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Advanced glycation end-products and advanced oxidation protein products levels are correlates of duration of type 2 diabetes

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ABSTRACT

Aims: Diabetes is associated with the excess formation of advanced glycation end-products (AGEs) and advanced oxidation protein products (AOPP), and low levels of ferric reducing ability of plasma (FRAP). However, the trend of oxidative and antioxidant markers levels according to diabetes duration is unclear.

Main methods: In a case-control study, 240 patients with diabetes and 100 healthy controls were enrolled. Patients were divided into four groups according to the duration of diabetes, including newly diagnosed, 1–5, 5–10, and 10–15 years. Serum AGEs, AOPP, and FRAP levels were compared among groups.

Key findings: AGEs and AOPP were higher and FRAP was lower in patients with diabetes compared to healthy controls. Serum levels of AGEs increased progressively with increasing in diabetes duration. AGEs levels were 68.97 ± 7.28% in newly-diagnosed, 73.43 ± 12.96% in 1–5 years and 80.44 ± 13.84% in 10–15 years of diabetes duration (pairwise p-values < 0.05). In linear regression analysis the correlation among AGEs, AOPP, FRAP, and diabetes duration remained significant after adjustment for age, BMI, HDL, HbA1c, waist circumference, microvascular complications, and coronary artery diseases. ROC analysis showed AGEs could predict the duration of diabetes when patients with 10–15 years duration of diabetes were compared to patients with 1–5 years duration of diabetes (AUC = 0.676, p-value = 0.003).

Significance: Diabetes promotes AGEs, and AOPP production, independent of glycemic control and patients age. Serum levels of AGEs increase progressively with increasing duration of diabetes. AGEs may be helpful in estimating chronicity of diabetes.

1. Introduction

The importance of hyperglycemia and oxidative stress in the pathogenesis of diabetes and diabetic complications has been reinforced by extensive evidence [1–3]. Chronic hyperglycemia results in excessive nonenzymatic glycation and the formation of advanced glycation end-products, AGEs [4]. Advanced oxidation protein products (AOPP) is a branch of protein products containing di-tyrosine, which signify summative of albumin damaged induced by oxidative stress [5]. Therefore AOPP is supposed as a marker of oxidative stress [6]. AGEs and AOPP contribute significantly to diabetes and its complications [6,7]. Studies have been reported that the concentration of AOPP and AGEs correlated with insulin resistance and the presence or severity of diabetic complications [8–11]. AGEs products are known as one of the mediators of hyperglycemia induced tissue damage. Intracellular production of AGE precursors can modify intracellular proteins such as ones related to gene transcription. In addition these precursors may alter cellular function by diffusing out of the cells and modifying of extracellular matrix. Besides, AGEs precursors diffusing out of cells can modify circulating proteins which can trigger inflammatory reactions mediated by producing cytokines and growth factors [12]. Moreover thermally processed food can form AGEs exogenously [13]; hence we are exposed to AGEs in our daily life.

The prevalence and severity of diabetes complications are associated with disease duration [14,15]. Ashraf et al. exhibited that in patients with type 2 diabetic with disease duration of 5–15 years autoantibodies bind to DNA-AGE more significantly as compared to patients with 1–5 years of disease duration [16]. Whether AOPP and AGEs accumulate over time and are associated with disease duration has not been clarified yet. The rise in AGEs and AOPP may go in parallel with the progression of the complications and thus quantitative estimation of these markers may help for better monitoring of diabetes

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complications.

Ferric reducing ability of plasma (FRAP) reflecting the total antioxidant capacity (TAC) is measured as an antioxidant index [17]. FRAP is decreased in diabetes and is associated with complications of diabetes [18]. FRAP is inversely correlated with glycemic control in a patient with diabetes [17].

Advanced oxidative end products such as AGEs were shown that play a role in diabetes vascular complication by accumulating in vessels and inducing the inflammatory cascades [19].

In type 2 diabetes, available studies did not explore the correlation of AOPP, AGEs, and FRAP levels with disease progression and duration. In newly diagnosed patients with type 2 diabetes it is a complex issue to estimate duration of disease, in many cases diabetes is diagnosed several years after starting the pathologic process. AGEs level may help for relative estimation of duration of diabetes. Here, we determined the levels of AOPP, AGEs and FRAP in newly diagnosed diabetes and patients with different duration of diabetes and also in healthy participants.

2. Material and methods

2.1. Study sample

We conducted a cross-sectional study of 240 patients with type 2 diabetes who were attending the diabetes clinic of Vali-Asr Hospital, affiliated to Tehran University of Medical Science, as well as 100 healthy controls. The patients were divided into four groups according to the duration of diabetes: patients who were diagnosed de novo, patients with known diabetes for 1–5 years; patients with known diabetes for 5–10 years, and patients with known diabetes for 10–15 years. Newly diagnosed patients were identified within 6 months and were not on any treatments. Diabetes was diagnosed according to the criteria of the American Diabetes Association ("Diagnosis and classification of diabetes mellitus" 2019). Exclusion Criteria included patients who suffered cancer, major mental illness, epilepsy, patients with liver autoimmune or viral diseases or liver cirrhosis, end stage renal disease (ESRD), patients consuming vitamin E, and women under hormone replacement therapy. Demographic and anthropometric data including age, gender, duration of diabetes, history of smoking, weight, height, and waist circumference were recorded. Microvascular complications of diabetes defined as a history of retinopathy, nephropathy, or neuropathy. History of myocardial infarction, coronary stent placement, and coronary artery bypass surgery was considered as a Coronary artery disease. The BMI (kg/m^2) was calculated according to Quetelet formula.

The research was carried out according to the principles of the declaration of Helsinki. The local ethics review committee of Tehran University of Medical Science approved the study protocol.

2.2. Blood samples

The patients' serums were collected after 12 h of fasting, centrifuged, and were kept at −70 °C until analysis. Serum glycemic markers, lipid profile, and creatinine were measured for all participants. Glomerular filtration rate (eGFR) was estimated by the Cockcroft-gault equation. Glucose measurements (intra-assay coefficient of variants (CV) 2.1%, inter-assay CV 2.6%) were carried out using the glucose oxidase method. Cholesterol, HDL-C, LDL-C, and triglycerides were determined using direct enzymatic methods (Parsazmun, Karaj, Iran). Serum AOPP was determined with spectrophotometric methods (FLUOstar OPTIMA, BMG, Germany) as described by Kalousova et al. (2002) [6]. In this method, 200 μL of serum is diluted by a factor of 5, in phosphate buffered saline (PBS). Also, 200 μL of chloramine-T (0–100 mmol/L) for calibration and 200 μL of PBS as blank are also added to different microplates. Finally, 10 μL of acetic acid and 20 μL of 1.16 M potassium iodide (KI) is added to preparations. The normal range was 82.3 to 232.7 (μmol/L). FRAP was measured with spectrophotometry as described by Benzie and Strain (1996) [20]. Based on this method, FRAP reagent is prepared with mixing 300 mmol/L of acetate buffer (pH: 3.6), 10 mmol/L of tripyridyl triazine (TPTZ) in 40 mmol/L HCL, and 20 mmol/L FeCl3.6H2O. Twenty-five μl of serum is then added to 750 μl FRAP reagent and absorbance is recorded at 593 nm. The normal range was 612 to 1634 (μmol/L). AGEs were assessed by the spectrophotometric method of Kalousova et al. (2002) [6]. Patients' serums were diluted by a factor of 50 in PBS pH 7.4. Fluorescence intensity at 350 nm excitation and 440 nm emission was recorded and is expressed as the percentage of fluorescent emission.

2.3. Statistical analysis

The statistical package SPSS 22 for windows (Chicago, IL, USA), was used for analysis. Variables were presented as mean ± standard deviation for continuous and percent for dichotomous variables. The study population was stratified into five groups, healthy control subjects without diabetes and four patients group based on the duration of diabetes. Comparisons between groups were performed using analysis of variances (ANOVA) and Chi-square test, as appropriate. Linear regression analysis was used to evaluate the independent association between AGES, AOPP, and FRAP with the duration of diabetes. Regression analysis was performed on the variables with unadjusted p-value < 0.2 for differences among groups to Adjust the possible confounders including age, gender, anti-diabetic medications, statin use, BMI, WC, SBP, DBP, HbA1c, FBS, HDL, coronary artery diseases, and microvascular complications were performed. Linear regression was used for data modeling. Receiver operating characteristic (ROC) curve analyses were performed in individual patient groups and all diabetic patients as a whole VS non-diabetic control to analyze the difference between AGEs and AOPP as a marker of oxidative damage. Statistical significance was considered at a p value of less than 0.05.

3. Results

The characteristics of the participants are presented in Table 1. There were no statistically significant differences among groups according to gender, weight, anti-diabetic therapy, serum cholesterol, triglyceride, LDL, eGFR, creatinine, the prevalence of hypertension, and smoking (all p-values > 0.05). Newly diagnosed patients with diabetes had significantly higher BMI and had more abdominal obesity according to waist circumferences than other participants, ($p < 0.05$). Patients with longer duration of diabetes were older with poorer glycemic control that other groups, ($p < 0.05$). FBS was higher in patients with 10–15 years of disease and HbA1c was higher in patients with duration of diabetes between 5 and 10 years, ($p < 0.05$). Also, microvascular complications and Coronary artery diseases were more prevalent in patients who suffered longer from type 2 diabetes mellitus ($p < 0.05$).

Serum AGEs and AOPP levels were significantly increased in all patients with diabetes, $p < 0.05$. According to pairwise comparisons, Patients with the longest duration of diabetes, 10–15 years, had a significantly higher level of AGEs compared to newly diagnosed patients (80.44 ± 13.84 vs. 68.97 ± 7.28 $p < 0.05$) and patients with diabetes duration of 1–5 years (80.44 ± 13.84 vs. 73.43 ± 12.96 $p < 0.05$). Likewise, serum AGEs level was higher in patients with 5–10 years duration of diabetes than newly diagnosed patients, ($p < 0.05$). As diabetes progressed, AGEs levels showed progressive levels and were significant at the intervals of 10 years.

The serum level of AOPP was higher in newly diagnosed diabetic patients (136.4 ± 28.75) than controls (110.2 ± 18.66) ($p < 0.05$) and also was higher in patients with diabetes duration of 1–5 years (166.8 ± 48.62) compared to newly diagnosed patients ($p < 0.05$). However, AOPP levels were not changed significantly as the duration of

Table 1
Baseline demographic and biochemical features of the study populations.

	Control (n = 94)	New diagnosed diabetes (n = 100)	Duration of diabetes			p value
			1–5 (n = 46)	5–10 (n = 46)	10–15 (n = 54)	
Gender, F:M	54:40	61:39	29:17	30:16	30:24	0.778
Age, year	50 ± 6.92	50.75 ± 8.62	56.33 ± 10.75*,#	56.31 ± 7.86*,#	58.67 ± 9.37*,#	< **0.001**
BMI, kg/m^2	26.88 ± 1.98	29.05 ± 3.98*	27.41 ± 4.58	26.48 ± 4.03#	26.53 ± 2.65#	< **0.001**
Weight, kg	69.15 ± 9.74	75.46 ± 12.29	72.11 ± 14.17	72.27 ± 9.22	71.66 ± 9.58	0.302
Waist circumference, cm	90.18 ± 7.58	97.71 ± 8.98*	94.53 ± 11.08	91.00 ± 8.56#	94.33 ± 7.54	**0.018**
SBP, mmHg	123.58 ± 10.90	123.16 ± 13.82	120.63 ± 21.93	127.51 ± 20.89	131.67 ± 22.08*,#,¥	**0.014**
DBP, mmHg	77.28 ± 8.47	78.67 ± 6.62	73.80 ± 11.24*,#	78.87 ± 11.95¥	79.13 ± 10.11¥	**0.016**
HTN, n (%)	25 (26.6%)	34 (34%)	16 (34.8%)	17 (36.9%)*	25 (46.3%)*	**0.032**
Duration of diabetes, year	–	–	2.36 ± 1.02	6.58 ± 1.39	11.90 ± 1.99	< **0.001**
Anti-diabetic medications, n (%)						0.798
Oral agents (Sulfonylurea ± metformin)	–	–	40 (87.0%)	38 (82.6%)	42 (77. 8%)	
Insulin	–	–	6 (13.0%)	8 (17.4%)	12 (22. 2%)	
Statin, n (%)	26 (27.6%)	45 (45.0%)*	36 (78.3%)*,#	35(76.1%)*,#	44 (81.5%)*,#	< **0.001**
FBS, mg/dl	88.62 ± 7.08	165.74 ± 56.31*	173.64 ± 52.94*	184.16 ± 46.54*	204.89 ± 56.52*,#	**0.001**
HbA1c, %	4.95 ± 0.33	7.53 ± 1.53*	8.24 ± 2.03*	8.42 ± 1.91*,#	8.22 ± 1.33*	**0.011**
Cholesterol, mg/dl	205.86 ± 23.1	196.17 ± 37.29	190.09 ± 37.75	187.15 ± 47.84	201.90 ± 42.16	0.338
Triglyceride, mg/dl	102.84 ± 23.06	174.18 ± 78.21	146.61 ± 47.50	185.84 ± 87.20	169.65 ± 85.12	0.142
LDL-C, mg/dl	113.84 ± 11.16	112.20 ± 29.76	114.83 ± 34.53	113.61 ± 36.95	115.76 ± 36.58	0.940
HDL-C, mg/dl	52.11 ± 10.9	46.59 ± 9.00*	47.85 ± 10.81*	42.41 ± 9.06*,#	43.95 ± 8.28*	**0.033**
Creatinine, mg/dl	0.95 ± 0.15	0.96 ± 0.14	1.03 ± 0.25	0.95 ± 0.23	0.89 ± 0.24	0.088
eGFR, ml/min	81.21 ± 10.7	78.67 ± 15.12	74.86 ± 24.37	84.20 ± 28.12	78.38 ± 20.08	0.523
Microvascular complications, n (%)	–	7 (7.0%)	14 (30.4%)#	21 (45.6%)#	32 (59.3%)#,¥	< **0.001**
CAD, n (%)	–	11 (11.0%)	6 (18.2%)	5 (13.5%)	8 (18.2%)	< **0.001**
Smoking, n (%)	7 (7.4%)	9 (9.0%)	2 (4.3%)	5 (10.9%)	5 (9.3%)	0.440
AGEs, %	52.53 ± 7.48	68.97 ± 7.28*	73.43 ± 12.96*	79.35 ± 14.41*,#	80.44 ± 13.84*,#,¥	< **0.001**
AOPP, μmol/L	110.2 ± 18.66	136.4 ± 28.75*	166.8 ± 48.62*,#	167.7 ± 36.60*,#	169.9 ± 36.84*,#	< **0.001**
FRAP, μmol/L	1330.9 ± 240.8	1098.0 ± 199.0	987.7 ± 193.4*,#	962.4 ± 314.9*,#	942.7 ± 298.7*,#	< **0.001**

Data is presented as mean ± SD or percent.
BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: history of hypertension, FBS: fasting blood sugar, HbA1c: glycated hemoglobin, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate, CAD: coronary artery diseases, AGEs: advanced glycation end-products, AOPP: advanced oxidation protein products, FRAP: ferric reducing ability of plasma.
* $p \leq 0.05$, versus healthy control.
# $p \leq 0.05$, versus new patients with diabetes.
¥ $p \leq 0.05$, versus patients with diabetes duration less than 5 years.

diabetes gets longer than 5 years. Patients with different durations of diabetes (1–5 years: 166.8 ± 48.62, 5–10 years: 167.7 ± 36.60 and 10–15: 169.9 ± 36.84) had the same levels of AOPP, ($p > 0.05$).

Serum FRAP levels were significantly decreased in diabetes than the control group (1330.9 ± 240.8), $p < 0.05$. There were no differences in FRAP levels among patients with duration of diabetes between 1–5 (987.7 ± 193.4), 5–10 (962.4 ± 314.9) and 10–15 years (942.7 ± 298.7) (all $p > 0.05$) but all had significantly lower FRAP than newly diagnosed patients (1098.0 ± 199.0, $p < 0.05$).

In linear regression analysis the correlation among AGEs, AOPP, FRAP levels, and diabetes duration remained significant after adjustment for age, gender, anti-diabetic medications, statin use, BMI, HDL, HbA1c, waist circumference, microvascular complications, and coronary artery diseases, Table 2.

To analyze the difference between AGEs and AOPP as a marker of oxidative damage, Receiver operating characteristic curve (ROC) analyses was performed in all diabetic patients as a whole vs. non-diabetic controls. ROC analyses also were used in patients with 1–5 years duration of diabetes vs. 10–15 years to assess the differences between AGEs and AOPP as diabetes progressed. When all of the patients with diabetes vs. controls where analyzed, the ROC analysis yielded statistically significant ($p < 0.001$) area under curve (AUC) values of 0.854 and 0.938 for AOPP and AGEs, respectively. In patients with 10–15 duration of diabetes vs. 1–5 years, the significant ($p = 0.003$) AUC value for AGEs was 0.676 but for AOPP was not significant, $p = 0.656$. In both comparisons, AGEs showed better AUC values than that of AOPP (Fig. 1).

Table 2
Linear regression analysis for the prediction of AGEs, AOPP and FRAP levels by DM duration after adjustment for potential confounders.

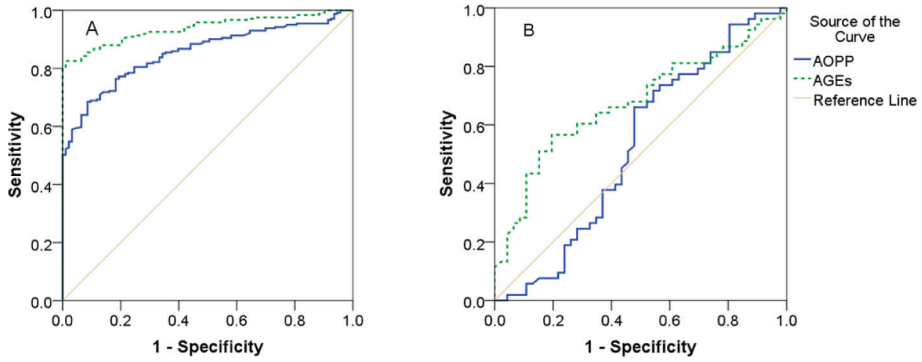
	R	Beta	*p*-Value
AGEs	0.742	0.572	0.000
AOPP	0.621	0.591	0.000
FRAP	0.532	−0.331	0.002

Linear regression analysis for the prediction of AGEs, AOPP and FRAP levels by DM duration after adjustment for potential confounders including age,gender, anti-diabetic medications, statin use, BMI, HDL, HbA1c, systolic and diastolic blood pressure, waist circumference, microvascular complications and coronary artery diseases.
AGEs: advanced glycation end-products, AOPP: advanced oxidation protein products, FRAP: ferric reducing ability of plasma, DM: type 2 diabetes mellitus, BMI: body mass index, HDL-C: high density lipoprotein cholesterol, HbA1c: glycated hemoglobin.

4. Discussion

Our results demonstrate excess production of AGEs and AOPP in all patients with diabetes compared to non-diabetic controls and these changes were more marked in patients with longer disease duration. AGEs levels represented a continuous, increasing pattern as the duration of diabetes progressed. Patients with 1–5 years of disease duration had a higher level of AGEs than a new patient group. Likewise, patients with diseases duration of more than 10 years had higher AGEs level than a group of patients with diabetes duration of 1–5 years.

To our knowledge, the association between AGEs level and duration



ROC	AGEs	AOPP
All patients with type 2 diabetes vs. controls		
AUC	0.938	0.625
p value	**<0.001**	**<0.001**
patients with duration of diabetes 10-15 years vs. patients with duration of diabetes 1-5 years		
AUC	0.676	0.625
p value	**0.003**	0.656

Fig. 1. Comparison of AUCs of AGEs and AOPP by receiver operating curve statistics. (A) All DM patients vs. controls, (B) patients with duration of diabetes 10–15 vs. 1–5 years. ROC, receiver operating characteristic curve; AEGs, advanced glycation end-products; AOPP, advanced oxidation protein products; AUC, area under curve.

of diabetes has not been studied before. Our findings are in accordance with previous studies that have reported elevated levels of AGEs in diabetes [[13]]. AGEs are a result of a non-enzymatic reaction between reducing sugars and amine residues on proteins, lipids, or nucleic acids [22]. Under normal physiology AGEs production and removal are efficient. But excess formation and consequent accumulation maybe link to diabetes complications [23]. In the study of anti-DNA-AGE autoantibodies in patients with diabetes, Ashraf et al. reported a correlation between anti-DNA-AGE autoantibodies and the duration of diabetes [16]. Therefore, it could be suggested that AGEs accumulate in pathological conditions such as diabetes. Besides, in a study plasma AGEs levels were significantly higher in the presence of diabetes complications or poorer glycemic control [6]. Also, AGE is implicated in aging and age-related diseases [24,25].

The same as AGEs, AOPP level was significantly different between new patients and those with duration of diabetes 1–5 years. AOPP has been reported that increased in patients with diabetes and to be associated with albuminuria [26] and micro- or macrovascular complications of diabetes [27,28]. In this study, after five years of disease, we did not find any significant further increment in AOPP level. In a study of serum AOPP level in patients with diabetes, its concentration was an independent risk factor for endothelial dysfunction in an early stage of diabetes [10]. In the current study, the maximum serum level of AOPP was detected in the first five years after the diagnosis of diabetes. However, AGEs level increased with diabetes duration, although with a slower slope after 5 years of diabetes.

We observed that the serum level of FRAP decreased in patients with diabetes in comparison to the control group and the same as AOPP its association with diabetes duration remained significant in patients with less than 5 years of the disease. Evidence also points out that the total antioxidant capacity of plasma was reduced in diabetes and was associated with poor glycemic control and complications of diabetes [29]. However, the correlation between serum FRAP levels and duration of diabetes has not been studied before.

Does diabetes duration, per se, have any effect on oxidative stress markers independent of glycemic control and patients' age? We found a significant difference in age and glycemic control among groups. Both variables were associated with AGEs levels. After controlling for potential cofactors, the differences between AGEs, AOPP, and FRAP levels remained significant among patients with different durations of diabetes.

From an overall point of view, we observed an association between higher serum oxidative damage biomarkers and T2DM duration. Complications of diabetes were associated with both chronicity of diabetes and oxidative stress markers. According to the results of the Receiver operating characteristic curve (ROC) analyses from the current study, both AGEs and AOPP could be a marker of oxidative damage in patients with diabetes. However, by comparing the different duration of diabetes only AGEs levels remained significant. AGEs accumulate and deposit over time and disrupt normal protein structure and function [30].

Advanced oxidative end products mediate vascular complications in diabetes mellitus included microvascular complications and coronary artery diseases. In the current study complications of diabetes increased with longer duration of disease. AGEs levels were also higher in patients with diabetes complications. Thus we performed the regression analysis to study the confounding effect of complications on advanced oxidative markers.

Therefore, the measurement of oxidative stress biomarkers may be useful in monitoring diabetes complications as well as the efficacy of medications. Moreover, it seems that current treatments are not restraining oxidative stress enhancement in diabetes. Therefore, targeting oxidative damage in patients with diabetes may provide a new antidiabetic strategy.

The main limitation of our study concerns the use of cross-sectional data, which prevented us from drawing causal relationships. Furthermore AGEs can be formatted during cooking which was called dietary advanced glycation end products (dAGEs). dAGEs are produced during heat-processed recipes, and foods contain more fat and proteins including animal-derived ones are more responsible to AGEs formation, both of them are popular in our modern diet [31]. Hence the diet of the participants should be considered in future studies about AGEs.

5. Conclusion

Diabetes promotes AGEs, and AOPP production, independent of glycemic control and patients age. Serum levels of AGEs increase progressively with increasing duration of diabetes. AGES may be helpful in estimating chronicity of diabetes.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Firouzeh Heidari: Conceptualization, Formal analysis, Data collection, Data curation, Writing - original draft. **Soghra Rabizadeh**: Supervision, Validation, Writing - review & editing. **Armin Rajab**: Formal analysis, Data curation, Writing - review & editing. **Farrokh Heidari**: Data collection. **Marjan Mouodi**: Data collection. **Hossien Mirmiranpour**: Laboratory analysis. **Alireza Esteghamati**: Supervision. **Manouchehr Nakhjavani**: Conceptualization, Supervision, Writing - review & editing, Project administration.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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