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Review Article

Nutritional aspects and vitamin D supplementation in ankylosing spondylitis

Aikaterini A. Kalogeropoulou

Clinical Dietitian - Nutritionist, Athens, Greece

Abstract

Ankylosing spondylitis (AS) is an inflammatory rheumatic disorder that burdens predominantly the spine and sacroiliac joints. The exact factors that define the development and evolution of the AS remain unclear. The ambiguity around the therapeutic treatment of vitamin D, regarding its immunomodulatory and anti-inflammatory effects in the development of the AS, provides an attractive field of investigation. The connection of the disease with intestinal gut microbiota is well documented, allowing for investigating the role of nutrition, including prebiotics and probiotics, on well-being and functionality of people with AS. The beneficial effect of low starch diet and the anti-inflammatory effect of the Mediterranean diet are landmarks in the development of AS. Additionally, it can be argued that the progression of the disease was compounded, among the Inuit population of Alaska, by the change in their nutrition that was rich in omega-3 polyunsaturated fatty acids and low carbohydrate, to a "Western-Diet" that is high in carbohydrate (sugar and starch) and saturated fat. This review investigates the relationship between diet and disease progression, as well as identifies a dietary pattern that could improve the well-being of people with AS. Finally, this review investigates the therapeutic effect of vitamin D supplementation in the disease progress.

Keywords: Ankylosing spondylitis, Vitamin D supplementation, Diet, Starch diet, Systemic inflammation

Introduction

Ankylosing spondylitis (AS) belongs to the group of inflammatory rheumatic disorders, such as psoriatic (PsA), reactive and enteropathic arthritis as well as arthritis related to inflammatory bowel disease (IBD), juvenile ankylosing spondylitis and undifferentiated spondylitis. As seronegative spondyloarthritis (SpAS) affects predominantly the spine and the sacroiliac joints as well as the peripheral joints, especially the lower limbs[1-3]. The well-being of patients is greatly affected as a result of the severe damage caused by the disease in the mobility of vertebral column, resulting in physical disability[4]. Based on the literature, it is believed that, on a worldwide basis, the disease prevalence is between 0.02% to 0.35% and even higher for people with low socioeconomic status[5]. The disease manifest more frequently in men than in women and its appearance is more usual during the third decade of life and rarely after the age of 45 years[6,7].

The cause of AS is still unknown, although genetic and infectious factors appear to have a significant contribution in triggering inflammatory mechanisms through which the disease can develop. An important risk factor in the AS is the histocompatibility antigen B27 (HLA-B27), as 90-95% of patients with AS are positive for this antigen. However, genetic factors cannot fully justify the cause of the disease. Moreover, there is considerable literature surrounding the role of the gut microflora in the occurrence of AS, but the exact mechanism of its impact has not been fully understood yet[8-10].

In recent years, more studies focus on the role of certain foods, including macronutrients and micronutrients, in the progression and development of chronic diseases, such as arthritis. Patients with AS often require costly and long-term medication, which may compromise their quality of life[11,12].

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Corresponding author: *Aikaterini A. Kalogeropoulou, Gorgopotamou 30, 15772 Zografou, Athens, Greece*

E-mail: *aik.kalog@gmail.com*

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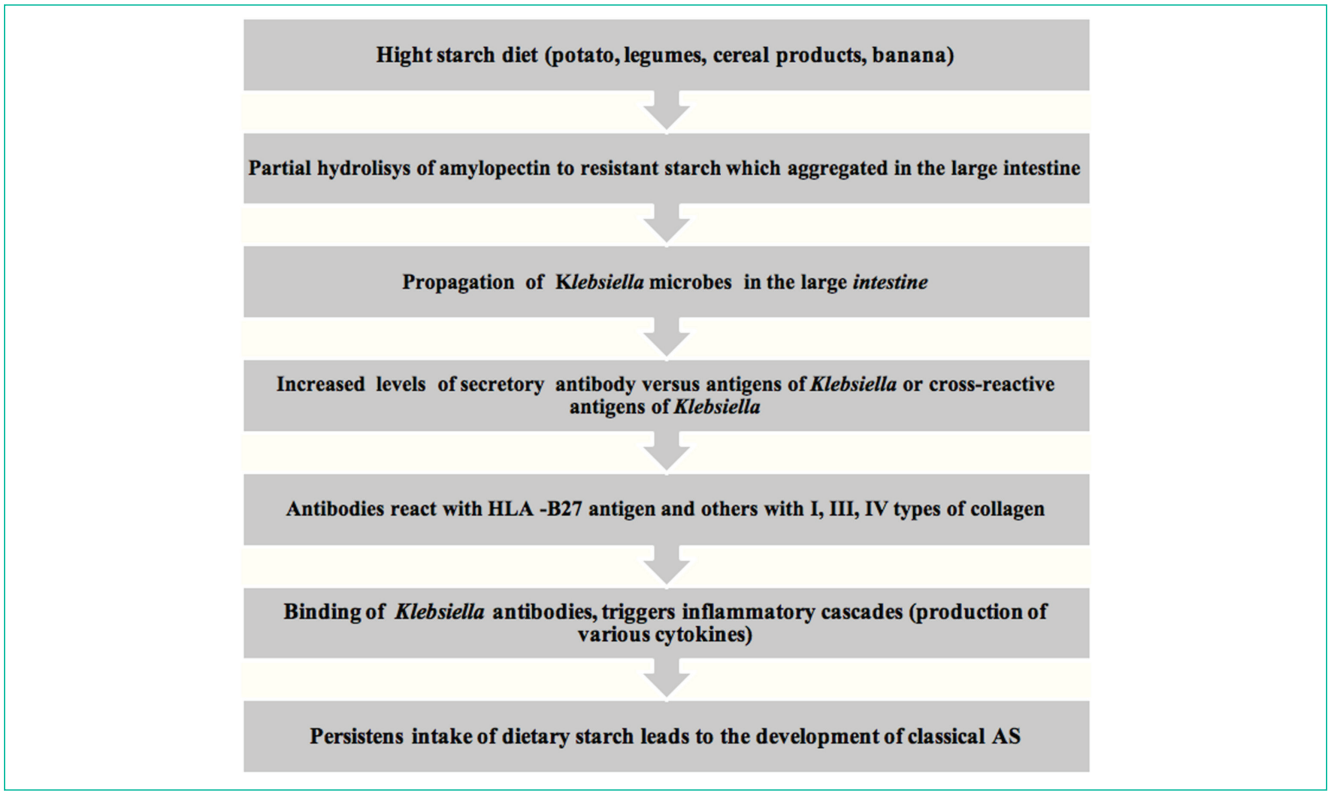

Figure 1. Possible sequential pathogenetic steps and the role of high starch intake in the development of ankylosing spondylitis (AS).

To reduce this burden in terms of expenditure and quality of life, particular attention should be devoted to all intervention measures and especially to the non-pharmaceutical. There is evidence, supporting that lifestyle, especially diet and supplementation of vitamin D, has a significant role in disease progression and improving the well-being of these patients[12-14]. Furthermore, significant evidence indicates that nutritional factors, such as high starch consumption and other factors, such as the blood phospholipids that are rich in arachidonic acid, fatty acids abnormality, and low levels of vitamin D, are related to the development of AS and psoriatic arthritis[14-17].

The purpose of this review is primarily to investigate the relationship between diet and disease progression as well as to identify a nutritional care process based on clinical practice guidelines that could improve the well-being of people with AS. Moreover, this review aims to assess whether the supplementation of vitamin D could have a therapeutic impact in the progression of the disease and consequently to improve the quality of life of AS patients.

The role of diet and its components in AS

The role of dietary starch

Numerous studies had proved the strong correlation between ankylosing spondylitis with inflammation of the intestine, and identified *Klebsiella* and HLA - B27 as dominant factors[18-20].

The development of microbial agents in the colon is primarily attributable to complex carbohydrates and resistant starch that are present in significant amounts at the intestine[21]. Dietary starch or macromolecular polysaccharides transported into cells after being hydrolyzed into smaller substrates through specific enzymes, pullulanase and isoamylases. Starch molecules are known to be consisted of 20% amylose and 80% by amylopyktini. Amylose as a polymer of glucose with linear structure, which is linked by a-(1-4) linkages, can be readily hydrolyzed by digestive enzymes, such as amylases. The amylopyktini is a branched polysaccharides consisting of linear amylose sequences linked to a-(1-4) bonds, but at 10 to 15 molecules, the side chains are inserted connected to a-(1-6) bonds. Digestive enzymes are unable to break a-(1-6) bonds, but these can be hydrolyzed by *Klebsiella pullulanase*, which are located in the colon. This results to the limited digestion of the starch in the small intestine and hence in the formation of "resistant starch", which accumulates in the large intestine. Indeed, a large percentage of consumption of dietary starch cannot be hydrolyzed by pancreatic amylase, thus ending up in the large intestine in resistant form, which is fermented by gut microbiota, providing source energy and carbohydrate in

plurality of bacteria, which are present in the colon as the *Klebsiella pullulanase*. Infections with *Klebsiella* lead to the production of types of cross-reactive antibodies. Some antibodies are reacting with type I, II, and IV of collagen, which form an important component of the vertebral tissues where the pathological lesions are located, while other antibodies are reacting with HLA-B27, an antigen which is expressed in most articular tissues. The binding of these *Klebsiella* cross-reactive antibodies, triggers inflammatory cascades (production of various cytokines) resulting in pathological changes that could develop AS[22-23] (Figure 1).

The above is confirmed by a study that compared the gut microbiota between vegetarian Adventists, who consumed mainly low fat dairy products and eggs, non vegetarian Adventists, who consumed mainly meat (3 to 5 meals per week) except for pork products and other biblically defined "unclean meat", and non Adventists, who followed a conventional American diet. From this comparison, it was observed that concentrations of *Klebsiella* in fecal of people with a diet of low protein/high carbohydrate were forty times higher as compared to those who had a diet with low carbohydrate/high protein[24]. Similar conclusions were derived by Van Laere et al, who reported that there is a positive correlation between the high intake of oligosaccharide and increasing levels of bacteria, such as *Klebsiella spp., Bifidobacterium spp., Clostridium spp., Escherichia coli spp*. in the colon[25]. Also, in vitro study was observed a significant increase in the average number of *Klebsiella* for three different simple sugars (glucose, lactose and sucrose) per gram of substrate, whereas following the incubation with eleven different aminoacids, the number obtained was much lower, thus showing that carbohydrates are an important substrate in the growing and replicationing of *Klebsiella*[26,27]. The large amount of microbes on the intestinal microbiota can be associated with high levels of immunoglobulin A (IgA), and increased inflammation in patients with AS[28]. Djuric et al., also pointed that high fat and high carbohydrates diets could facilitate the absorption of bacterial lipopolysaccharide (LPS) by the bacterial of the intestine and thus stimulate inflammatory reactions in the intestine[29]. All of the aforementioned indicated the key role of prebiotics and complex carbohydrates in growth, reproduction and the time life of many enterobacteriaceae factors in the colon.

Additionally, the literature shows the positive effect of low starch diet in patients with AS, which may act protectively by suppressing the growth of microbes in the gut microbiota. Specifically, in a study of 36 individuals with AS, who consumed a low starch diet by reducing significantly the intake of bread, potatoes, cakes and pasta and by increasing their intake of meat, fish, fruits and vegetables, for 9 months, it was observed that there was a reduction in the sedimentation rate of the erythrocyte, in the total concentrations of IgA as well as a decrease in the intake of antiinflammatory drugs, after the intervention period[28]. In addition, the Ebringer A. et al. provided evidence from a study of 36 individuals with AS who experienced significant improvement of disease symptoms and a reduction of the medication after 9 months of intervention with a diet low in starch[26].

Therefore, we could assume that a low-starch diet combined with the appropriate drug treatment could result in the reduced inflammation and remission of the disease, thus improving health and quality of life of the patients, whereas a high-starch diet could encourage the creation of bacteria, such as *Klebsiella pullulanase*, which may have adverse effects in patients' health and their well-being.

"Paradox" of Inuit diet and AS

The relationship of HLA-B27 gene with AS, discovered forty-four years ago by research groups in London and Los Angeles[30,31]. In the general population the distribution of HLA-B27 antigen seems to run parallel to that of HLA-B27-associated diseases, especially AS[32]. Nevertheless, in some population, the ethnic distribution for the HLA-B27 genes is uneven, as HLA-B27 index appear to be similar to patients with AS and normal HLA-B27 positive people. This shows us there are no obvious defects to make HLA-B27 gene responsible for the appearance of AS[33].

This is confirmed by a study in which it was observed that while the presence of HLA-B27 in the population of Chukotka (residence of Russia) was 34% and between Inuit 25-40%, the prevalence of AS was only 1.1%[34]. Moreover, of great interest is the fact that the prevalence of AS in the population of Inuit in Alaska is similar to that of Caucasians (~2%), despite the fact that the population of Inuit has much higher incidence of HLA-B27 (25%) compared to the Caucasians (6.9%)[35]. This disparity between the presence of HLA-B27 and the manifestation of AS to residents of various continents, predisposes us that there are other factors that give rise to AS. Among these factors, we should take into consideration the dietary patterns of the population, the involvement of the other genes and the existence of gut microbiota that we have already mentioned above (*Klebsiella pneumonia*).

During the last decades it has been observed an increased prevalence of SpA, including AS, in the population of the Northern Norway, from 0.036% to 0.21%[36]. This increase triggered the necessity to identify additional factors that could be responsible for this upwards trend. Significant changes have been observed over the years in the eating habits of these populations. Particularly, the traditional diet of Eskimos during the winter consisted of plant foods, dairy products and increased consumption of fish and sea horses, whereas there is much less consumption of meat. During the summer months, their diet consisted of vegetarian foods, such as greens, wild berries, roots etc. Over the years and particularly in recent decades, the diet of the inhabitants of the more northern regions of Alaska, completely changed compared to that of their ancestors[27,37]. This also confirmed by a study that examined the eating habits of Inuit in Nunavut,

as the results showed that their diet comprised of foods with high sugar and fat content[38].

Changes in eating habits of Eskimos in Alaska (from a nutrition rich in omega-3 polyunsaturated fatty acids (PUFA) and low carbohydrate on a "Westernized high starch containing" foods, like fast food), could explain the paradox, showing one possible mechanism protection of the population against the manifestation of AS, even in cases where HLA-B27 is in high rates of occurrence. Certainly, further studies are required to confirm the above and one should not underestimate the role and contribution of other factors, such as the existence of more specialist diagnostic tools over the last years.

Mediterranean diet and gut microbiota

The Mediterranean diet is an anti-inflammatory dietary pattern, which is rich in complex carbohydrates and fiber, high in monounsaturated fat (MUFA) and low in animal fat and protein. Many of the anti-inflammatory effects of the Mediterranean diet are associated to the consumption of foods with low ratio omega-6/omega-3 PUFA and extra virgin olive oil which, with its high content of phenolic compounds and MUFAs, has been found to have anti-inflammatory effects both in vivo and in vitro studies[13]. Due to the above, the Mediterranean diet helps in maintaining the good intestinal microflora, which is capable to favor the production of short chain fatty acids by promoting saccharolitic microbiota[39]. These metabolites seem to have a positive effect on the immune system, by promoting and maintaining the integrity of the intestinal epithelial barrier, by preventing intestinal inflammation and regulating the acetylation of lysine residues[40]. The aforementioned is a covalent modification that affects proteins involved in a variety of significantly and metabolic processes.

There are extensive arguments that there is a connection between microbial disbiosis and many inflammatory rheumatic diseases, including spondyloarthropathies[41]. Various studies suggest that bowel disbiosis could be prevented and deterred by the anti-inflammatory abilities of the Mediterranean and vegetarian diets[42-44]. In a study of 165 patients, aged 18 to 70 years, diagnosed with AS, it was observed a correlation between gastrointestinal pain with a diet comprising the consumption of food rich in flour, dairy products, vegetables, fruits and fatty foods, despite the fact that there was no correlation between diet and the activity of the disease[45].

Moreover, according to the literature, dietary patterns with high fat and carbohydrates and low fiber, such as the "Western Diet", can lead to serious disbiosis[43,44]. In addition, Sundstrom B. et al. indicated that the increased delta-5-desaturase (D5D) activity is associated with an enhanced biosynthesis of AA which resulted in the increased incorporation of plasma phospholipids that are rich in arachidonic acid and which are correlated with development of AS[46].

The anti-inflammatory effects of the Mediterranean diet could result in a life of better quality for patients with AS. This dietary pattern, due to the functional abilities that it offers, deserves further research on individuals with AS.

Probiotics and/or prebiotics as therapeutic treatment of AS

Probiotics are 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'. These microorganisms survive during their stay and their passage through the gastrointestinal tract, as they are not affected by the acidic environment of the stomach and bile, and they are promoting the health of the host[47-49]. Prebiotics are called the components of foods, especially fibers, which assist in the growth of beneficial bacteria in the gut. They consist the "food" to grow more probiotic strains in order to enhance the health of the host. The beneficial abilities of probiotics and prebiotics in connection with the modulation of intestinal microbiota, the immunomodulation and the strengthening of the epithelial barrier[50-52]. Study that was contacted on specific pathogen-free conditions (SPF) HLA-B27 transgenic rats, showed that a combination of chicory-derived long- chain inulin and oligofructose (Synergy - 1) reduced the development of intestinal inflammation[53]. Dieleman et al. in a study of transgenic rats, which were free of HLA-B27, showed that the oral provision of probiotics species *Lactobacillus rhamnosus GG* (LGG) could partially prevent the relapse of colitis. In addition to the above, another study demonstrated that probiotics, such as, *Lactobacillus casei* has strong anti - inflammatory and antiarthritic effect on collagen - induced arthritis rat model[54]. Also, in one pilot study, patients with active SpA and quiescent ulcerative colitis, consumed probiotics *(Lactobacillus acidophilus and Lactobacillus salivarius)*, and the result showed that there was a significant reduction of Visual Analogue Scale Score and Bath AS Disease Activity Index (BASDAI)[55].

The results of the studies, which correlate probiotics and prebiotics with AS, are very interesting but many of these do not confirm their therapeutic effect in the disease. Specifically, in a randomized controlled trial, which included 63 patients with spondyloarthritis, showed that there were no significant deviations in the progression of the disease for patients receiving probiotics for 12 weeks *(Streptococcus salivarius, Bifidobacterium Lactis and Lactobacillus acidophilus)* as compared to patients receiving placebo for the same period of time[56]. Similarly, another randomized controlled trial, which categorized 147 patients with spondyloarthropathy in two groups (group consumed *Lactobacillus salivarius, Lactobacillus paracasei, Bifidobacterium infantis, Bifidobacterium bifidum* and group consumed placebo) examined whether probiotics improved the symptoms of spondyloarthropathy. Specifically, researchers found that probiotics and placebo had similar effects[57].

The above results show a possible attractive therapeutic strategy of probiotics and prebiotics for people with AS.

Age group	RDI's (patients at risk for vitamin D deficiency)	Loading dose	Maintenance therapy
0-1 years	400-1000 IU/day	2000 IU/day or 50000 IU/week for six weeks	400-1000 IU/day
1-18 years	600-1000 IU/day	2000 IU/day or 50000 IU/week for at least 6 weeks	600-1000 IU/day
Adults	1500-2000 IU/day	6000 IU/day or 50000 IU/week for eight weeks	1500-2000 IU/day
Obese children and adults	2 to 3 times more	6000 -10000 IU/day at least	3000 -6000 IU/day
Adults on medication affecting vitamin D metabolism	2 to 3 times more	6000 -10000 IU/day at least	3000 -6000 IU/day
IU: International Units, RDI: Recommended dietary intakes			

Table 1. Treatment and prevention for vitamin D deficiency as recommended by the Endocrine Society Clinical Practice Guideline.

However, more studies are required to evaluate their role in AS, as well as in the determination of which strain of bacteria will be provided, the appropriate dosage and duration of their provision. Additionally, further research is required to determine at which stage of the disease the provision of the probiotics could show their beneficial effects.

Vitamin D and Ankylosing spondilitis

Vitamin D and severity of AS

The AS as a disease of inflammatory nature, could increase the production of proinflammatory cytokines, such as some interleukins (ILs) (IL-1, IL-6, IL-17, IL-23) and tumor necrosis factor alpha (TNF-a). IL-6 in a great extent participates in initiation and maintenance of inflammation, and is involved in the production of acute phase reactants, including C-reactive protein (CRP). Besides, initiation and progression of AS, determined by the adaptive T cell immunity[58].

The 1,25 Dihydroxyvitamin D (1,25(OH)$_2$D), operates as a regulator by reducing the aforementioned proinflammatory cytokines[59,60]. Specifically, 1,25(OH)$_2$D acts via the specific receptor of vitamin D (VDR). These receptors can be found in most tissue cells (macrophages, B and T lymphocytes, dendritic cells) including inflammatory cells. Thus, it is able to inhibit the differentiation and maturation of monocytes into dendritic cells resulting in the reduction of nuclear factor kappa B (NF-kB) and the T helper (Th)1 response suppression. Additionally, can alter both B and T cell immune actions and may reduce the proinflammatory effects of anti-*Klebsiella* antibodies in AS. In general, 1,25(OH)$_2$D has the ability to alter immune cells' production of anti-inflammatory/proinflammatory cytokines and impair their interactions in this way, modulate immune reactions[14].

Although the anti-inflammatory properties and immunomodulatory action of vitamin D, the relationship of the activity of AS disease remains controversial. While several studies had shown the aggravating effect of vitamin D's deficiency in the activity markers of AS disease[61-64], other studies have not found any correlation[65-67]. Although, there is evidence for increased risk of AS in people with deficiency of vitamin D[68-70] further studies are required to clarify the causal relationship between the deficiency of vitamin D and activity of AS disease.

Therapeutic effect of vitamin D supplementation in AS

Several epidemiological studies, highlighted the possible linkage between adequate serum levels of 25 hydroxyl vitamin D (25(OH)D) and the reduced risk of AS[68,71,72]. In a study of 48 AS patients has been reported a significant correlation between plasma 25(OH)D levels and erythrocyte sedimentation rate (ESR)/CRP, but did not observe any significant correlation with BASDAI[61]. Hmamouchi et al. showed that there is a significant inverse correlation between 25(OH)D and Bath AS Functional Index (BASFI)/BASDAI adjusted to gender and age[62]. Additionally, Hmamouchi et al. in another study, with 653 axSpA patients, mentioned that 25(OH)D had a significant inverse correlation with AS disease activity score, using CRP and Bath Ankylosing Spondylitis Metrology Index (BASMI)[73]. In studies that examined the relationship of 1,25(OH)$_2$D with disease activity markers, found a significant inverse correlation between 1,25(OH)$_2$D and ESR, BASDAI and CRP[63,64].

In contrast, there are studies that indicated that there is no correlation between 25(OH)D and disease activity[74-76]. It is important to note, that most of these studies used parametric test with risk of type 2 error.

According to the literature, although that it is clear that supplementation of vitamin D may be beneficial in patients with AS, but it is not considered as a therapeutic treatment for the whole AS population. It has not been determined yet whether the systematic screening for the deficiency of vitamin D in the patients with AS will provide the benefits to

improve their health[14]. The current guidelines, state that only patients with AS who have a risk factor deficiency in vitamin D or those confirmed with deficiency in vitamin D, should be subject to systematic inspection and treatment of vitamin D[12] (Table 1). Unanswered remains the question whether the deficiency in vitamin D may be the cause of AS or simply reinforces systemic inflammation and poor health status of these patients. Reflecting the immunomodulatory role of vit D, systematic supplementation with vitamin D in conjunction with the disease modifying antirheumatic drugs (DMARDs) of all AS patients, might have an effective therapeutic action to reduce disease activity and comorbidities. Therefore further studies are needed which will help create guidelines for the role of the vitamin D and the manner of treatment in patients with AS.

Vitamin D and common comorbidities in AS patients

It is well known that individuals with AS, have a high possibility of developing cardiovascular disease (CVD). In particular the hazard of CVD in AS population is higher by 1.6 to 1.9 times than people without the disease. The classical risk factors for CVD are diabetes, hypertension, dyslipidemia, smoking, body mass Index (BMI), sedentary lifestyle, chronic inflammation and taking DMARDs[77,78]. Recent data, showed that deficiency of vitamin D is related to the poor endothelial function and the development of atherosclerotic plate, leading to an additional burden factor for CVD in the population[79]. According to the above, and considering the aggravating role of vitamin D on systemic inflammation, we could argue that people with AS which have deficiency in vitamin D have higher possibility to be diseased with CVD compared to the general population.

Osteoporosis, is another comorbidity disease afflicting approximately 62% of patients with AS. The prevalence of osteoporosis in individuals with AS is approximately 25% and vertebral fractures approximately 10%. Osteoporosis usually occurs after 10 years of AS disease[80]. Individuals with AS having a deficiency of vit D, have higher prevalence of osteoporosis instead of patients with normal status of 25(OH)D. Several studies have indicated the relative low status of 25(OH)D with the appearance of osteoporosis, and that vitamin D deficiency leads to osteoporosis through the promotion of inflammatory activity[62,64,81]. As mention patients with AS, frequently present increased rate of osteoporosis, poor quality of bones and vertebral fractures. Therefore, a screening of osteoporosis within a period of 10 years since the diagnosis is suggested and an assessment of the identified risk factors as well as the duration and activity of AS should also be considered[14,80].

Conclusion

In conclusion, it can be argued that the pathogenesis of AS is the result of factors that have genetic and environmental origination. The anti-inflammatory action of vitamin D is an important field of research, since the disease is characterized by intense inflammation. Although, several experimental studies indicated the immunomodulatory and antiinflammatory effects of vitamin D, its relationship with the AS remains unclear. The additional benefit of vitamin D supplementation, as a means of therapy in AS, is still at the theoretical level, as there is not strong evidence to establish guidelines. However, the indicative beneficial effects of supplementation of vitamin D in conjunction with DMARDs to patients with AS, reinforces the requirements for further research and investigation. The adhering to Mediterranean diet in combination with the addition of prebiotics and probiotics, could offer substantial benefits to the quality of life in AS patients, as the existing literature highlighted the relationship of the disease with microflora of the gut. In addition, Mediterranean diet, due to anti-inflammatory properties, shows a protective effect against the comorbidity and health burden of these patients. A low starch Diet, rich in omega-3 PUFA, in combination with medication, could reduce inflammation and improve the quality of life in patients with AS, whereas a high-starch diet, which results in the aggregation of resistant starch in the intestine, could encourage the creation of bacteria *(Klebsiella pullulanase)* that would have adverse effects in patients' health and their quality of life. Definitely, there is need for more supportive studies to be able to conclude on a beneficial protective standard diet for patients with AS. Furthermore, there is a need for future longitudinal prospective studies and well-designed randomized controlled trial, as there is incomplete literature in investigating the effect of supplementation of Vitamin D in combination with a protective standard diet, in progression of AS.

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