RESEARCH ARTICLE

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Association between CTX-1 and Fibulin-1 Serum Levels with Pathogenesis of Multiple Myeloma Cancer

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Abstract

Background: Multiple myeloma (MM) is the second most prevalent blood cancer after non-Hodgkin lymphoma. It is identified by the excessive production of abnormal monoclonal immunoglobulins, which can result in various clinical symptoms such as destructive bone lesions, renal dysfunction, anemia, and immunodeficiency. The current study aims to evaluate the serum levels of carboxy-terminal collagen crosslinks 1 (CTX-1), Fibulin-1, vitamin D3, LDH, and albumin in MM patients and their significance for early diagnosis. **Materials and Methods:** This study included 30 healthy controls (11 males, 19 females) and 60 patients with multiple myeloma (37 males and 23 females), aged between 40-60 years. Five-milliliter blood samples were collected and stored at -20°C. Afterward, enzyme-linked immunosorbent assay (ELISA) kits were used to estimate the concentrations of CTX-1, Fibulin-1, and vitamin D3. Additionally, LDH and albumin levels were determined using the automated biochemistry analyzer. **Results:** This study revealed that the majority of patients with multiple myeloma are between the ages of 51 and 60 years. The serum concentrations of CTX-1, Fibulin-1, and LDH were significantly increased in the multiple myeloma patients compared to the healthy control group. In contrast, the serum level of vitamin D3 was significantly decreased in patients with MM. **Conclusion:** Our results indicate that the incidence of multiple myeloma is higher in males than in females. Additionally, the serum concentrations of CTX-1 and Fibulin-1 were significantly higher in the multiple myeloma patients compared to the healthy control group, indicating their potential for early detection and as therapeutic targets.

Keywords: Multiple Myeloma- CTX-1- Fibulin-1- Vitamin D3- Albumin- Cancer

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Introduction

Multiple myeloma (MM) is a type of cancer that originates from plasma cells (PCs) and is known for its tendency to affect the bone marrow (BM), as well as for the presence of detectable monoclonal immunoglobulin (Ig) in both serum and urine [1]. Although MM is the second most commonly diagnosed hematologic malignancy in the Western world, it is often mistakenly perceived as a rare disease due to its shorter survival compared to many other hematologic neoplasms and uniformly fatal patient outcomes. Attention reduces the incidence of MM. Population [2]. The incidence of MM is higher in men than in women, higher in African populations, and lower in Asian populations compared to Caucasians. Despite extensive epidemiological studies, specific modifiable risk factors for MM have not yet been definitively identified. According to the findings of Siegel et al., MM accounts for approximately 1% of all cancers and 10% of all hematologic malignancies [3].

More than 32,000 cases of the disease are diagnosed in the United States each year, and nearly 13,000 patients die from it [4]. For several years, the annual age-adjusted incidence in the United States has remained stable at four per 100,000. MM appears to be slightly more common in men than in women, and African Americans are twice as likely to have the disease as Caucasians [5]. Draper et al.'s study revealed that the average age of patients at diagnosis was around 65 years. Unlike other cancers that spread to the bone, osteolytic bone lesions in multiple myeloma do not show any new bone formation [6]. Magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT), and whole-body computed tomography (WB-CT) are the best techniques for identifying bone diseases [7]. During the initial diagnosis, other important clinical symptoms include anemia, hypercalcemia, renal failure, and an elevated risk of infections. Extra medullary disease (EMD) affects 1-2% of patients, and 8% of patients experience EMD at some point during their illness [8].

Almost all individuals with MM experience a premalignant stage known as monoclonal gammopathy of

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undetermined significance (MGUS) [9]. More than 3% of people over 50 have it, while Black individuals are almost twice as likely to have it as White individuals [10]. In addition, multiple myeloma or other related malignancies can develop from MGUS at a rate of 1% per year [3, 11]. It should be noted that MGUS is asymptomatic, and over half of clinically diagnosed individuals have had the condition for over ten years (Landgren, 2021). Clinically, smoldering multiple myeloma (SMM), a more advanced premalignant stage that is initially asymptomatic, can be identified in some individuals [12].

Multiple myeloma develops at a rate of 10% per year in the first five years after diagnosis, 3% per year for the subsequent 5 years, and 1.5% per year thereafter. The genetic makeup of the disease influences the rate of progression of multiple myeloma in patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM) [13]. In order to quantify bone turnover and analyze the efficacy of bisphosphonate drugs, it may be useful to measure the serum concentration of collagen carboxy-terminal cross-links (CTX-1) [14]. Low-dose whole-body CT (WB-CT) or PET/CT imaging is the most effective method for assessing the severity of bone disease [7]. Magnetic resonance imaging (MRI) scans are useful for individuals suspected of having smoldering multiple myeloma (SMM) to identify focal bone marrow abnormalities that may be present before true osteolytic disease develops.

The process of bone destruction in multiple myeloma appears to be associated with an increase in the breakdown of bone tissue by osteoclasts, without a corresponding increase in bone formation. As a result, the characteristic feature of myeloma bone disease is that the bone lesions often do not heal, even when the patients are in complete remission. This is consistent with the observation that bone scans are frequently negative in myeloma patients with extensive lytic lesions, providing limited information for monitoring bone disease in these patients [15]. Osteolytic bone disease is a common complication of multiple myeloma, leading to significant morbidity and mortality due to skeletal complications [16]. X-rays are not very effective in monitoring bone destruction during anti-myeloma or anti-resorptive treatment. Biochemical markers of bone turnover, such as NTX, CTX/ICTP, and tartrate-resistant acid phosphatase isoform 5b, can provide insights into bone dynamics, which may reflect disease activity in the bone. Studies have indicated that these markers are often elevated in myeloma patients and can indicate the extent of bone disease. Some studies have shown a correlation between bone resorption markers and survival. These markers may also help identify patients likely to respond to bisphosphonate treatment and monitor the effectiveness of bisphosphonate therapy in managing myeloma bone disease [17].

Fibulin-1 is a glycoprotein that is secreted and consists of 703 amino acids, with a molecular weight of approximately 70 kDa. Studies have demonstrated that the levels of FBLN1 are higher in the plasma of multiple myeloma (MM) patients compared to the control group [18]. Research has indicated a significant increase in the mRNA level of Fibulin-1 in MM cells and the protein expression in the serum of MM patients. It has been suggested that FBLN1 plays a role in the proliferation, invasion, and movement of myeloma cells [19].

Furthermore, magnetic resonance imaging (MRI) can also be used to assess extramedullary disease, suspected cord compression, or when detailed imaging of a specific problem site is required. Conventional skeletal studies are less sensitive than WB-CT and low-dose PET/CT. Therefore, they should only be utilized when resources for more advanced imaging are unavailable. For a monoclonal (M) protein to be considered measurable, it must be present in amounts of less than 1 g/dL in the blood and/or 200 mg/day in the urine. A blood-free light chain (FLC) assay and serum protein electrophoresis (SPEP) are used to measure M protein levels and assess the efficacy of the drug. These tests are conducted monthly during treatment and every three to four months when the patient is not receiving treatment [20]. For individuals without detectable monoclonal (M) protein, a serum-free light chain (FLC) assay is particularly useful when the FLC ratio is abnormal and the FLC level is below 100 mg/L. Urine protein electrophoresis should be conducted every three to six months to monitor levels of M protein in the urine and to screen for kidney issues that may lead to albuminuria. Assessment of response to therapy and minimal residual disease (MRD) is conducted using the latest global response criteria established by the Global Myeloma Task Force [21]. In this current study, our aim was to evaluate the serum levels of carboxy-terminal collagen crosslinks 1 (CTX-1), Fibulin-1, vitamin D3, LDH, and albumin in individuals diagnosed with multiple myeloma, and to ascertain their importance in the early detection process.

Materials and Methods

Study population (patients and Healthy)

The research participants consisted of 60 individuals diagnosed with multiple myeloma, including 37 males and 23 females, aged 40 to 60 years. These patients were seeking diagnosis and/or treatment at the hematology consultation clinic. The diagnosis of multiple myeloma was confirmed by a specialized hematologist through cytologic examination of bone marrow aspirate, which revealed at least 10% plasmacytes, the presence of monoclonal proteins in serum or urine, and osteolytic lesions in the bones. Additional diagnostic criteria included complete blood counts (CBC), serum protein electrophoresis, and renal function tests (urea and creatinine). The study included patients who had received first-line bortezomib- or lenalidomide-based chemotherapy as initial treatment. The control group consisted of 30 individuals (11 males, 19 females) aged 40 to 60, who were free from any illness. All participants provided informed consent before participating in the study.

Collection of blood samples

Venous blood samples were collected from both patients and control subjects using disposable syringes. Each subject provided 5 mL of blood, with 2 mL placed in ethylenediamine tetraacetic acid (EDTA) tubes for

complete blood counts (CBC), and the remaining 3 mL slowly pushed into disposable gel tubes. The blood in the gel-containing tubes was left to clot at room temperature for 15 minutes, then centrifuged at 3000 rpm for 15 minutes to obtain serum, which was subsequently stored at -20°C until needed.

Serological evaluation

Enzyme-linked immunosorbent assay (ELISA) kits were utilized to analyze the concentrations of CTX-1, fibulin-1, and vitamin D3 following the manufacturer's instructions (Elabscience, China). The concentration of LDH and albumin was assessed using specialized kits following the manufacturer's instructions (Zybio, China).

Statistical analysis

All experiments were conducted three times independently, and the results are presented as the mean ± standard deviation. The data was analyzed using SPSS software (version 26, SPSS Inc., Chicago, Illinois, USA). Descriptive statistics (mean ± standard error) were calculated, and statistical analysis was conducted using a chi-square test followed by a Student's t-test to compare the two groups. A p-value of ≤0.05 was considered statistically significant, and differences were assessed using one-way ANOVA. Additionally, the relationship between the studied parameters was evaluated using Pearson's correlation coefficient (r).

Results

As shown in Table 1, the ELSA results indicated a significant increase in serum levels of CTX-1 and Fibulin-1 in multiple myeloma patients compared to healthy controls. The serum level of vitamin D3 in patients decreased compared to the control group (26.67 ± 2.3 vs. 51.90 ± 1.7; $p \leq 0.001$). Additionally, the results of LDH indicated significant differences between the patients and control groups (168.87 ± 12.3 vs. 122.70 ± 7.5; $P \leq 0.05$). The serum albumin levels showed a significant decrease in multiple myeloma patients compared to controls (2.96 ± 0.2 vs. 3.59 ± 0.1; $p \leq 0.05$).

Table 2 presents a comparison of gender and biochemical markers (CTX-1, Fibulin-1, vitamin D3, LDH, and albumin) in multiple myeloma patients. The serum levels of CTX-1 in males were higher than in females (2.94 ± 0.6 vs. 2.24 ± 0.2; $p \leq 0.05$). Also, the levels of Fibulin-1 and LDH are higher in males than in females (10.73 ± 1.1 vs. 8.96 ± 1.2; $p \leq 0.05$; 187.14 ± 10.5 vs. 150.42 ± 11.2; $p \leq 0.05$). On the other hand, the serum levels of vitamin D3 were relatively higher among females than males, with no significant differences (27.31 ± 2.8 vs. 25.39 ± 3.4; $p \geq 0.05$).

Table 3 presents the correlation between the serum concentrations of CTX-1, Fibulin-1, vitamin D3, LDH, and albumin with the age of patients diagnosed with MM. The findings indicate that the serum levels of CTX-1 and Fibulin-1 were significantly higher in the 40-50 age group compared to other age groups. Conversely, no significant differences were observed in the levels of vitamin D3 and albumin across the three age groups. Additionally, the serum level of LDH was found to be elevated in the 51-60 age group. Table 4 presents the concentrations of CTX-1, Fibulin-1, vitamin D3, LDH, and albumin in patients within the MM group in comparison to their BMI. The average concentration of CTX-1 in individuals with a BMI of 18.5-24.9 was found to be higher than those with a BMI of 25-29.9 and greater than 30, with a significance level of $p \leq 0.05$. The findings concerning Fibulin-1 in MM patients across different BMI groups did not show any significant differences. However, the results did demonstrate a significant disparity in vitamin D3 levels among the three BMI groups.

The study's findings revealed a significant difference

Table 1. The Serum Levels of Biochemical Markers in Multiple Myeloma Patients and Healthy Control Group

Parameters	Healthy	Patient	P-value
	Mean± S.D		
CTX-1(ng/mL) Carboxy-terminal Telopeptide of type -1 collagen	2.1 4± 0.3	3.52±0.1	006** .0
Fibulin-1 (ng/mL)	4.76± 0.5	9.55± 1.1	0.001**
Vitamin D3 (ng/mL)	51.90±1.7	26.67±2.3	0.001**
Lactate dehydrogenase (U/L)	122.70±7.5	168.78±12.3	0.012*
Albumin(g/L)	3.59±0.1	2.96± 0.2	0.031*

*Significantly different at P≤0.05; **Significantly different at P≤0.001, Mean± S. E, student T test was used.

Table 2. Comparison between Gender and Biochemical Markers (CTX-1, Fibulin-1, vitamin D3, LDH, and Albumin) in the Multiple Myeloma Patients.

Parameters	Male	Female	P-value
	Mean± S.D		
CTX-1(ng/mL) Carboxy-terminal Telopeptide of type -1 collagen	2.94±0.6	2.31± 0.2	0.024*
Fibulin-1 (ng/mL)	10.73±1.1	8.96±1.2	0.032*
Vitamin D3 (ng/mL)	25.39±3.4	27.31±2.8	0.390
Lactate dehydrogenase (U/L)	187.14±10.5	150.42±11.2	0.041*
Albumin (g/L)	3.01±0.2	2.94±0.7	0.725

Table 3. Comparison between Age and Biochemical Markers (CTX-1, Fibulin-1, vitamin D3, LDH, and albumin) in the Multiple Myeloma Patients.

Age (year)	40-50	51-60	>60
Parameters	Mean ±S.D		
CTX-1 (ng/mL) Carboxy-terminal Telopeptide of type -1 collagen	3.63±0.4 [b]	2.65±0.1 [a]	2.21±0.2 [a]
Fibulin-1 (ng/mL)	12.65±1.4 [c]	8.33±0.7 [a]	10.85±0.5 [b]
Vitamin D3 (ng/mL)	27.03±4.4 [a]	26.06±3.8 [a]	27.46±1.9 [a]
Lactate dehydrogenase (U/L)	148.95±4.2 [a]	188.51±10.2 [c]	168.62±6.3 [b]
Albumin (g/L)	2.82±0.6 [a]	3.04±0.2 [a]	2.88±0.5 [a]

Table 4. Comparison between BMI and Biochemical Markers (CTX-1, Fibulin-1, vitamin D3, LDH, and albumin) in the Multiple Myeloma Patients.

Body mass index/BMI (kg/m2)	18.5-24.9	25-29.9	>30
Parameters	Mean± S. D		
CTX-1(ng/mL) Carboxy-terminal Telopeptide of type -1 collagen	2.89±0.3 [c]	2.38±0.1 [b]	1.94±0.3 [a]
Fibulin-1 (ng/mL)	9.77±1.8 [b]	9.97±1.4 [b]	7.05±1.1 [a]
Vitamin D3 (ng/mL)	23.40±3.3 [a]	28.37±2.8 [b]	30.08±7.4 [b]
Lactate dehydrogenase (U/L)	149.60±6.4 [a]	167.18±8.6 [b]	189.42±10.6 [c]
Albumin (g/L)	2.97±0.6 [a]	2.90±0.1 [a]	3.22±0.4 [a]

in albumin levels among the different BMI groups. Furthermore, the serum LDH levels showed a significant difference between patients with BMI and MM. The differences in hematological markers (WBC, RBC, and PLT) between MM patients and the control group are presented in Table 5. The results showed significant differences between groups of patients and healthy individuals regarding white blood cells (WBCs) and red blood cells (RBCs). While there were no significant differences between the study groups in relation to platelet levels (PLTs).

Discussion

In many countries, myeloma is more prevalent in men than in women, as indicated in Table 2, as observed in studies conducted in Iraq, India, and Nigeria. The reason for this is not clear, but it may be attributed to various factors such as heredity, lifestyle, exposure to radiation, and geographical location. Moreover, the population in developed countries is aging as a result of advancements in healthcare and sedentary lifestyles. The average life expectancy in the West is approximately 77.5 years, leading to variations in the average age of disease contraction compared to countries in the Middle East and Africa, as indicated by statistics and studies from the World Health Organization (WHO, 2020). Researchers examined cytogenetic changes in numerous patients. They concluded that the fundamental genetic events of immunoglobulin transfusions, which are more prevalent in women and hyper-diploid in men, may impact sex differences. These findings are significant because they illuminate the cause of the clear sex-dependent disparities in survival. The female sex is associated with a higher frequency of genetic lesions linked to poor clinical outcomes, leading to a worse chance of survival. Additionally, these findings raise the possibility that sex may impact the etiology. Myeloma is more prevalent in men than in women and is often caused by abnormal class switch recombination events [22, 20]. In general, the prevalence of the disease in the countries of America is almost similar to that in East Asian countries, despite differences in civilization development and available health and environmental conditions. However, psychological conditions, stress, increased working hours, and the use of certain medications such as sedatives can impact the transmission of the disease in both men and women. Bird and his colleagues found that the incidence of MM was 57% in males and 43% in females [23].

As individuals age, their likelihood of developing hematologic and general cancers increases. Moreover, the incidence of multiple myeloma has been on the rise over time [24]. Table 3 shows that the results of the current study were somewhat consistent with those of Mjali et al. in 2021. They conducted a descriptive study

Table 5. The Differences between Hematological Markers (WBC, RBC, and PLT) in MM Patients and Control Groups.

Parameters	Healthy	Patient	P-value
	Mean ±S. D		
White blood cells (WBCs ML)	5.55±.237	12.493±3.4031	0.001**
Red blood cells (RBCs ML)	3.903±.1087	2.832 ± 1.132	0.001**
Platelets (PLTs ML)	280.8±9.0508	225.87 ±121.49	0.003**

*, Results with one a strike is significantly different at P≤0.05; **, Results with two strikes are significantly different at P≤0.001.

at the Al-Hussein Center in Karbala Governorate, Iraq, involving a total of 78 patients with MM. The study found that the average age of the patients was 59.8 years. The percentage of infection in females was higher than in males, with 42 cases (53.85%) compared to 36 cases (46.15%), respectively. The age group with the highest disease rate is 70 years or older, with an infection rate of 33.33% [25]. In the current study, the highest incidence of the disease was observed in the 41-60 age group, with a rate of 56.67%. This finding is consistent with the results of other researchers in Iraq and other countries who found that male patients in the 60-69 and 50-59 age groups had a higher incidence of the disease (30%, 20%) and (36%, 16.7%) respectively, compared to females in the same age groups. This study was conducted on numerous patients visiting the major hospitals in Baghdad [26]. In 2020, researcher Amin and his colleagues discovered in Iraqi Kurdistan that the infection rate was highest among males compared to females in the 50-60 age group, with a rate of 58% among males and 42% among females [27].

Obesity is another risk factor supported by the study, as some of the patients in this study had body mass indices (kg/m²) that reached 27, as shown in Table 4. The body mass index (BMI) results for females in the current study, categorized as (18-24.9, over 30, and above), were not statistically significant compared to those of males. Despite experiencing a loss of appetite, the majority of the patients were of normal weight. Most researchers have found that there is no relationship between obesity and MM [28]. While a few other researchers have found a relationship between obesity and disease [8]. According to recent research, the increasing incidence of multiple myeloma (MM) and the transition from monoclonal gammopathy of undetermined significance (MGUS) to MM may be influenced by obesity. The data on the impact of obesity on the prevalence of MGUS are debatable. If obesity influences the onset of monoclonal gammopathy of undetermined significance (MGUS) or the progression of MGUS to MM, further research is necessary. Furthermore, a higher BMI is linked to a decreased chance of survival in MM patients. However, there is limited information on the impact of obesity on individuals newly diagnosed with the disease or those who have undergone an autologous stem cell transplant [29]. According to a study on the correlation between excess body weight and the risk of cancer-related mortality, the prevalence of obesity in the US may account for 14% of all cancer deaths in men with excess body weight and 20% in women with excess body weight. Men had a 1.52 relative risk of dying from cancer, while women had a 1.62 relative risk, with BMI being strongly associated with mortality from MM in particular. For individuals who are overweight (BMI ≥ 25) or obese, pooled analyses of prospective studies from 2011 to 2014 revealed a higher risk of mortality from MM of 9-15% and 52-54%, respectively. In African American populations, mortality rates rise as BMI increases, with hazard ratios reaching 1.43 for BMIs of 35 kg/m² or higher [30]. However, not all studies support this assertion, as the connection between obesity and clinical outcomes after a new MM diagnosis is not strongly supported by the evidence. It remains unclear whether the higher mortality among individuals with higher BMI is due to an increase in cancer incidence, a decrease in post-diagnosis survival, or a combination of both factors [31]. Regardless of race (not specifically for African Americans or European Americans). The study found no relationship between BMI and overall survival (OS) in MM. Compared to individuals with a normal BMI at the time of diagnosis, the data indicated that female patients with a higher BMI had longer survival. However, a higher BMI was associated with worse overall survival (OS) among male patients. The findings of a gender-related impact modification warrant further research due to their novelty. Given that BMI can be influenced by lifestyle changes, these findings could have important clinical implications [28].

One of the most important blood tests for detecting and assessing myeloma patients is the Complete Blood Count (CBC). When multiple myeloma (MM) infiltrates the bone marrow, it disrupts erythropoiesis, leading to anemia. Furthermore, the study's findings revealed a significant decrease in the number of red blood cells (RBCs) and hemoglobin (Hb) levels in myeloma patients of both genders. Table 5 shows significant differences between the study groups in relation to white blood cells (WBCs) and red blood cells (RBCs). While there were no significant differences between study groups in relation to platelets (PLTs). A comprehensive blood count in numerous studies revealed that approximately 87.18% of the patients experienced anemia [25, 32, 33]. The capacity of hematopoietic stem cells to produce new blood cells is reduced when the bone marrow becomes filled with malignant plasma cells, which leads to anemia. Alternatively, this decline may be caused by an increase in inflammatory cytokines and renal toxicity of para-proteins [34, 35].

According to the studies by Baiee and Al-Rubies, 29 patients (72.5%) had hemoglobin levels below 10 g/dL, and all the Iraqi patients with MM under study had severely deficient red blood cell, white blood cell, and platelet counts. Only four out of forty patients (10%) had an absolute neutrophil count of less than 2000 cells/mm3, indicating that neutropenia and thrombocytopenia were not very common [36]. In a similar study, Bhuyan and colleagues in India found that patients with MM had significantly reduced levels of hemoglobin (ranging from 3.2 to 9.8 g/dL), white blood cell count (ranging from 900 to 2945 cells/mm3), and a low platelet count in 72% of patients [37]. Abnormal plasma cells, known as myeloma cells, develop in the bone marrow. Different types of antibodies are produced by plasma cells in healthy individuals to help fight infection. Patients with myeloma experience abnormal plasma cells that produce excessive amounts of the M protein, a type of antibody that serves no useful purpose, cannot fight infection, and lowers immunity. Additionally, as the myeloma cells develop and spread within the bone marrow, they hinder the production of healthy blood cells and disrupt the normal functioning of the bone marrow [38]. To the best of our understanding, the prevalence of multiple myeloma is higher in males than in females. The symptoms of the disease vary significantly among patients for reasons that

are not yet fully understood. Additionally, the serum levels of CTX-1, Fibulin-1, and LDH were significantly elevated in patients with multiple myeloma compared to the healthy control group. The delayed detection of the disease results in heightened disease severity and treatment expenses. It has been observed that in the majority of cases where the disease has progressed, it is due to the patient's failure to seek medical attention when symptoms manifest.

Author Contribution Statement

Aseel Mohammed Ali Abed Al- Janabi: Methodology, Investigation, Data curation, Original draft preparation. Hussein Jasim Obaid Al-Harbi: Methodology, Investigation, Data curation, Original draft preparation. Hamid Reza Momeni: Supervision, Conceptualization, Writing- Reviewing and Editing.

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Availability of data and materials

The data and materials that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical Approval and Consent to participate

This research protocol was evaluated and approved by research committee of Arak University.

Conflict of interest

The authors declare that they have no conflict of interests.

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