Behcet’s disease; a narrative review with a focus on autoimmunity processes in involved organs

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Abstract
Behcet’s disease (BD) is an autoimmune and inflammatory disease that is mainly characterized by involvement of the gastrointestinal tract, cardiovascular system, genital tract and joints. The disease is more common in the Middle Eastern and Far Eastern countries and the frequency of recurrences and attacks varies among populations. Although the pathogenesis is not fully understood, there is evidence to suggest that immunodeficiency and specific patterns of production of immune regulatory mediators are important. Impaired autocrine and inflammatory cells, target endothelial cells and prompt vasculitis in the involved organs. Elucidating the immunological mechanism of BD can facilitate the development of new therapies and therapeutic immunoregulatory interventions to prevent possible complications. New therapies, including manipulation of immune-regulating mediators such as interferon-alpha antagonists, have shown promising results in patients with BD. This review aims to consider the role of auto-inflammatory and autoimmune processes and related factors which give rise to the different manifestations of the disease in each involved organ.

Introduction
Behcet’s disease (BD) is a chronic, variable, multi-systemic vasculitis characterized by recurrent episodes of oral, genital, cutaneous and gastrointestinal ulcers and also neurological, cardiovascular, ocular and articular manifestations (1). Involvement of the ocular, vascular and central nervous systems is considered an important cause of death (2). Recently, Greco et al described ophthalmological impairments in patients with BD, including hearing loss and problems with balance (1).

The variable duration of successive attacks and episodes affecting different organs is the characteristic that distinguishes BD from other types of vasculitis (3). The onset of severe inflammatory episodes of BD occurs mostly in the fourth decade of life, since the disease is not common in children and adults older than 50 years. According to published reports, men are more susceptible than women (1,2).

Behcet’s disease is named after the Turkish dermatologist Hulusi Behçet, who first described the triad of complex symptoms; anterior uveitis with oral and genital aphthous lesions (2). The disease first emerged as a common disease along the ancient Silk Road in the Middle East and Far East. As a result of migration patterns, the disease is now rare in Northern Europe, North America, Australia and Africa. BD is most prevalent in Turkey, Iran, Northern China and Korea, followed by Saudi Arabia, Iraq and Kuwait (1,2).

Immunopathogenesis
There is much disagreement about the immunopathogenesis of BD, as a result of probable interactions among genetic predisposition, immunological anomalies and environmental factors. Some studies suggest that the disease is an autoinflammatory process, in light of the increase in neutrophils...
Mucocutaneous manifestations

Mucosal lesions, characterized by lymphocyte infiltration, immunoglobulin and complement deposition are characteristic of the disease. Oral ulcers, genital ulcers and skin lesions are more common in patients with BD. Oral ulcers are painful, with erythematous halos and marked margins. They are the most common manifestations of BD, appearing in 92-100 patients. Oral ulcers are more common on the lips, tongue, gums and mucous membranes, but can also occur on the tonsils, soft, hard palate and throat. Genital ulcers are less common than oral ulcers and occur in 57%-93% of patients. Morphologically, they are similar to oral ulcers but have irregular margins and are larger and deeper. Male genital ulcers are more common in the scrotum; however, the foreskin, penis, flanks and epididymis can be affected. In women, ulcers of the vagina, vulva and cervix are more common. About two-thirds of genital ulcers in BD leave scars depending on the size of the ulcer. Skin involvement, the main diagnostic criterion, is found in approximately 38%-99% of patients with BD and includes papulopustular lesions, nodosal erythema and extra-genital lesions and also pathergy reactions. Erythema nodosum-like lesions are followed by neutrophilic vasculitis, lymphocytic vasculitis, and necrobiosis and also IgM deposits in the vessel walls. In addition, increased IL-23p19 mRNA expression was found in erythema nodosum-like lesions of BD.

Reports also indicated that intra-epidermal pustules, spongiosis, neutrophilic lymphocyte exocytosis and basal keratinocyte vacuolization are the main features of papulopustular lesions. The pathergy reaction, that is, skin hyperactivity to a minimal trauma, is characterized by perivascular infiltrates of mononuclear cells, vasculitis (neutrophilic or leukocytoclastic), the presence of mast cells and IgM, IgA and C3 deposits (13).

Interestingly, no association was found between IL-17 mRNA expression and serum levels in patients with mucocutaneous ulcerations, arthritis and phlebitis; however, serum levels were higher in patients with a positive pathergy test.

Scientists recommended various mechanisms for aphthous ulcers. However, none of these has been proven. T cell-mediated immunologic reactions, blockage of mucosal healing by cytokines, nutritional deficiencies (vitamin B12, folic acid) and viral or bacterial attack are the example of these mechanisms. In addition, immunoreactant deposits on the vessel walls and augmented serum levels of pro-inflammatory cytokines (IL-1, IL-4, IL-6 and TNF-α) have been found in patients with BD who had mucocutaneous involvement (13).

One of the members of IL-1 family and a mediator of natural killer cells is IL-37. Patients with systemic involvement had lower level of IL-37 than patients with mucocutaneous lesions. Additionally, this cytokine can be considered a major pathogenic factor in mucocutaneous disease activity.

Transforming growth factor beta (TGF-β) can be suppressed by Smad3 which is protein coding gene. Smad3 can also inhibit production of inflammatory cytokine by mediating IL-37.

Increased pro-inflammatory responses in the skin of patients with BD can be explained by the lack of intact TGF-β signaling via Smad3. Notably, the IL-37/Smad3
association may be impaired in these patients. A recent study showed that IL-37 is a thymic stromal lymphopoietin suppressor that increases BD skin lesions and leads to impaired skin integrity (7).

A study of 11 patients with BD showed that IFN-γ, IL-17 and CD4+ T cells were increased in their skin lesions. The expression of IL-23R mRNA was upregulated in naive CD4+ T cells in patients with BD and naive CD4+ T cells in the presence of IL-23 showed increased IL-17 mRNA expression. It was also reported that CD4+ T cells infiltrating BD skin lesions expressed TGF-β1 at higher levels than those infiltrating non-BD erythema nodosum lesions. In patients with BD, elevated levels of IL-8 were reported in the serum, skin lesions and small vessel endothelial cells. Serum IL-8 levels are reportedly correlated with disease activity and vascular involvement. Serum levels of IL-33, a significant mediator of innate immunity and its receptor soluble ST2, were measured by Kim et al, who found that both were elevated in patients with BD. Moreover, IL-33 and soluble ST2 expression in the epidermis was higher in patients with BD. Hamzaouini et al (14) also provided evidence that IL-33 mRNA expression is elevated in peripheral blood mononuclear cells and skin lesions in patients with BD. These authors also proposed that the increase is explained by the role of IL-33 released by keratinocytes and/or endothelial cells as a result of tissue damage. In another study, Th1 cell cytokines including TNF-α, INFγ, IL-8 and IL-12 were reported to be increased in oral ulcers in patients with BD compared to normal healthy controls.

Regulatory T cells arise via two distinct pathways: naturally occurring Treg cells are activated directly in the thymus; in addition, when predictable CD4+ T cells meeting their antigen in a tolerogenic condition, they are named adaptive Treg cells. Although Penkiner et al (15) did not report a significant difference in Tregs between patients with BD with or without aphthous ulcerations, Gündüz, found higher levels of CD4+ CD25+ Tregs in patients with recurrent aphthous ulceration. In addition, a special subgroup of T lymphocytes (γδT lymphocytes) responsible for mucosal immunity was detected in increased numbers in the blood stream and mucosal lesions (13).

Patients with BD significantly had higher level of IL-17-expressing CD4+ memory T cells. Interestingly, increased IL-17 expression was also reported in CD8+ T cells in the same study, demonstrating that CD8+ T cells in inflammatory skin diseases such as those that appear in BD are a significant source of Th17-related cytokines such as IL-17 and IL-22.

In addition to cellular immunity, humoral immunity takes part in the pathogenesis of BD. A number of reports have noted the association of high levels of IgM with ulcerative lesions in the oral mucosa, while IgG was observed only on the surfaces of the ulcers (16).

Both cellular and humoral immunity is involved in the pathogenesis of BD. IgG is found only on wound surfaces, while many studies have suggested that wound lesions in the oral mucosa are associated with high levels of IgM. Of note, skin biopsies of patients with BD showed upregulated mRNA expression of B cell-activating factor, a member of the TNF family, again suggesting the possible role of humoral immunity in BD. Djaballah-Ider et al designed a study to assess the effects of corticosteroid therapy on serum immunoglobulin isotypes and antiphospholipid autoantibody production in Algerian patients with BD. Given that IgA production is mediated by T cell-dependent responses, these authors found that it can be prompted by the CD40L pathway, which is involved in the pathogenesis of mucocutaneous events in patients with active BD (17). Another study indicated that concomitant IgA production, anti-prothrombin, high anticardiolipin and anti-β2 glycoprotein I were associated with mucocutaneous manifestations and also ocular and vascular involvement (18). In confirmation of previous work, anti-CL-IgM autoantibodies were found to be a possible risk factor for the development of various lesions, atherothrombosis and visual acuity loss (18). In this connection, Prado et al, conducted a study to evaluate IgM anti-Alpha enolase antibodies in patients with BD. They reported that alpha-enolase as a target antigen was commonly found in patients with mucocutaneous and articular involvement (19), and plays a role in the immunopathogenesis of the disease.

In summary, mucocutaneous involvement is the most frequent manifestation of BD and both innate and adaptive immunity are responsible for these manifestations. More detailed studies are required to clarify the anticipated sequence of pathogenesis and the role of all immune cells and mediators. Future works will no doubt identify promising therapeutic interventions with clinical potential.

**Ocular manifestations**

In ~70% of cases, BD affects the eyes, which may lead to blindness and a high rate of morbidity (20). The prevalence of ocular manifestations in Iranian patients is 56.8%. Anterior uveitis has been reported in 41% of patients, posterior uveitis in 44.4% and retinal vasculitis in 30% (3). The most common ocular symptom is non-granulomatous pan-uveitis with bilateral involvement, which can recur and affect the anterior and posterior sections (21). When inflammation is acute, the patients have no ocular signs and the eye can gradually be destroyed with consequent vision loss. When inflammation is extreme, the first signs occur in uveal and retinal cells prone to inflammatory cytokines and result in unexplained pain, tenderness, poor vision quality, photophobia, redness and epiphora.

In terms of pathology, two types of ocular manifestations can be distinguished; reversible disease that occurs when inflammation begins and ceases only when the disease is deactivated and irreversible, permanent damage. Although the pathways involved in thrombosis pathogenesis in patients with BD are not yet apparent, increased levels of...
factor V gene, also known as factor V Leiden, were found to correlate with thrombosis and ocular involvement in BD although the findings were inconsistent.

Since BD, like lupus erythematosus, is caused by a disorder of the immune system due to environmental and genetic factors, autoantibodies are seen in patients with ocular involvement. One of these autoantibodies is anti-annexin V, a ubiquitous involved in apoptosis. Serum endocan, serum growth differentiation factor 15, serum alpha 1-acid glycoprotein, IL-32, TNF-α, IL-20, IL-6, TNF-α, IL-26 and IL-2 were reported to be significantly higher in patients with uveitis-findings which reflect the fundamental role of these factors in BD pathogenesis (22). Furthermore, Chi et al reported markedly higher amounts of IL-23p19 mRNA, IL-23 and IL-17 in patients with BD who had uveitis and proposed the IL-23/IL-17 pathway for intraocular inflammation in BD. Of note, serum IL-17 levels in patients with active uveitis were lower than in patients with inactive uveitis (23). The IL-18 gene, which has a GG polymorphism, is one of the main polymorphisms found in patients with BD who have ocular manifestations (1). In this connection, IL-8 has been associated with increased inflammation inside the eye in the presence of HLA-B27, commonly found in iris inflammation. IL-33, which is secreted by several immune and nonimmune cells such as mast cells, macrophages, dendritic cells, fibroblasts and endothelial cells, can induce the secretion of pro-inflammatory or anti-inflammatory factors in some situations. Increased levels of IL-33 are found in patients with BD, especially those with retinal involvement. Elevated IgA production has been suggested as a risk marker of uveitis in naïve patients with active disease (18-20).

The general treatment for BD is corticosteroids to reduce inflammation and these drugs are also useful for anterior and posterior uveitis (21). While TNF-α plays an important role in inflammation and disease development, appropriate inhibition therapy may improve the patient's condition. In addition, anti-TNF-α monoclonal antibody has shown positive effects on extreme panuveitis in BD.

Neurological manifestations
Neuro-BD (NBD) comprises neurological manifestations, which are very rare but are associated with poor outcomes in terms of morbidity and mortality. The manifestations contain central and peripheral nervous system involvement. Central nervous system involvement affects parenchymal and non-parenchymal tissues. Parenchymal manifestations can appear in the brainstem, hemispheres, spinal cord and as meningoencephalitis. Non-parenchymal lesions include dural sinus thrombosis, arterial occlusion and aneurysms. Three and 0.2% of patients had central and peripheral nervous system involvement respectively (24).

Higher levels of IgG were observed in NBD of viral etiology. One of the NBD’s possibilities arising from streptococcal infection is the existence of anti-neural antibodies, such as ABGA (anti-basal ganglia antibodies) which may impair motion. Matrix metalloproteinases (MMP) are involved in leukocyte invasion along with other cytokines and chemokines in the central nervous system. Enzymes in the MMPs family were found at raised levels in the cerebrospinal fluid (CSF) of patients with NBD. Anti-annexin V is also increased in neurological manifestations such as ocular and skin lesions. Among T cells, Vγ1 subtype cells play an important role in the activation of natural killer cells, in addition to other important immune cells. In patients with NBD, the Vγ9 and Vδ2 T cell subtypes were seen at higher levels in the CSF.

Chemokines play key roles in the division and development of T cells and B cells. For instance, IL-6 acts as a pro-inflammatory agent in NBD. Therefore, we administered tocilizumab in treatment because it acts as monoclonal antibody against IL-6. In addition, Th-mediated pathogenic mechanisms exist in NBD that suppress Treg cells.

Accordingly, chemotactic factors are essential to the recruitment of inflammatory immune cells. Specifically, a member of the chemokine (C-X-C motif) ligand (CXCL) family, CXCL10 (IP-10). When we have high concentration of chemotactic factor attracts in CSF in patients with NBD. Another chemotactic factor, CXCL8, attracts neutrophil in meningitis, especially in cases of viral origin, which have been reported in NBD.

BD is considered a chronic inflammatory disease that is affected by anti-inflammatory factors such as IL-10, a descriptive factor for distinguishing between NBD and multiple sclerosis (25). There are several unresolved issues regarding whether IL-12 should be considered a marker for NBD. It should be noted that the highest levels of this cytokine related to low level of CSF concentration.

The inflammatory cytokines IL-6, TNF-α, and IFN-γ have also been investigated in the CSF of patients with NBD. Patients with headache attributed to BD have lower level of T-Box Transcription Factor 21, related orphan receptor C (RORC) and FOXP3 (forkhead box P3) than patients with NBD. Moreover, an increase in RORC/FOXp3 and TBX21/GATA3 ratios was detected in patients with NBD.

Cardiovascular manifestations
Given that the most important vessels in the body are located in the cardiovascular system, manifestations of BD in these vessels can be deadly. Cardiovascular manifestations are seen in 7-46% of patients, with arterial involvement in 8-18% and venous involvement in 29%. Among these manifestations are thrombus, arterial occlusion and aneurysm, commonly in arteries. Typically, BD affects veins; however, arterial involvement in rare cases is associated with a high mortality rate. Coronary aneurysm can lead to cardiac problems and although the
aneurysm is risky itself, it is likely to be lethal if it involves the pulmonary artery, particularly because it increases the risk of hematemesis by influencing the bronchi. In the heart, any of the three tissue layers can be involved; the endocardium, pericardium and myocardium. Because of etiological factors, there is also a possibility of heart valve involvement. The resulting cardiomyopathy can be ischemic or non-ischemic. In the pathophysiology of vascular inflammation, other primary factors such as IL-1, IL-6, IL-17, TNF-α and CXCL8 are known to be implicated in some manifestations. One type of immune cell that can trigger endothelial dysfunction is neutrophils, which disturb the mechanism of coagulation by affecting fibrin (26, 27). In view of its cardiovascular manifestations, the classification of BD as a type of neutrophilic vasculitis has been suggested.

Thromboembolism in BD is associated with dysregulations of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, MMP-9 (matrix metalloproteinase-9,) and coagulation factor V. An elevated level of IL-9 in pulmonary manifestations, especially in pulmonary aneurysms, indicates polymorphonuclear infiltration in these vessels (28). Vascular endothelial growth factor (VEGF) produced by neutrophils is known to be an important factor that is markedly elevated in BD. In addition, the neutrophil-to-lymphocyte ratio is considerably higher in patients with active vasculitis and this ratio is a valuable marker of disease activity given that it predicts vascular involvement and deep vein thrombosis (22).

Intestinal manifestations

Intestinal BD occurs when the alimentary tract is involved, with manifestations appearing most commonly in the ileocecal area. The gastrointestinal system is involved in 10-15% of patients with BD and intestinal BD is found in 3%-60% of patients. After the onset of oral ulcerations, it usually takes 4.5 to 6 years for gastrointestinal manifestations to appear. Nausea, vomiting, diarrhea, abdominal pain and gastrointestinal bleeding are the most common gastrointestinal symptoms of BD. Although intestinal BD has a genetic background, environmental factors such as lifestyle, medications, smoking, diet and infectious pathogens have a notable effect in triggering inflammation. The activity of T CD4+, CD8+, γδ, Th1 and Th17 cells is higher in BD. In this regard, Ferrante et al, compared Th1 and Th17 axis cytokines in patients with gastrointestinal symptoms associated with active BD, axial spondyloarthritis and Crohn’s disease with healthy individuals. Th1 cytokines such as IL-12, TNF-α and IFN-γ in serum and ileal mucosal samples were higher in patients with BD than in patients with axial spondyloarthritis and healthy individuals. In contrast, serum levels of IL-23 and IL-17 were lower in patients with BD compared with patients with axial spondyloarthritis and Crohn’s disease. The Th17 axis plays no role in the pathogenesis of gastrointestinal attacks in BD.

Articular manifestations

Joint involvement is seen in 40% to 70% of patients with BD. Worldwide, the highest rate is found in the UK (93%), followed by Australia (87%) (29,30).

Arthritis and arthralgia are the most frequent articular manifestations of BD. Arthritis is rarely accompanied by osteonecrosis, enthesisopathy, avascular necrosis, myositis, myalgia and fibromyalgia as other clinical manifestations. Favorable presentations of Behçet’s arthritis are characterized by episodic, self-limited, non-deforming, non-destructive, asymmetric oligo– or mono-arthritis. Large joints such as the knees, ankles, wrists and elbows are most frequently involved in BD. Erosive forms of BD arthritis seldom appear solely in axial and peripheral joints.

An analysis of synovial fluid (SF) disclosed mucin clots and inflammatory mediators. To discriminate between BD joint inflammation and seronegative arthritis, Ahn et al (31) evaluated levels of 123 metabolites in synovial fluid from six Patients with BD. Augmented levels of glutamate, citramalate and valine were reported to be potential BD arthritis biomarkers. Furthermore, elevations were found in other metabolites including leucine, methionine and phosphate. The authors noted increased levels of sulfoxide and citrulline in relation to oxidative stress, reflecting neutrophil hyperactivity in BD.

The immunological features of BD synovitis can be expressed as neutrophilic infiltration and the accumulation of B and T lymphocytes. Cañete et al, compared BD and psoriatic arthritis (30) and confirmed elevated levels of CD68+ macrophages – a global marker of inflammation – in the synovial sub-lining. Additionally, the authors reported high levels of CD15+ neutrophil infiltration in the intimal lining layer. The expression of CD117 was depleted on mast cells and levels of CD3+, CD4+ and CD8+ T lymphocytes were elevated. Characterization of the cytokine profile disclosed augmented levels of IFN-γ, TNF-α, IL-2 (Th1), IL-17 (Th17), IL-4 and IL-10 (Th2) in patients with BD compared to healthy persons. The expression of CD56 by cytotoxic T cells and natural killer cells was slightly higher in patients with BD than in patients with psoriatic arthritis. Cetin et al, evaluated plasma and synovial fluid levels of IL-2, IL-5, IL-8, IL-10, IL-12, IFN-γ and TNF-α in CD3+ T lymphocytes. Confirming previous studies, the authors found that CD4, CD25, intracellular and synovial fluid IL-12, IFN-γ and also TNF-α levels in CD3+ T lymphocytes were elevated in patients with BD compared to the healthy group. Higher levels of IL-8 were seen not only in arthritic involvement; concentrations also appeared to be high in patients with vascular, neural and oral manifestations. These authors also showed that BD is a disorder representing Th1 polarization. Glu-Leu-Arg (ELR)-containing leukocyte-regulating chemokines are classified as CXC and CC. The electronic laboratory
and synovial fluid levels of soluble tumor necrosis factor perforin, a cytotoxic effector, in patients with BD. Serum and synovial fluid immunostaining detected higher levels of the reasons for the non-destructive nature of BD arthritis. Notably, IL-6 was particularly high in patients with active artritic manifestations, indicating its potential as a biomarker for these manifestations and disease activity (32). The crucial role of Th17 and IL-17 led to anti-IL-17 antibodies as an efficacious treatment for articular involvement in BD (33).

NO is considered a cytotoxic free radical responsible for articular symptoms in BD. In a study of 23 patients with active articular involvement, reciprocal increases in NO concentrations were reported in serum and synovial fluid and were suggested to be the reason for the patients’ articular inflammatory process. Increases in the concentration of TNF-α, soluble IL-2 receptor, IL-6 and IL-8, as previously reported, stimulate NO synthesis and neutrophil functions. The detection of plasma cells in synovial tissue along with the buildup of immunoglobulins on the synovial surface pointed to the involvement of B lymphocytes in synovial inflammation. Elevated blood concentrations of IgG, IgM and IgA in patients with BD accompany B cell pathogenesis. Additionally, levels of anti-alpha-enolase antibodies, i.e. IgM anti-alpha-enolase antibodies, were reportedly higher in patients with recurrent flares of BD arthritis. Consequently, IgM anti-alpha-enolase antibodies may be a predictor of BD flares.

Other studies of IL-β1 levels in synovial fluid suggested that elevated levels of this interleukin were involved in BD pathogenesis. Regarding IL-18, lower quantities compared to rheumatoid arthritis and osteoarthritis reflect the less pronounced inflammation and non-pannus characteristics of BD arthritis. Matrix metalloproteinase 3 (MMP-3), an erosion-stimulating factor in arthritis, was found to be lower in synovial fluid from patients with BD compared to rheumatoid arthritis. The authors thus proposed that the lower level of MMP-3 may account for the non-erosive characteristic of BD arthritis. In contrast to the non-erosive nature of BD arthritis, high levels of MMP-1, a collagen-degrading enzyme, were seen in synovial fluid of patients with rheumatoid arthritis. Elevated plasminogen activator inhibitor-1, found in the synovial fluid of patients with BD, which is also viewed as one of the reasons for the non-destructive nature of BD arthritis. Synovial fluid immunostaining detected higher levels of perforin, a cytotoxic effector, in patients with BD. Serum and synovial fluid levels of soluble tumor necrosis factor 1 (sTNFR-1) and sTNFR-2 were significantly increased in patients with BD, particularly those with active arthritis and the association between sTNF-2 concentrations and arthritis activity merits attention.

In summary, artritic manifestations in BD are characterized by non-erosive, non-deforming, recurrent mono- and oligo-arthritis. Overall, a number of cytokines, chemokines and immunes cells have been reported to be higher than their normal ranges in patients with BD. Further studies of immune processes involved in BD arthritis will undoubtedly point to new potential treatment pathways in the future.

Conclusion

BD is a multi-systemic disease whose etiology and pathogenesis remain poorly understood. It is characterized by a combination of autoimmune and auto-inflammatory processes which appears to be related to genetic background and environmental factors. Human leukocyte antigens class I and II have shown major effects on prognosis of different disease presentations (34). In addition, immune-related vasculitis of mucocutaneous, gastrointestinal, ocular, cardiovascular, neurological and articular manifestations, were discussed. In conclusion, according to the important role of immune-mediating factors such as interleukins, tumor necrosis factors, leukocytes, interferons and antibodies, this multi-systemic disease could be easily anticipated. By detecting such serum factors, prognosis, probability of rise of each manifestation and disease severity would be simply predictable which leads to less mortality and morbidity.

Further studies are needed to fully elucidate the pathogenesis and the sequence of immune cell involvement, and to resolve controversies raised by the results of different studies. More research will pave a way to novel and promising preventive, prognostic and therapeutic strategies.

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Authors’ contribution

MM, KJ, ZH and JK were the principal investigators of the study. MM, JK, ZE and JB were included in preparing the concept and design. ZEF, AK, SMB, KJ, ZH, ZE, AK and JB revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

The Ethics Committee of Qom University of Medical Sciences approved the study protocol. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.
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