Multifaceted aspects of chronic disease: do diffuse idiopathic skeletal hyperostosis affect the quality of life?

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Abstract

Diffuse idiopathic skeletal hyperostosis (DISH) is a common condition that affects the spine and peripheral joints, characterized by the progressive ossification of ligaments and tendons. It is a non-inflammatory degenerative disease that affects predominantly the elderly population. It has been associated with reduced mobility and chronic pain, which can have a significant impact on patients’ quality of life (QOL). Although DISH has always been considered a benign condition, patients with DISH report higher levels of pain, stiffness, and disability compared to the general population. It can affect their ability to perform daily activities and participate in social and recreational activities. In addition, extra-spinal manifestations such as enthesopathy and involvement of peripheral joints, but still dysphagia and airway obstruction have been described in DISH. These, although not as common, when present result in signs and symptoms significantly impacting the patient’s QOL. The objective of this review is to assess the QOL in individual with DISH. This involves an examination of various facets of the condition, including pain, spinal and extraspinal manifestations, fractures, and metabolic syndrome.

Keywords

Diffuse idiopathic skeletal hyperostosis, quality of life, chronic pain, spinal involvement, extra-spinal involvement

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH), also known as ankylosing hyperostosis and Forestier’s disease, has traditionally been considered a non-inflammatory condition characterized by progressive calcification and ossification of ligaments and entheses [1]. Since its first description by Forestier, it has been recognized that DISH primarily affects the axial skeleton, particularly the thoracic portion. Consequently, the classification most commonly historically used was proposed by Mader et al. [2], Resnick and Niwayama [3]. However, the involvement of extra-spinal sites such as peripheral enthesopathies has been reported, as well as some metabolic and clinical entities that appeared to be associated [4].
The pathogenic mechanisms leading to skeletal hyperostosis in DISH have not been fully elucidated. Involvement of the enthesis is also common in inflammatory conditions, such as psoriatic arthritis (PsA), ankylosing spondylitis (AS), and related forms of spondylarthritic (SpA) [5]. In particular, the tendency for enthesal new bone formation, either in spinal or peripheral sites is shared features in both SpA and DISH, with the lower part of the thoracic spine and the upper part of the lumbar spine appearing to be the most commonly affected regions [6]. The radiographic findings in the two diseases are very similar, making the differential diagnosis a challenging issue at the time [6]. Additionally, the co-occurrence of DISH and AS has been recently reported [7]. Although the pathogenetic mechanisms underlying the two conditions appear to be different, the presence of both raises suspicion of a possible common denominator between these two disease entities [7].

In SpA, the pathogenic mechanisms that lead to enthesitis and subsequent new bone formation are preceded by localized inflammation at the entheseal sites. The new bone formation appears to be subsequent to the inflammatory phase. The inflammation at the entheseal sites can also involve the adjacent synovial lining, leading to subsequent articular damage [5]. However, knowledge about the pathogenesis of DISH is very limited. In contrast to SpA, it was traditionally considered a non-inflammatory disease [7]. However, a genetic susceptibility has been suspected, since a few cases of familiar DISH have been described. The main hypothesis is based on the belief that metabolic derangements, such as an excess of growth factors (insulin, insulin-like growth factor 1, transforming growth factor 1, prostaglandin I2, endothelin 1) that might induce the transformation of mesenchymal cells into fibroblasts and osteoblasts, and reduced activity of inhibitors of bone-promoting peptides (e.g., Wnt-β-catenin pathway inhibition) exist in patients with DISH [1, 8]. The hyperostotic process just explained might lead to stiffness of anatomic structures around the peripheral joints, resulting in increased intra-articular pressure [1].

The reported prevalence of DISH varies depending on factors such as sex, age, country development, and radiographic tools, with a range of 2.9% to 27% [1, 9–11]. Specifically, it appears to be more common in male than female subjects and to increase with age, as demonstrated by several authors [10, 12]. An epidemiological study conducted in Hungary found that the prevalence of DISH increased from 10% in the fifth decade to 36% after the age of 75 in male subjects, and from 1.9% to 26% in female subjects [11]. Overall, although the etiology of DISH is largely unknown, there have been several reported associations with obesity, metabolic syndrome, arterial hypertension, and diabetes mellitus [9].

Quality of life
The World Health Organization defines the quality of life (QOL) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns”. Standard indicators of the QOL include wealth, employment, the environment, physical and mental health, education, recreation and leisure time, religious beliefs, safety, security, and freedom. Since the concept of QOL was introduced in literature in the 1960s, it has become clear how the presence of any disease can influence an individual’s QOL. Therefore, physicians in every discipline must take this into account in the diagnostic pathway and therapeutic objectives for each patient. For this reason, the concept of health-related QOL (HRQOL) has been introduced, slightly tailored to the medical field. However, in recent years, a major step has been taken in which the scientific community has recognized the importance of evaluating HRQOL as a tool to better define therapeutic objectives and improve management, especially in diseases characterized by chronic pain or disability [13].

In this context, the aim of this review is to examine the QOL of patients with DISH, by evaluating different aspects of the disease such as pain, spinal and extraspinal involvement, fractures, and metabolic syndrome. A worldwide review of studies related to this topic using 2 electronic medical databases, i.e., PubMed and EMBASE, was performed. The following keywords were selected: “Diffuse idiopathic skeletal hyperostosis”, “Quality of Life”, “Pain”, “Spinal involvement”, “Extraspinal involvement”, “Fracture risk”, and “metabolic syndrome”. Studies published in English with available abstracts were included.
Pain and spinal involvement

DISH is a condition characterized by calcification and ossification of tendons and ligaments, predominantly affecting the spine [1]. In this site, the ossification slightly affects the spinal longitudinal ligaments and entheses leading to a decreasing mobility until complete ankylosis of the involved regions occurs [10]. Since most patients with DISH are asymptomatic, the first diagnostic criteria set by Resnick and Niwayama [3] was based on radiographic findings. Overall, even if data are conflicting, pain is a reported symptom of DISH, and together with spinal stiffness, it can be quite debilitating for patients. The pain associated with DISH is typically chronic and can be localized to the affected area (thoracic, lumbar, and/or cervical pain) [14]. In one of the first reports about clinical symptoms among patients with DISH, Utsinger [15] showed that in a cohort of 200 patients, 72% of them complained of back pain and 84% spinal stiffness, and in a controlled study between DISH patients and healthy controls pain was demonstrated to be higher in patients with the disease [16]. In contrast, some studies have pointed out that pain in DISH may not be the main symptom, finding no significant difference between patients and healthy controls and defining it as a symptom that is not clinically relevant in the absence of complications [17, 18]. In particular, it has been observed that back pain among DISH patients could be complained more in the early stage than in the matured stage of the disease [9]. What has just been described once again raises the question about DISH on may be an inflammatory disease. Local inflammation may precede or initiate the formation of enthesopathies leading to pain in the early stages [19]. In the later stages, the responsibility for the stiffness of the spine would be morphological changes in the bone structures, leading to the postural abnormalities typically observed in patients with AS [1]. However, as previously stated, there are several differences between DISH and AS. Firstly, AS typically affects the thoracic spine only in its later stages, while DISH involves it frequently and has been defined by this involvement [3]. Patients with DISH tend to have preserved intervertebral disc height, as opposed to what in AS occurs where a reduction in disc height is commonly reported. The differences are likely due to the distinct pathological processes at play, with AS targeting the intervertebral disc cartilage and DISH hitting the enthesis sparing the intervertebral discs. Osteophytes in AS are usually transverse, while those in DISH are coarse, vertical, and bridging [20].

As Holton and colleagues [18] have well outlined, although back pain does not correlate with spinal damage and is therefore not a good indicator of physical impairment, this does not mean that DISH does not impact QOL. Banno et al. [21] revealed that DISH affects physical function in the elderly population. The activities of daily living (ADLs) requiring flexibility in the spine might be inhibited for the characteristic ossification on the anterior longitudinal ligament in DISH. This is clearly shown in the Rancho Bernardo study that suggests DISH has to be considered a predictor of poor physical function [12].

An interesting topic that has been emerging in recent years is the possible sharing of pathogenetic mechanisms between DISH and the ossification of the posterior longitudinal ligament (OPLL). Both conditions are characterized by abnormal bone growth within the spine, but it is thought that there is some overlap and potential links in their pathogenesis [22].

OPLL is primarily defined by the ectopic OPLL in the spinal canal. Its pathogenesis is not fully understood, but it is thought to involve a combination of genetic and environmental factors [23]. While DISH predominantly affects the anterior longitudinal ligament, it shares similarities with OPLL in terms of abnormal bone growth. Since the specific mechanism and genetic factors involved in these conditions may differ, there may be common pathways related to bone remodeling and ossification, such as the genetic variants in COL6A1 associated with both diseases [24].

Otherwise, emerging evidence underscores a particular focus on the role of heterozygous and compound heterozygous ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) pathogenetic variants, which can induce autosomal recessive hypophosphatemic rickets type 2 (ARHR2). These genetic variants predispose individuals to DISH and OPLL [22]. It may be attributed to the loss of inhibitory plasma pyrophosphate, a critical regulator of ectopic calcification and enthes mineralization. Additionally, the identification of ENPP1 haploinsufficiency in patients with DISH and early-onset osteoporosis suggests shared molecular mechanisms also involving this other condition [22]. Further investigation into the
intricate interplay of genetic factors and pyrophosphate dysregulation is essential to unravel the underlying mechanism linking osteoporosis, DISH, and OPLL.

Finally, the occurrence of radiculopathies, caused by compression of nerve roots by osteophytes, is not uncommon in DISH [14]. The most common location for radiculopathy in DISH is the thoracic spine, where osteophytes are commonly found. However, it can also occur in the cervical and lumbar spine. The clinical presentation of radiculopathy in DISH can vary depending on the severity and location of the nerve compression, but common symptoms include pain, numbness, tingling, or weakness that radiates from the spine to the affected area, such as the arms or legs [1, 14].

**DISH and extraspinal involvement**

DISH is not limited to spinal involvement, and has been reported to affect extraspinal locations such as entheses and peripheral joints [1, 4, 8, 14, 25]. If the spinal involvement of DISH goes in differential diagnosis with the axial manifestations of SpA, when discussing extraspinal involvement, a comparison with osteoarthritis (OA) cannot be ignored, as these two conditions often coexist due to the age of the affected population [4].

As demonstrated by Resnick’s study in 1975, DISH predominantly affects peripheral joints that are not typically involved in OA, such as elbows, shoulders, wrists, ankles, and metacarpophalangeal (MCP) joints [26]. To understand the clinical impact of articular involvement, it is worth noting that, according to a descriptive study, alterations of the articular lining affecting the MCP joints in DISH can affect up to 56% of the population considered, compared to 10% in individuals with OA [23].

In the extra-spinal involvement of DISH, the hallmark radiographic finding is a much more prominent hypertrophic change compared to OA. However, pain is not always complained, and it depends primarily on the affected site. There is a discrepancy between radiographic and clinical findings [4]. According to Beyeler’s reports, the presence of hyperostotic changes in the shoulder seems to always be associated with pain [27], which is not the case when the elbows are affected [28]. Therefore, the impact of the disease on QOL depends on the affected sites.

DISH also involves changes in the sites adjacent to joints, with bone spurs, calcifications, and ossifications [14]. These changes can lead to a reduction in the range of motion, resulting in stiffness and increased intra-articular pressure that triggers the destructive processes typical of OA [8].

Peripheral enthesopathies are typical manifestations of DISH and are usually large and symmetrical, easily found in the tibial spine, patella, olecranon, and heel [4]. Particular attention should be paid to the presence of pelvic enthesopathy, which is highly characteristic of DISH and is considered a good indicator of the radiographic presence of the disease in the spine. Pelvic enthesopathy includes enthesopathy of the sacro-tuberous and ilio-lumbar ligaments, as well as the insertion of tendons such as the iliopsoas [25].

Due to excessive bone growth in the anterior cervical spine that can displace the trachea and esophagus, patients affected by DISH could present airway obstruction and dysphagia [9]. Although they have always been considered rare manifestations, a systematic review of the literature has identified at least 200 patients with cervical DISH-related symptoms between 1980 and 2009 [29]. Given the high impact of these events on the QOL, physicians should consider cervical hyperostosis as a possible cause of dysphagia or airway obstruction, in order to recognize the condition and treat it as soon as possible.

As previously mentioned, there is often a discrepancy between radiographic and clinical findings, and not all individuals with radiographic evidence of extra-articular involvement will experience symptoms. Therefore, careful monitoring and individualized treatment plans are important for managing extra-articular manifestations of DISH.

**DISH and fracture risk**

Although DISH may be considered by many to be a benign disease, it is not uncommon for structural changes in the spine to result in conditions that impact QOL such as fractures [9]. Patients with DISH in
whom there is an ankylosed spine are four times more at risk of vertebral fractures than subjects without ankylosis of the spine [10].

The reason lies in the fact that in an ankylosed spine, if there is a force applied to the column as in the case of a trauma even a low-energy, the spine is not able to dissipate the force as it does in a healthy spine. This is a consequence of the fact that the structures responsible for this, such as the intervertebral discs, facet joints, and ligaments, have undergone pathological remodeling that does not allow them to dissipate the energy by distributing it in multiple segments [30]. Consequently, patients with DISH more frequently have spinal fractures, even due to low-energy trauma such as a fall from standing to sitting [9, 10].

Spinal fracture in patients with DISH is a serious condition. Namely, the fact that the disease predominantly strikes in old age, when the comorbidity rate is high, results in a condition that should not be underestimated [18]. Thus increases the incidence rate of surgical complications and mortality. In particular, in the study by Okada et al. [31], nearly 20 percent of patients with vertebral fracture as a consequence of DISH had surgical complications, while Bernstein et al. [32] demonstrated an almost 30 percent mortality rate among patients with DISH undergoing surgery for vertebral fractures.

Furthermore, as they are often caused by low-energy trauma, as they are not often accompanied by the appearance of pain, and as radiographic evaluation is difficult to interpret due to the abnormalities already present, the diagnosis of fractures in patients with DISH often suffers major delays, resulting in an increased frequency of neurological consequences [33]. Vertebral fractures in DISH are associated with increased instability and a high risk of spinal damage, elements that can substantially impact the QOL of these patients [9].

According to the systematic review conducted by Westerveld and colleagues [10], the spine tract most affected by the presence of fractures was the cervical tract, followed by the thoracic and lumbar tracts [10], while Okada et al. [33] showed that the most frequently affected segment among 46 patients with AS was the thoracic tract.

Evaluating data reported by Bransford et al. [34], spinal fractures occurring in patients with DISH more frequently lead to neurological deficits, surgical and pulmonary complications, and death. Moreover, it is well known that the complications following a cervical fracture, which is more frequent in DISH, are much more serious than those reported in thoracolumbar fractures. In the latter indeed, an open-wedge fracture and posterior compression of the spinal cord could occur as a consequence of posterior injury [33].

While spinal fractures in DISH are relatively rare, they can lead to significant morbidity and should be carefully monitored and managed in affected individuals. Early diagnosis and treatment can help prevent complications and improve outcomes for subjects with DISH-related spinal fractures [1, 10, 33].

**DISH and metabolic syndrome**

DISH has been associated with several metabolic disorders, including diabetes mellitus, cardiovascular diseases, hyperuricemia, dyslipidemia, and metabolic syndrome [31, 35–37].

Metabolic syndrome is a cluster of metabolic abnormalities that includes obesity, insulin resistance, dyslipidemia, and hypertension [38]. As previously mentioned, several studies demonstrated a significant association between DISH and metabolic syndrome [35]. Additionally, individuals with DISH and metabolic syndrome had a higher incidence of cardiovascular disease and other metabolic complications [36].

The exact mechanism underlying the association between DISH and metabolic syndrome remains unclear, but it is believed to be related to a combination of genetic and environmental factors. In particular, insulin resistance and chronic low-grade inflammation may play a role in the development of both DISH and metabolic syndrome [1]. Management of metabolic syndrome in individuals with DISH typically involves lifestyle interventions such as weight loss, regular exercise, and dietary modifications to improve metabolic parameters. In addition, medications such as statin and antihypertensive drugs may be prescribed to manage dyslipidemia and hypertension [35].
The presence of metabolic syndrome in individuals with DISH may also impact the management of the condition itself. For example, individuals with metabolic syndrome may be at an increased risk of developing spinal fractures due to the increased risk of osteoporosis associated with the condition, indeed, as shown by von Muhlen and colleagues [39], the risk of nonvertebral osteoporotic fractures in women with metabolic syndrome was almost 4 times higher the group of women without metabolic syndrome [odds ratio (OR) = 3.76, 95% confidence interval (CI) 1.27–11.13] [31].

The association between DISH and metabolic syndrome highlights the importance of considering metabolic parameters in the management of individuals with DISH. The connection of metabolic factors with DISH remains a subject of ongoing research, as common age-related diseases like diabetes and hypertension are prevalent but not conclusively interdependent with DISH. However, early diagnosis and management can help to reduce the risk of complications and improve outcomes in individuals with this condition.

Conclusions
DISH is a condition characterized by several clinical manifestations. While it is typically considered a benign condition, it can lead to a range of complications that can significantly impact an individual’s QOL [12].

DISH can cause pain, stiffness, and reduced mobility in affected joints, as well as neurological symptoms such as radiculopathy or myelopathy [8]. Additionally, DISH can lead to complications such as spinal fractures or compression of the trachea and esophagus, which can cause airway obstruction and difficulty swallowing [33, 40]. However, it is essential to note that DISH is primarily a degenerative condition with a genetic component, rather than a proven inflammatory, and it often appears in subsequent generations.

The impact of DISH on an individual’s QOL is multifaceted with physical, psychological, and social factors. Early diagnosis and management of DISH-related complications are important for optimizing outcomes and improving QOL in affected individuals.

Abbreviations
AS: ankylosing spondylitis
DISH: diffuse idiopathic skeletal hyperostosis
OA: osteoarthritis
OPLL: ossification of the posterior longitudinal ligament
QOL: quality of life
SpA: spondylarthritis

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GP: Conceptualization, Investigation, Writing—review & editing. VG: Writing—review & editing. PSP: Conceptualization, Writing—review & editing, Validation, Supervision. All authors read and approved the submitted version.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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Not applicable.
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