.004). We did not find a statistically significant correlation between serum uric acid levels and the participants’ age, BMI, or HDL cholesterol level. Hyperuricemia was associated with hypertension (p = 0.000), hyperlipidemia (p = 0.000), and arterial thrombosis (p = 0.000), while there was no significant association between hyperuricemia and venous thrombosis (p = 0.3) (Table 4).

Dependency of the obtained results

Using multivariate logistic regression, after adjustment for hypertension and hyperlipidemia, hyperuricemia remained significantly associated with CVA (B = 0.87, p = 0.04) and peripheral neuropathy (B = 1.25, p = 0.04) but not with psychosis (B = 1.2, p = 0.1) or headache (B = 1.01, p = 0.05) (Table 3).

After adjustment for age and BMI, hyperuricemia remained significantly associated with hypertension (B = 2.05, p = 0.000), hyperlipidemia (B = 1.62, p = 0.006), and arterial thrombosis (B = 1.6, p = 0.001) (Table 4).

Discussion

Hyperuricemia and SLE

In the current study, hyperuricemia was detected in 16.1% of SLE patients (22% in men and 16.4% in women), which was higher than the prevalence of hyperuricemia in the normal

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Table 3 – Association between hyperuricemia and different neuropsychiatric manifestations of SLE.

<table>
<thead>
<tr>
<th>Neurologic manifestations of SLE</th>
<th>Hyperuricemia</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 33)</td>
<td>No (n = 171)</td>
<td></td>
</tr>
<tr>
<td>CVA (n = 19)</td>
<td>8 (24.2%)</td>
<td>11 (6.4%)b</td>
<td>4.65 (1.7–12.69)</td>
</tr>
<tr>
<td>Seizure (n = 22)</td>
<td>5 (15.1%)</td>
<td>17 (9.9%)</td>
<td>1.61 (0.55–4.74)</td>
</tr>
<tr>
<td>Headache (n = 55)</td>
<td>16 (48.5%)</td>
<td>39 (22.8%)c</td>
<td>3.18 (1.47–6.88)</td>
</tr>
<tr>
<td>Peripheral neuropathy (n = 12)</td>
<td>6 (18.2%)</td>
<td>6 (3.5%)</td>
<td>6.11 (1.83–20.34)</td>
</tr>
<tr>
<td>Psychosis (n = 10)</td>
<td>4 (12.1%)</td>
<td>6 (3.5%)</td>
<td>3.79 (1.14–12.27)</td>
</tr>
<tr>
<td>Depression (n = 23)</td>
<td>5 (15.2%)</td>
<td>18 (10.5%)</td>
<td>1.51 (0.52–4.42)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; OR, odds ratio; 95% CI, 95% confidence interval; CVA, cerebrovascular accident.

a Adjusted for hypertension and hyperlipidemia.

b p < 0.05 for the comparison between two groups with and without hyperuricemia after performing logistic regression.

c p < 0.05 for the comparison between two groups with and without hyperuricemia.

Table 4 – Association between hyperuricemia and different known risk factors of CVA.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hyperuricemia</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 33)</td>
<td>No (n = 171)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (n = 69)</td>
<td>25 (75.8%)</td>
<td>44 (25.7%)b</td>
<td>9.02 (3.79–21.46)</td>
</tr>
<tr>
<td>Hyperlipidemia (n = 43)</td>
<td>17 (51.5%)</td>
<td>26 (15.2%)b</td>
<td>5.92 (2.66–13.19)</td>
</tr>
<tr>
<td>Hx of arterial thrombosis (n = 20)</td>
<td>9 (27.3%)</td>
<td>11 (6.4%)b</td>
<td>5.45 (2.04–14.53)</td>
</tr>
<tr>
<td>Hx of venous thrombosis (n = 50)</td>
<td>10 (30.3%)</td>
<td>40 (23.4%)</td>
<td>1.42 (0.62–3.24)</td>
</tr>
</tbody>
</table>

OR, odds ratio; 95% CI, 95% confidence interval; CVA, cerebrovascular accident; Hx, history.

a Adjusted for age and body mass index (BMI).

b p < 0.05 for the comparison between two groups with and without hyperuricemia.
population, as reported by studies conducted in the same region using the same cutoff points.\textsuperscript{14} This is in accordance with other studies that showed higher levels of uric acid among SLE patients.\textsuperscript{8,9} Higher prevalence of hyperuricemia in SLE patients might be due to several endogenous and exogenous mechanisms such as inflammation, hypertension, and renal involvement, which are prevalent in SLE patients and have been identified as provoking hyperuricemia through different mechanisms.\textsuperscript{15–19} On the other hand, increased levels of uric acid can aggravate inflammation, hypertension, and renal disease,\textsuperscript{15–19} thus creating a vicious cycle. Hyperactivity of the xanthine oxidase enzyme in SLE patients,\textsuperscript{8} and some of the drugs used in the treatment of SLE,\textsuperscript{20} are among the other possible reasons for the higher prevalence of hyperuricemia in SLE patients.

\textbf{Hyperuricemia and hyperlipidemia}

In our study, the serum uric acid level was significantly correlated with the serum TG, LDL, and total cholesterol levels, and hyperuricemia was significantly associated with hyperlipidemia, independent of age and BMI. These findings are in accordance with other studies that involved both human and animal models.\textsuperscript{21,22} Hyperuricemia appears to have a mutual interaction with high serum TG and cholesterol levels, thus forming a vicious cycle, whereas some studies have shown that lipids and hypertriglyceridemia increase serum uric acid levels through increasing its absorption in the renal tubules and also through increasing uric acid production by accelerating the de novo purine synthesis.\textsuperscript{23} Other studies have documented that uric acid might have a contributory role in increasing serum TG, LDL, and total cholesterol levels. Nakagawa et al., in their study of the effect of uric acid on metabolic syndrome, documented that lowering uric acid improves insulin sensitivity, obesity, and hypertriglyceridemia. They also indicated that uric acid might be involved in either the overproduction or the reduction of TG clearance.\textsuperscript{23} In another study, Bowden et al. documented that hyperuricemia is associated with higher total cholesterol, LDL, and apolipoprotein B (Apo B) levels, and a reduction causes a decrease in serum LDL and total cholesterol levels. They indicated that uric acid is a major cause of oxidative stress and reduced nitrous oxide (NO) release, and combined with an increase in the activity of lipoprotein lipase may cause higher lipid levels and particle numbers. Furthermore, hyperuricemia is thought to impair endothelium-dependent vasodilatation primarily through lipid oxidation, which can cause an increase in the total cholesterol level.\textsuperscript{22}

\textbf{Hyperuricemia and hypertension}

In this study of SLE patients, hyperuricemia was significantly associated with hypertension, independent of age and BMI. Grayson et al. in their meta-analysis of hyperuricemia and incident hypertension, which included data from 55,607 patients, found a significantly increased adjusted risk ratio for incident hypertension in subjects with hyperuricemia, independent of traditional risk factors for hypertension.\textsuperscript{15} It is now believed that hyperuricemia has a causative role in hypertension through different mechanisms; uric acid activates the renin–angiotensin system and down-regulates nitric oxide (NO) production, thus leading to vasoconstriction. Another effect of uric acid, which develops overtime, is uric acid mediated arteriolosclerosis; uric acid uptake into vascular smooth muscle cells causes the activation and production of growth factors and monocyte chemoattractant protein-1, which results in vascular smooth muscle cell proliferation, vascular wall thickening, loss of vascular compliance, and a shift in pressure natriuresis.\textsuperscript{1,2,15–17}

\textbf{Hyperuricemia, hypercoagulability state, and CVA}

In the current study, hyperuricemia was significantly associated with CVA in SLE patients, independent of hypertension and hyperlipidemia. This is in accordance with other studies conducted in general populations. A recently published 12–15 years prospective study by Storhaug et al. that included 5700 participants without known risk factors for cardiovascular diseases documented that a 1 SD (1.47 mg/dl) increase in serum uric acid was significantly associated with a 22% increased risk for ischemic stroke and 13% increased risk for all-cause mortality.\textsuperscript{24} Additionally, in our study, hyperuricemia was independently associated with a history of at least one arterial thrombosis event. These important findings suggest that hyperuricemia might increase the risk for CVA not only by increasing the risk for developing hyperlipidemia and hypertension as mentioned earlier, but also through other mechanisms; hyperuricemia has been associated with platelet activation and increased platelet adherence.\textsuperscript{25,26} Thus, patients with hyperuricemia might have an increased risk of thrombus formation. In addition, hyperuricemia has been associated with the progression of atherosclerosis through the promotion of oxygenation of LDL cholesterol and facilitation of lipid peroxidation.\textsuperscript{3,4,6} Furthermore, hyperuricemia can cause endothelial dysfunction and reduce NO production leading to an impaired vascular tone that could contribute to ischemic changes.\textsuperscript{1,2,15,24}

\textbf{Hyperuricemia and peripheral neuropathy}

In our study, hyperuricemia was significantly associated with peripheral neuropathy in SLE patients, independent of hypertension and hyperlipidemia. This important finding suggests that hyperuricemia might have an injurious effect on the peripheral nervous system. Similar results were found in diabetic patients. Papanas et al., in their study of 64 diabetic patients, detected a significant correlation between serum uric acid and the neuropathy disability score. They also indicated that diabetic patients with peripheral neuropathy had increased serum uric acid levels compared to levels in those without neuropathy.\textsuperscript{7} The exact role of uric acid in peripheral neuropathy remains unknown; however, uric acid might play a role in peripheral neuropathy through its role in oxidative damage and vascular endothelial dysfunction. Studies have shown that when uric acid exceeds its physiologic value in the plasma, it can propagate oxidative damage and cause oxidative stress.\textsuperscript{1,2,22} which has been shown to induce neuronal damage; oxidative stress is the central mediator of apoptosis, neuro-inflammation, and bioenergetic failure in neurons.\textsuperscript{27} In addition, hyperuricemia promotes
Conclusion

Hyperuricemia is prevalent among SLE patients and is significantly associated with CVA and peripheral neuropathy in SLE patients. It is also significantly associated with hypertension, hyperlipidemia, and a positive history for arterial thrombosis, which are the major CVA and myocardial infarction risk factors. Follow up studies are needed to measure serum uric acid at the beginning and through the course of the disease to evaluate the effect of hyperuricemia on the progression of neuropsychiatric manifestations of SLE and its morbidity through the course of the disease. Additionally interventional studies are needed to determine the practical usefulness of lowering serum uric acid levels in SLE patients.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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REFERENCES

