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A Hospital-Based Case-Control Study on Whole- and Refined-Grain Intake and Risk of Stroke

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Original Article

Abstract

INTRODUCTION: The aim of the present study was to ascertain the correlation between the intake of whole and refined grains and the risk of stroke in the Iranian adult population.

METHOD: This hospital-based case-control study was conducted at Alzahra University Hospital, Isfahan, Iran, in 2008. The cases (n=195) were stroke patients admitted to the neurology ward, and the controls (n=195) were patients admitted to other wards in this center, with no prior history of cerebrovascular accident or any neurological disorders. The usual dietary intakes of the study participants during the previous year were assessed using a validated semi-quantitative food frequency questionnaire. Whole and refined grains were defined according to the definition of the American Association of Cereal Chemists International; foods that contained at least 8 g per 30 g of their weight were considered as whole grains.

RESULTS: The mean age of the case and control groups was 68.0 (±13.5) and 61.5 (±10.5) years, respectively; 40% of the cases and 53.3% of the controls were female. The total intake of whole grains (27.8±4.3 vs. 29.4±3.6 g/d, P=0.77) and refined grains (264±11 vs. 296±13 g/d, P=0.07) was not significantly different between the cases and controls. After adjusting for potential confounders, individuals in the second tertile of refined grain intake had a two-fold higher odds of stroke (OR: 2.02; 95% CI: 1.08-3.71), compared to those in the first tertile. Furthermore, no significant relationships were observed between the consumption of whole grains and the risk of stroke, before or after adjustment for confounding variables. No significant trend was found between the tertiles of refined or whole grain intake and the risk of stroke.

CONCLUSION: The authors did not find a statistically significant association between the intake of whole and refined grains and the risk of stroke. Further prospective studies on the relationship between both whole and refined grains and stroke are warranted.

Keywords: Whole grain, Refined grain, stroke, Case-control study

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Introduction

Stroke refers to a group of disorders that include cerebral infarction, subarachnoid hemorrhage, and cerebral hemorrhage [1]. It is the second leading cause of death worldwide, with the highest mortality in low- and middle-

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income countries [2]. Stroke accounts for 50% of disabling conditions in survivors in industrialized countries [3, 4], and about 80% of all stroke deaths occur in developing countries [3, 4]. Recent evidence indicates that the incidence of stroke in Iran is significantly higher than in most Western countries, with an estimated incidence of 113 (95% CI, 104 to 123) per 100,000 population per year [5]. As stroke is a highly preventable disease globally, recognizing modifiable risk factors is crucial in reducing its incidence and resulting disease burden [6, 7].

Although the dietary intake of several nutrients [8-10], foods [11, 12], and food groups [13, 14] has been linked to the risk of incident stroke, comparatively little emphasis has been placed on the specific contribution of whole-grain foods [15]. Whole grains contain high amounts of dietary fiber, vitamin E, magnesium, folate, and phytoestrogens, which have demonstrated beneficial effects on human health [16, 17]. Refined grains contain lower amounts of minerals, vitamins, dietary fiber, and phytochemicals than whole grains [18, 19].

Earlier studies have shown an inverse association between whole grain intake and the risk of obesity [20, 21], metabolic syndrome [22], diabetes [23, 24], and cardiovascular disease [15, 25], while the intake of refined grains has been associated with an increased risk of chronic diseases [26-29]. Although several studies have assessed whole- and refined-grain intake in relation to human health, limited data are available linking these foods to the risk of stroke [15, 29]. Among female nurses in the US, high intake of whole-grain foods has been associated with a 31% lower risk of incident ischemic stroke [30]. A meta-analysis published in 2016 concluded that high intake of whole grains protects against stroke [31]. Such findings have also been confirmed in an 11-year prospective cohort study in African Americans. However, the investigators failed to find a significant association between refined-grain intake and ischemic stroke in this cohort [32].

It must be kept in mind that available documents have been reported from Western nations, and data on the association of grain intake and human health are scarce in developing countries. Finding the relation between whole- and refined-grain intake and the risk of stroke is particularly relevant for Middle-Eastern countries such as Iran, where grains are the staple food [33]. Although grain consumption in these countries has been linked to the metabolic syndrome and hypertriglyceridemic waist phenotype [22, 34], the authors are not aware of any study assessing the association between grain intake and the risk of stroke in this region. Given the high incidence of stroke in the region, particularly in younger ages, examining the relationship between the consumption of grains and the risk of stroke might add additional knowledge to the field. Therefore, this study was performed to assess the relationship between whole- and refined-grain intake and the risk of stroke in a hospital-based case-control study.

Materials and Methods

Participants and Study Design

The present hospital-based case-control study was conducted at Alzahra Hospital of the Isfahan University of Medical Sciences, one of the main centers for admitting patients with stroke in the central area of Iran, in 2008. Data on each pair of case and control were collected simultaneously. Cases were selected using a convenience non-random sampling procedure, and symptomatic stroke was confirmed by a neurologist. Computerized tomography scanning or magnetic resonance imaging was used to rule out other neurological causes. The control group consisted of participants without a prior history of cerebrovascular accident or any neurological disorders. Controls were randomly selected from patients hospitalized in the surgical or orthopedic wards of the center. The participation rate in the study was 100% for cases and 93% for controls. All participants were conscious and able to answer questions and fill out the information form. Written informed consent, including the research question and outcome measures, was obtained from each participant. Finally, a meeting was organized to provide feedback on the research results to the participating members.

Assessment of Dietary Intake

The usual dietary intakes of the study participants in both groups were assessed using a validated food frequency questionnaire (FFQ) [35]. All questionnaires were administered by trained dietitians. The FFQ contained 168 food items. The reliability and validity of the FFQ were previously reported in the Iranian population [35]. For each food item, patients were asked to report portion sizes and consumption frequency during the last year. Each participant reported their food items on a daily (e.g., bread, fruit), weekly (e.g., rice, dairy, meat), and monthly (e.g., nut, fish) basis. For this analysis, all food items were converted to daily intakes by dividing weekly consumption frequency by 7 and monthly frequency by 30. According to the definition of the American Association of Cereal Chemists International [36], foods were defined as whole grains if at least 8 g per 30 g of their weight was from whole grains. Total refined grain consumption was calculated by summing up the consumption of white flour, white breads, sweet bread, rice, toasted bread, pasta, noodles, starch, milled barley, ice cream bread, and biscuits. Total whole grain consumption was obtained by summing up the consumption of dark breads (sangak, whole grain breads), barley bread, whole grain pasta, wheat germ, popcorn, whole grain breakfast cereal, and whole grain biscuits.

Assessment of stroke

Patients with the first-ever symptomatic acute stroke (arterial) confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI) were included. Patients with head trauma, primary intracranial hemorrhage, or subarachnoid or subdural hemorrhage were excluded. Ischemic stroke was defined as an episode of focal neurologic deficit with acute onset due to a vascular cause and lasting more than 24 hours. Data were collected by prospective chart review from January 2008 to December 2008. The study protocol was approved by the local Ethics Review Committee.

Assessment of other variables

Required information about socioeconomic and demographic data (sex, age, education, and occupation), physical activity and smoking status, and medical history was obtained using questionnaires. Height measurement was done barefoot, and weight measurement was done in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Waist circumference was determined as the minimum circumference at the costal margin, and hip circumference at the supreme circumference. Blood pressure was measured after 10 minutes of rest with the subject in the sitting position.

Statistical methods

Tertile cut-points of whole- and refined-grain intake were used for categorizing participants. General characteristics and dietary intakes of participants across tertiles of grain intake were compared using analysis of variance and chi-square, as appropriate. All dietary intakes were obtained using a General Linear Model with age and total energy intake as covariates.

To explore the associations between grains (whole- and refined-grain intake) and stroke, logistic regression was applied in different models. The potential confounders were selected based on earlier investigations on grain consumption and stroke [19, 30, 37]. Initially, adjustments were made for age, sex, and total energy intake. Further adjustments were made for physical activity and smoking. In the third model, additional control was applied for dietary intakes, including fruits, vegetables, pulses, low-fat dairy, high-fat dairy, partially-hydrogenated vegetable oil, non-hydrogenated vegetable oil, nuts, sugar-sweetened beverages, total meats, butter, margarine, and egg consumption. Finally, adjustments were made for BMI to explore the independent-of-obesity association between whole- and refined-grain and stroke.

All models were done by treating the first tertile of refined-grain intake as a reference category. The overall trend across tertiles of grain intake consumption was examined using the Mantel-Haenszel extension chi-square test. Two-tailed P values less than 0.05 were considered statistically significant. The

Statistical Package for Social Science (SPSS Inc., Chicago IL. Version 16.0) was used for all statistical analyses.

Results

In this study, a total of 195 cases and 195 controls were included. The general characteristics of the study participants between cases and controls, as well as across tertiles of whole- and refined-grain intake, are presented in Tables 1 and 2. Stroke patients were more likely to be older, male, smokers, and to have lower BMI or obesity prevalence than controls. The distribution of participants in terms of physical activity was not significantly different between cases and controls.

Table 1. General characteristics of study participants across case and control groups

	Case (n = 195)	Control (n = 195)	P[2]
Age (y)	67.97±13.48	61.47±10.54	0.01
Weight (kg)	86.47±13.15	72.39±14.76	0.05
BMI (kg/m^2)	25.24±4.36	28.46±13.98	0.01
Female, n (%)	78 (40)	104 (53.3)	0.01
Physical activity, n (%)			0.14
Low	56 (28.7)	74 (37.9)	
Moderate	71 (36.4)	59 (30.3)	
High	68 (34.9)	62 (31.8)	
Smoking, n (%)	27 (13.8)	11 (5.6)	0.01
Obesity[3], n (%)	22 (11.3)	57 (29.2)	0.01

1 Data are mean ± standard deviation unless indicated.
[2]ANOVA for continuous variables and chi-square test for categorical variable
3 BMI≥30

Among participants, whole grain intake ranged from 0-530 g/d and refined grain intake ranged from 0-1417 g/d. The mean intake of whole grain in tertiles 1, 2, and 3 were respectively 1.4 (±0.1), 8.7 (±0.3), and 76.6 (±6.8); while the average intake of refined grain in tertiles 1, 2, and 3 were respectively 129.9 (±3.8), 272.8 (±2.9), and 475.3 (±18.8). Compared with those in the lowest tertile, individuals in the highest tertile of refined grain intake were younger and had higher weight. No significant statistical differences were found in the prevalence of obesity, smoking, and physical activity levels across tertiles of refined grain intake. Participants in the highest tertile of whole grain intake had lower age, higher weight, and were more likely to be physically inactive compared with those in the lowest tertile. Mean weight, BMI, as well as prevalence of obesity and smoking were not significantly different across tertiles of whole grain intake.

Age, sex and energy adjusted dietary intake of study participants across tertiles of whole and refined grain intake is shown in Table 3. Participants in the highest tertile of refined grain intake had higher intake of energy, and high-fat dairy, as well as lower meat intake compared with those in the lowest tertile. High intake of whole grains was associated with greater intake of energy and vegetables and lower intake of hydrogenated vegetable oils (HVOs). No overall significant differences were found in other dietary intake across tertiles of whole and refined grain intake.

Table 2. General characteristics of study participants across tertile of refined and whole grain intake

	Tertile of refined grain intake				Tertile of whole grain intake			
	T1 (Lowest) (n=135) (< 190.2 g/d)	T2 (n=146) (190.2-322.4 g/d)	T3 (Highest) (n=108) (>322.4 g/d)	P[2]	T1 (Lowest) (n=119) (< 3.7 g/d)	T2 (n=143) (3.7-19.9 g/d)	T3 (Highest) (n=127) (>19.9 g/d)	P[2]
Age (y)	67.7±12.6	64.9±12.0	61.0±12.2	0.001	66.2±12.0	65.5±13.5	62.5±11.6	0.04
Weight (kg)	67.1±15.0	72.2±11.5	73.9±14.8	0.001	68.1±12.7	72.4±15.7	72.1±13.1	0.04
BMI (kg/m^2)	25.8±5.7	26.6±4.2	28.6±18.3	0.14	25.8±4.9	28.1±16.4	26.8±5.0	0.23
Female (%)	51.1	48.6	38.6	0.14	48.7	49.7	41.7	0.38
Physical activity, n (%)				0.72				0.03
Low	43 (36.1)	48 (33.6)	39 (30.7)		58 (43.0)	48 (33.6)	39 (30.7)	
Moderate	38 (31.9)	44 (30.8)	48 (37.8)		43 (31.9)	44 (30.8)	48 (37.8)	
High	38 (31.9)	51 (35.7)	40 (31.5)		34 (25.2)	51 (35.7)	40 (31.5)	
Smoking, n (%)	7 (5.2)	18 (12.3)	13 (12.0)	0.08	11 (9.2)	14 (9.8)	13 (10.2)	0.97
Obesity[3], n (%)	23 (17.0)	30 (20.5)	25 (23.1)	0.49	19 (16.0)	32 (22.4)	28 (22.0)	0.39

[1]Data are mean ± standard deviation unless indicated.
[2]ANOVA for continuous variables and chi-square test for categorical variable
3 BMI≥30

Table 3. Dietary intakes of study participants across tertiles of energy adjusted refined grain intake and whole grain intake. [1]

	Tertiles of refined grain intake				Tertiles of whole grain intake			
	T1 (Lowest) (n=135) (< 190.2 g/d)	T2 (n=146) (190.2-322.4 g/d)	T3 (Highest) (n=108) (>322.4 g/d)	P[2]	T1 (Lowest) (n=119) (< 3.7 g/d)	T2 (n=143) (3.7-19.9 g/d)	T3 (Highest) (n=127) (>19.9 g/d)	P[2]
Total energy (kcal/d)	1912.0±77.0	1965.6±73.8	2498.1±86.5	<0.001	1986.0±83.8	1995.7±75.9	2310.9±81.2	0.01
Low fat dairy (g/d)	302.4±21.7	325.5±20.7	283.8±24.9	0.43	260.3±22.9	327.9±20.7	323.0±22.3	0.06
High fat dairy (g/d)	137.2±14.1	113.6±13.4	52.9±16.1	0.001	110.0±15.1	97.7±13.7	108.2±14.8	0.81
Fruits (g/d)	328.4±27.2	336.6±26.0	294.7±31.2	0.58	291.1±28.6	301.0±25.9	374.4±27.9	0.08
Pulses (g/d)	29.5±2.4	29.7±2.3	29.2±2.8	0.99	27.4±2.5	29.9±2.3	31.0±2.5	0.61
Vegetables (g/d)	263.1±15.5	269.9±14.8	264.2±17.8	0.94	225.1±16.1	256.8±14.6	314.1±15.7	<0.001
Total meat (g/d)	102.1±13.5	69.3±12.9	31.4±15.5	0.01	57.7±14.4	91.2±13.1	57.8±14.1	0.13
SSB[3] (g/d)	55.0±7.1	38.3±6.8	53.7±8.2	0.17	46.8±7.5	48.2±6.8	50.1±7.4	0.95
HVO[4] (g/d)	20.9±2.7	16.6±2.6	18.1±3.1	0.51	30.6±2.8	15.9±2.5	10.3±2.7	<0.001
Non-HVO[5] (g/d)	12.9±1.1	13.7±1.0	17.1±1.2	0.05	16.0±1.1	13.9±1.0	13.4±1.1	0.26

[1] Data are means± SEM. Data for energy intake are adjusted for age. Data for other dietary variables are adjusted for age, sex and total energy intake.
2Obtained by the use of ANCOVA
3SSB: consumption of soft drink and fruit drinks
4HVO: Hydrogenated vegetable oils.
5 Non-HVO: Hydrogenated vegetable oils.

Multivariate-adjusted odds ratios for stroke across tertiles of refined grain consumption are indicated in Table 4. No significant association was found between refined grain intakes and risk of stroke in the crude model. After adjustment for age, sex, and energy intake, individuals in the highest tertile of refined grain intake were 35% less likely to have stroke compared with those in the lowest tertile; however, this association did not reach statistical significance. Further adjustment for physical activity, smoking, and dietary intakes had little effect on the relationship between refined grain intake and stroke. After additional adjustment for BMI in the final model, individuals in the second tertile of refined grain intake had higher odds of having stroke compared with those in the first tertile. No significant trend across tertiles of refined grain in relation to stroke was found.

Multivariate-adjusted odds ratios for stroke across tertiles of whole grain consumption are presented in Table 5. In the crude model, no significant relationships were observed between the consumption of whole grains and the risk of stroke. This relationship remained non-significant after adjusting for age, sex, and energy intake in the first model. Further controlling for physical activity, smoking, and dietary intakes in the third model, and additional adjustments for BMI in the final model, did not significantly alter the findings. No significant trend was found across tertiles of whole grain in relation to stroke.

Table 4. Multiple logistic regression model (OR and 95% CI) for stroke across tertiles of refined grain intake

	Tertiles of refined grain intake			
Cases (n)	T1 (Lowest) (n=135) (< 190.2 g/d)	T2 (n=146) (190.2-322.4 g/d)	T3 (Highest) (n=108) (>322.4 g/d)	P_{trend}[6]
Crude	1.00	1.20 (0.75-1.92)[5]	0.63 (0.38-1.06)	0.35
Model 1[1]	1.00	1.28 (0.77-2.13)	0.65 (0.36-1.17)	0.47
Model 2[2]	1.00	1.22 (0.73-2.03)	0.59 (0.32-1.07)	0.63
Model 3[3]	1.00	1.55 (0.86-2.77)	0.74 (0.35-1.54)	0.69
Model 3[4]	1.00	2.02 (1.08-3.71)	1.01 (0.47-2.17)	0.55

1 Adjusted for age, sex and energy intake
2 Adjusted for age, sex, energy, physical activity and smoking
3 Adjusted for age, sex, energy, physical activity, smoking and dietary intakes of low-fat, high-fat dairy, fruits, vegetables, pulses, total meat, SSB, HVO and non-HVO
4 Adjusted for age, sex, energy, physical activity, smoking, dietary intakes (including: fruits, vegetables, pulses, low fat-fat dairy, high-fat dairy, partially-hydrogenated vegetable oil, non-hydrogenated vegetable oil, nuts, sugar sweetened beverages, total meats, butter, margarine, and egg consumption) and BMI
5 Odds ratio (95% confidence interval)
6 Obtained by the use of Mantel-Hanszel Chi-Square test

Table 5. Multiple logistic regression model (OR and 95% CI) for stroke across tertiles of whole grain intake

	Tertiles of whole grain intake			
	T1 (Lowest) (n=119) (< 3.7 g/d)	T2 (n=143) (3.7-19.9 g/d)	T3 (Highest) (n=127) (>19.9 g/d)	P_{trend}[6]
Cases (n)				
Crude	1.00	1.41 (0.87-2.30)[5]	1.09 (0.66-1.80)	0.19
Model 1[1]	1.00	1.47 (0.87-2.47)	1.24 (0.72-2.15)	0.23
Model 2[2]	1.00	2.52 (0.89-2.58)	1.29 (0.74-2.25)	0.45
Model 3[3]	1.00	1.44 (0.78-2.65)	1.11 (0.56-2.16)	0.37
Model 3[4]	1.00	1.44 (0.76-2.69)	1.22 (0.61-2.46)	0.33

1 Adjusted for age, sex and energy intake.
2 Adjusted for age, sex, energy, physical activity and smoking
3 Adjusted for age, sex, energy, physical activity, smoking and dietary intakes of low-fat, high-fat dairy, fruits, vegetables, pulses, total meat, SSB, HVO and non-HVO
4 Adjusted for age, sex, energy, physical activity, smoking, dietary intakes (including: fruits, vegetables, pulses, low fat-fat dairy, high-fat dairy, partially-hydrogenated vegetable oil, non-hydrogenated vegetable oil, nuts, sugar sweetened beverages, total meats, butter, margarine, and egg consumption) and BMI.
5Odds ratio (95% confidence interval)
6Obtained by the use of Mantel-Hanszel Chi-Square test

Discussion

In the current study, no statistically significant association was found between the intake of whole and refined grains and the risk of stroke among a group of Iranian adults. This remained true even after adjusting for potential confounders. According to the Mashhad Stroke Incidence Study (MSIS) [5], the incidence of stroke in Iran is higher than in most other regions of the world, and it tends to occur at relatively younger ages [5]. Despite grains being a staple food in many Middle-Eastern countries such as Iran [33], no studies linking grain intake to the risk of stroke were found.

Many people worldwide are increasingly consuming refined carbohydrates such as potatoes, processed grain products, sugar-sweetened beverages, and corn syrup. Compared to whole grain products, refined grains have a higher starch content and contain lower levels of vitamins, minerals, phytochemicals, and dietary fiber [24]. Numerous metabolic studies have shown that a high intake of these can increase levels of fasting triglycerides, reduce levels of HDL, and lead to hypertriglyceridemia and hyperinsulinemia, thereby creating a profile expected to increase the risk of cardiovascular disease and stroke [31, 24].

The protective association between whole grain intake and cardiovascular disease (CVD) is well-documented. Based on the Trowell study (1972), whole-grain foods are protective against ischemic heart disease (IHD) [32]. Morris et al. (1977) reported an 80% reduction in heart attacks in men when comparing the highest cereal-fiber intake with the lowest intakes [33]. There are few studies to date that specifically examine the relationship between whole grain and their physiological effects with the risk of stroke [34]. However, the trends strongly suggest a protective effect of whole grain on the risk of stroke[15].

Some prospective studies in Western countries have shown that greater intakes of whole grain foods are associated with a lower risk of cardiovascular disease [17]. The Iowa Women's Health Study and the Nurses' Health Study indicated that whole-grain consumption had a significant negative association with coronary heart disease (CHD) or ischemic stroke, whereas refined-grain intake was not related [30, 35]. Jacobs et al. (1999) reported that women with the highest level of refined-grain intake, compared with those with the lowest level, had a 9% increase in CHD risk (P=0.70) [36]. According to Liu et al [30], nurses in the highest quintile of whole-grain intake had a 31% lower risk for ischemic stroke compared with those in the lowest quintile. However, women with the highest level of refined-grain intake had ischemic strokes at the same rate as women with the lowest intake. Flight et al [14] also reported that consumption of whole grain foods clearly protected against heart disease and stroke [14].

Refined grains contain lower amounts of beneficial nutrients than whole grains. Findings on the relationship between refined grain intake and the risk of stroke are inconsistent. Over an 11-year follow-up period in the ARIC Study, consumption of refined grains was not related to the risk of incident ischemic stroke [25]. This finding has also been reached by the investigators in the Nurses' Health Study [30]. In the present study, no significant association was found between refined-grain intake and stroke.

This study has several strengths. It examined the association of whole and refined grain intake with stroke in both men and women, allowing the findings to be generalized to both male and female adults. Adjustments were made for several potential confounders in the analysis to obtain independent associations between whole and refined grain intake and the odds of stroke. Moreover, the study selected newly diagnosed patients with stroke, which could reduce the possibility of changes in long-term dietary intakes in these subjects.

Study limitations

In this study, the FFQ was used to assess the intake of whole and refined grains. While this method may have potentially misclassified whole-grain and refined-grain intake, it was deemed appropriate for this study due to the time-consuming nature and high cost of alternative methods such as multiple dietary records or dietary recalls.

The study's case-control design is another limitation, as it is prone to biases such as selection and recall bias. Furthermore, causality cannot be inferred from case-control studies. It's also important to note that the data for this investigation was collected in 2008, and the present study is a secondary analysis; the primary study aimed to assess the relationship between major dietary patterns and stroke, and the related article was previously published [37].

Despite these limitations, adjustments were made for potential confounders (including age and sex) in the analysis. However, no significant association was found between the consumption of whole and refined grains and the risk of stroke. More prospective studies are needed to further investigate the relationship between both whole and refined grains and stroke.

Declarations

Ethics approval and consent to participate: This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were ethically approved by the "Isfahan University of Medical Sciences" (IUMS). Written informed consent was obtained from all subjects.

Consent for publication: Each author acknowledges he/she has participated in the work in a substantive way and is prepared to take public responsibility for the work.

Availability of supporting data: Supporting data for this investigation can be available by contacting the supervisor of the research (AE).

Competing interests: None of the authors declared potential personal or financial conflicts of interest.

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Authors' contributions: FS, MS, FS, AHK, PS and AE designed the research, conducted the study, analyzed the data, wrote the manuscript and had the responsibility for the final content. All authors read and approved the final manuscript.

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