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Topical Review

Thijs van Meulenbroek*, Ivan P.J. Huijnen, Laura E. Simons, Arnoud E.A. Conijn, Raoul H.H. Engelbert and Jeanine A. Verbunt

Exploring the underlying mechanism of pain-related disability in hypermobile adolescents with chronic musculoskeletal pain

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Abstract

Objectives: A significant proportion of adolescents with chronic musculoskeletal pain (CMP) experience difficulties in physical functioning, mood and social functioning, contributing to diminished quality of life. Generalized joint hypermobility (GJH) is a risk factor for developing CMP with a striking 35–48% of patients with CMP reporting GJH. In case GJH occurs with one or more musculoskeletal manifestations such as chronic pain, trauma, disturbed proprioception and joint instability, it is referred to as generalized hypermobility

spectrum disorder (G-HSD). Similar characteristics have been reported in children and adolescents with the hypermobile Ehlers-Danlos Syndrome (hEDS). In the management of CMP, a biopsychosocial approach is recommended as several studies have confirmed the impact of psychosocial factors in the development and maintenance of CMP. The fear-avoidance model (FAM) is a cognitive-behavioural framework that describes the role of pain-related fear as a determinant of CMP-related disability.

Content: Pubmed was used to identify existing relevant literature focussing on chronic musculoskeletal pain, generalized joint hypermobility, pain-related fear and disability. Relevant articles were cross-referenced to identify articles possibly missed during the primary screening. In this paper the current state of scientific evidence is presented for each individual component of the FAM in hypermobile adolescents with and without CMP. Based on this overview, the FAM is proposed explaining a possible underlying mechanism in the relations between GJH, pain-related fear and disability.

Summary and outlook: It is assumed that GJH seems to make you more vulnerable for injury and experiencing more frequent musculoskeletal pain. But in addition, a vulnerability for heightened pain-related fear is proposed as an underlying mechanism explaining the relationship between GJH and disability. Further scientific confirmation of this applied FAM is warranted to further unravel the underlying mechanism.

In explaining disability in individuals with G-HSD/hEDS, it is important to focus on both the physical components related to joint hypermobility, in tandem with the psychological components such as pain-related fear, catastrophizing thoughts and generalized anxiety.

Keywords: chronic musculoskeletal pain; fear-avoidance model; hypermobile Ehlers-Danlos syndrome; generalized hypermobility spectrum disorder; generalized joint hypermobility; pain-related disability.

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Introduction

In the Netherlands, 25% of schoolchildren and adolescents have chronic pain [1]. Internationally, prevalence rates for chronic musculoskeletal pain (CMP) in schoolchildren and adolescents vary between 4 and 40% [2]. CMP refers to pain lasting longer than 3 months and it is localized in muscular, ligamentous and bony structures [3]. In approximately 40% of adolescents with CMP, pain has a disabling impact on physical functioning, mood and social functioning, with concomitant reductions in quality of life [3, 4].

Generalized joint hypermobility (GJH) is a non-symptomatic condition characterized by increased range of motion in multiple joints. The prevalence of GJH in the general Dutch child population (10–16 years) is 25% (cut-off Beighton score \geq 4) [5], whereas 35% of Dutch adolescents (12–21 years) with disabling CMP have GJH (cut-off \geq 5) [6]. GJH associated with soft tissue injury, joint instability and CMP was referred to as joint hypermobility syndrome (JHS) [7]. However, a lack of clarity existed on the exact labelling of hypermobility and pain, as JHS showed overlap with the Hypermobility Type of Ehlers-Danlos syndrome (EDS-HT) [8]. Therefore, a recently consensus statement has been published with a unified set of criteria. JHS is now referred to as generalized hypermobility spectrum disorder (G-HSD) [9] and EDS-HT is now referred to as hypermobile EDS (hEDS) [10] (Figure 1). Both conditions have no specific genetic profile and in the present article it is referred to as G-HSD/hEDS. Although the increased prevalence of GJH in disabled adolescents with CMP is striking, the underlying mechanism explaining the relation between G-HSD/hEDS and pain-related disability is currently still unclear.

In adults, pain-related fear plays a disabling role in the development and maintenance of CMP [11]. The fear-avoidance model (FAM) is a biopsychosocial model (Figure 2), which explains this disabling role of pain-related fear [12]. It states that pain experience can be interpreted in two different ways, often in response to an injury; although, it can also begin spontaneously. First, pain can be experienced as non-threatening and pain is considered as part of a life experience. As a consequence, a person will confront and accept pain and perform activities as usual thus maintaining his/her habitual activity pattern. Secondly, pain can be interpreted as threatening based on catastrophic thoughts causing pain-related fear, which in turn leads to avoidance behaviour and hypervigilance. Long-term

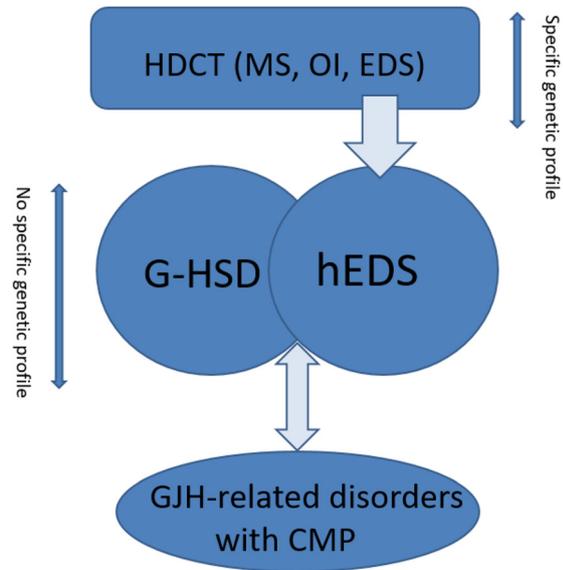


Figure 1: Different types of symptomatic GJH-related disorders. Abbreviations: HDCT, Hereditary Diseases of the Connective Tissue; MS, Marfan Syndrome; OI, Osteogenesis Imperfecta; EDS, Ehlers-Danlos syndrome; G-HSD, Generalized Hypermobility Spectrum Disorder; hEDS, hypermobile Ehlers-Danlos syndrome; GJH-related, Generalized Joint Hypermobility-related; CMP, chronic musculoskeletal pain.

avoidance may lead to disuse, depression and disability and these long term consequences may decrease the pain threshold at which ensuing pain will be experienced [11], thus causing a vicious circle [12]. Recently, this framework has been applied to paediatric chronic pain [13, 14] and extended to incorporate parents fear and behaviours [15]. Pain-related fear is also present in individuals with G-HSD/hEDS [16, 17]. It can be hypothesized that GJH and pain-related fear, two frequently encountered phenomena in adolescents with CMP, are important factors in the development and maintenance of CMP leading to disabling pain.

Aim

The aim of this topical review is to integrate knowledge from different research fields of expertise in CMP, hypermobility-related disorders and rehabilitation medicine. The current state of evidence on physical and psychological functioning in G-HSD/hEDS is summarized and presented using the individual components of the FAM as a framework. Based on this, a vulnerability for heightened pain-related fear and generalized anxiety among

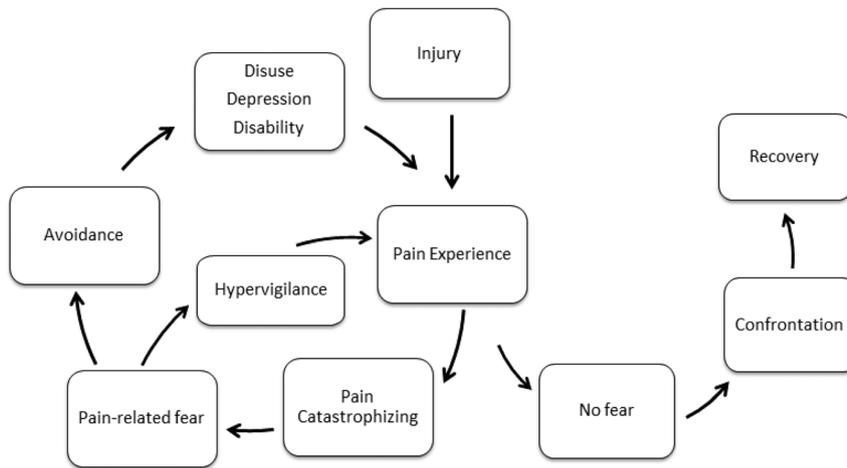


Figure 2: The fear-avoidance model according to Vlaeyen and Linton [12].

individuals with G-HSD/hEDS as a potential underlying mechanism explaining the relation between GJH and disability is discussed and a FAM applied to G-HSD/hEDS in adolescents is proposed.

Methods

Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>) was used to identify existing literature on the different topics “generalized joint hypermobility, hypermobile Ehlers-Danlos syndrome, generalized hypermobility spectrum disorder, joint hypermobility syndrome and chronic musculoskeletal pain, fatigue, proprioception, balance, muscle strength, disability, psychological functioning, depression, anxiety, pain-related fear, activity limitations, physical activity”. Relevant publications (original articles, case reports, editorial letters, reviews and meta-analyses) published in English were included if existing evidence were related to the individuals components of the FAM. In addition, references of the included articles were cross-referenced to identify more articles of interest. There were no restraints for the year of publication.

Evidence for the fear-avoidance model components related to G-HSD/hEDS

In the next paragraphs, the current scientific evidence for the different components of the FAM (Figure 2) to explain functioning among adolescents with G-HSD/hEDS will be discussed.

Injury

Individuals with G-HSD/hEDS have higher incidence of injuries, such as sprain, tendon injuries or dislocation,

compared to non-hypermobile pain-free peers [18–20]. In addition, micro-traumas (due to joint instability or connective tissue fragility) might occur as a result of repetitive injuries on joint surfaces, which may lead to adaptations and compensation of movement patterns, resulting in overload in other areas of the musculoskeletal system [21]. Recovery from injury seems more prolonged in individuals with G-HSD/hEDS compared to non-hypermobile pain-free peers. In a 5-year follow up study in ballet dancers G-HSD/hEDS was associated with a significant greater risk of a prolonged recovery period after injury compared to ballet dancers without G-HSD/hEDS [20]. Furthermore, individuals with asymptomatic GJH have an increased risk of knee injury during contact sports such as soccer or basketball [22]. In conclusion, individuals with asymptomatic GJH and G-HSD/hEDS as compared to others have an increased risk of injury. Furthermore, individuals with G-HSD/hEDS have delayed recovery after injury compared to non-hypermobile pain-free peers.

Pain experience

In G-HSD/hEDS joint pain is one of the most common complaints [23, 24] and recurrent musculoskeletal pain is an essential part of the classification of G-HSD/hEDS [9, 10]. The most commonly reported pain areas are the neck, shoulders, knees and ankles [25, 26]. Pain severity is one of two important potential determinants of disability [27]. Studies also showed that exercise-induced muscle pain is a distinctive symptom in individuals with G-HSD/hEDS, mostly in the knee and the shoulder [25, 28]. Recently, the presence of generalized hyperalgesia has been documented in individuals with G-HSD/hEDS compared to healthy controls [29, 30]. This could suggest that pain experience is a result of abnormal central processing of the

nociceptive input, possibly associated with descending modulatory system dysfunction and peripheral involvement such as a reduction in the pain threshold. As a result, pain could occur even in response to non-painful stimuli [31]. Two longitudinal cohort studies showed that during adolescence, GJH represents a risk factor for the development of musculoskeletal pain. Tobias et al. [32] found that GJH had a 2-fold increased risk factor of musculoskeletal pain in shoulder, knee, or ankle/foot. In addition, Sohrbeck-Nohr et al. [33] found that GJH had a 3 times higher risk of developing joint pain in adolescence. These findings are consistent with those in previous studies showing that GJH was a predictor of pain recurrence and pain persistence in adolescence [34, 35].

In summary, individuals with G-HSD/hEDS experience more frequent pain and generalized hyperalgesia might contribute to the heightened occurrence of pain. Furthermore, GJH represents a risk factor for the development of persistent musculoskeletal pain.

Pain catastrophizing

Pain catastrophizing is defined as an exaggerated negative interpretation of actual and anticipated pain experience [36, 37]. For example, individuals with high levels of catastrophizing are convinced that pain is threatening, which means that their body is vulnerable and needs careful protection to prevent further harm. In a recent cross-sectional study in adults with hEDS half of the patients reported high levels of pain catastrophizing (Pain Catastrophizing Scale [PCS] >30) [16]. In addition, a study of Rahman et al. [38] performed in adults with G-HSD showed high levels of pain catastrophizing (average PCS score of 27.9; scale 0–42). Thus, maladaptive cognitions about pain are present in adults with G-HSD/hEDS. No study in adolescents with G-HSD/hEDS are present in the literature yet.

Pain-related fear

Pain-related fear is defined as fear that emerges when stimuli that are related to pain are perceived as a main threat, such as fear of movement, fear of (re)injury or fear of pain [11]. In a general population of individuals with G-HSD/hEDS aged 15–61 years, pain-related fear is a common characteristic [16, 17]. In previous cross-sectional studies an overwhelming majority of individuals with G-HSD/hEDS met the cut-point for heightened fear of movement (75% [16] and 93% [17]; Tampa Scale for Kinesiophobia [TSK] score >37). It has also been shown that fear

of injury is a barrier to exercise in patients with G-HSD/hEDS [39]. This finding was confirmed by the results of a qualitative semi-structured interview study [40], in which women with G-HSD reported that fear of pain or re/injury reduced or altered particular activities. In a recent cross-sectional study 61% of adolescents with CMP had clinically elevated levels of pain-related fear, assessed with the Fear of Pain Questionnaire-Child report (FOPQ-C > 50) [6]. However, there were no significant differences on levels of pain-related fear between hypermobile and non-hypermobile adolescents with CMP [6]. Recent published data in adolescents with asymptomatic GJH showed that the negative impact of pain-related fear, measured as perceived harmfulness, was not more pronounced in asymptomatic GJH compared to non-hypermobile pain-free peers [41]. In summary, pain-related fear is a common symptom in G-HSD/hEDS, but was not higher in adolescents with asymptomatic GJH compared to non-hypermobile pain-free peers.

Hypervigilance

Hypervigilance is increased attention toward the source of the threat, such as pain/somatic sensations [11]. To the best of our knowledge, no studies have investigated the relationship between hypervigilance and G-HSD/hEDS in adolescents and adults. The pain vigilance and awareness questionnaire (PVAC) was developed as a broad measure of attention to pain and could be used in further research in adolescents with G-HSD/hEDS [37].

Avoidance behaviour

Avoidance behaviour refers to behaviour aimed at postponing or preventing a potentially aversive situation from occurring [42] and might be influenced by the beliefs and recommendations of health-care professionals [43]. In some situations avoidance behaviour could be a strategy for a specific medical condition influencing daily life functioning such as acute musculoskeletal pain. However, in children and adolescents with G-HSD/hEDS avoidance behaviour is maladaptive. For instance, children with G-HSD/hEDS report a tendency to avoid dynamic activities, such as sports or outdoor games requiring more joint stability. In addition, children with G-HSD/hEDS also reported a higher need to rest, which may reduce the possibility of being active in daily life activities and might be a result of avoidance behaviour [44]. Furthermore, as previously mentioned, activity-triggered pain is often seen in children

and adolescents with G-HSD/hEDS [25]. In addition, pain (87%), fatigue (78%) and fear of injury (50%) are common reported barriers to exercise in individuals with G-HSD/hEDS [39]. Adolescents and young adults with asymptomatic GJH tend to avoid dynamic activities (for instance sports) and prefer static activities (such as cycling and walking during leisure time), which require less balance and stress on ligamentous joints [45]. In summary, avoidance behaviour is reported in both children and adolescents with asymptomatic GJH and with G-HSD/hEDS.

Disuse

The term disuse can be described as performing at a reduced level of physical activity (PA) in daily life and according to the FAM is a result of avoiding movements and activities (avoidance behaviour) [46]. In individuals with G-HSD/hEDS several cross-sectional studies demonstrate reduced levels of PA when compared to pain-free controls [25, 44, 47]. Children and adolescents with G-HSD/hEDS report more withdrawal from physical education, sports or outdoor games and physical related activities in their social time [25, 44]. Furthermore, children and adolescents with G-HSD/hEDS report playing more non-sports (such as board games or electronic games) and report needing more time to rest [44]. In cross-sectional studies, no differences in total PA levels appeared to be present between asymptomatic GJH and non-hypermobile pain free controls (as assessed based on the Short Questionnaire to Assess Health assessing physical activity) [45] nor accelerometry [41]. However, adolescents with GJH tend to prefer walking and cycling over sports and outdoor activities when compared to non-hypermobile pain-free peers [45].

A long term consequence of physical inactivity is physical deconditioning [46], which can be expressed in decreased muscle strength and reduced cardiorespiratory fitness. Individuals with G-HSD/hEDS showed a decrease in lower and upper extremity muscle strength as compared to non-hypermobile pain free peers [47–49]. It is important to note that these results might be influenced by pain experienced during testing and psychological factors, such as pain catastrophizing and pain-related fear. Individuals might decide to stop or perform submaximally, resulting in a lower score [50]. Decreased muscle strength is also found to be associated with more activity limitations in adults with G-HSD/hEDS [49]. In addition, reduced cardiorespiratory fitness has been observed in children and adolescents with G-HSD/hEDS compared to non-hypermobile pain-free peers [51, 52]. It remains unclear if decreased muscle strength and reduced cardiorespiratory fitness in individuals with

G-HSD/hEDS may be long term consequences of avoidance behaviour due to CMP or an inherent characteristic of having a symptomatic GJH-related disorder. Some studies performed in children and adolescents with asymptomatic GJH indeed showed decreased muscle strength [45, 53] and lower levels of cardiorespiratory fitness [54] compared to non-hypermobile pain-free peers, while other studies could not confirm this [41, 55, 56].

In summary, disuse is shown in individuals with G-HSD/hEDS, which might be a result of avoidance behaviour. Disuse will eventually result in physical deconditioning characterized by decreased muscle strength and reduced cardiorespiratory fitness which significantly influence each other. It can be hypothesized that decreased muscle strength and reduced cardiorespiratory fitness in individuals with G-HSD/hEDS are a result of deconditioning after pain has started or submaximal performance due to pain interference during testing and psychological factors, such as pain catastrophizing and pain-related fear.

Depression

Depression refers to a condition that negatively affects mood, self-concept and self-esteem [57] and is more common in adults with G-HSD/hEDS compared to non-hypermobile pain free peers [58, 59]. However, a cross-sectional study in young adults with and without asymptomatic GJH using multiple linear regression models showed no significant association between GJH and depression as measured with the HADS depression subscale [54].

In conclusion, depression among adults with G-HSD/hEDS is common compared to non-hypermobile pain free individuals. However, there is a notable lack of evidence in childhood populations with G-HSD/hEDS regarding depression [58].

Disability and quality of life

Disability is an umbrella term that encompasses not only physical impairments, but also activity and participation limitations across home and school [11, 60]. Within the FAM, disability is conceptualized as a long-term consequence of prolonged avoidance behaviour. In studies of adolescents and adults with G-HSD/hEDS both pain and fatigue are associated with disability [27, 60]. Furthermore, a study reported that children and adolescents with G-HSD/hEDS have general difficulties at school and specifically handwriting problems [25]. When compared to

non-hypermobile adolescents with CMP, no differences in the level of disability emerged [6]. A possible explanation for this finding might be that in both cohorts of CMP patients, persistent avoidance behaviour, regardless of the triggering mechanism, resulted in deterioration of daily functioning. A recent longitudinal study in children with G-HSD/hEDS showed that multi-systemic dysfunction was found to be the most important construct for functional impairment measured in terms of performance and capacity. Furthermore, an increase of pain, fatigue and loss of postural control were related to disability over time [61].

Regarding Health-Related Quality of life (HRQoL), cross-sectional studies in individuals with G-HSD/hEDS found lower levels of HRQoL compared to non-hypermobile pain free peers [26, 62–65]. In addition, a longitudinal study showed that severely affected children with G-HSD/hEDS in terms of functional impairment had consistently lower HRQoL over the course of 3 years [61]. In addition, poorer emotional functioning levels measured with the Pediatric Quality of Life Inventory were observed in children with G-HSD/hEDS compared to pain-free peers [66]. Lower levels of HRQoL in children with G-HSD/hEDS were associated with pain [63, 65, 66], fatigue [64–66] and stress incontinence symptoms [66].

In conclusion, disability and reduced quality of life are common in children and adults with G-HSD/hEDS. Pain, fatigue, reduced postural control and multi-systemic disorders may potentially be important determinants of disability in individuals with G-HSD/hEDS.

Discussion

Many studies support the increased injury rate in adolescents with asymptomatic GJH and G-HSD and also pain experience in these adolescents is common. The

psychological involvement of pain catastrophizing and pain-related fear is also known. As these factors might lead to avoidance behaviour, this is proposed to result in disuse, depression, disability and reduced quality of life. Eventually, deconditioning may occur, further fueling the vicious circle in adolescents with G-HSD/hEDS. Based on the evidence presented for the different components of the FAM it can be hypothesized that pain-related fear and GJH are important factors in the development and maintenance of CMP eventually leading to disabling pain in adolescents with G-HSD/hEDS. According to this hypothesis, we would like to propose a FAM applied to adolescents with G-HSD/hEDS (Figure 3).

Earlier studies showed that individuals with asymptomatic GJH and G-HSD/hEDS both have an increased risk of injuries [18–20, 22] and repetitive trauma, due to compromised structural integrity of connective tissue, might lead to (re)injury [21]. In addition, individuals with G-HSD/hEDS experience more frequent pain [23, 24] and GJH represents a risk factor for developing musculoskeletal pain during adolescence [32, 33]. *Therefore, it is hypothesized that being hypermobile makes you more vulnerable for developing CMP due to an increased risk of (re)injury and experiencing more frequent pain.*

In addition it is proposed that individuals with G-HSD/hEDS have a vulnerability for heightened pain-related fear, which is confirmed in several studies [16, 17, 39]. Literature also showed that more generalized anxiety is present in individuals with G-HSD/hEDS [67, 68]. Furthermore, an increased incidence of other psychiatric disorders, including panic disorders [58, 69] and anxiety disorders [67, 68, 70] were found to be associated with G-HSD/hEDS. It could even be hypothesized that the relationship between anxiety disorders and G-HSD/hEDS might also have a dysautonomic component, since several dysautonomia symptoms related to anxiety such as hyperventilation, nausea and light-

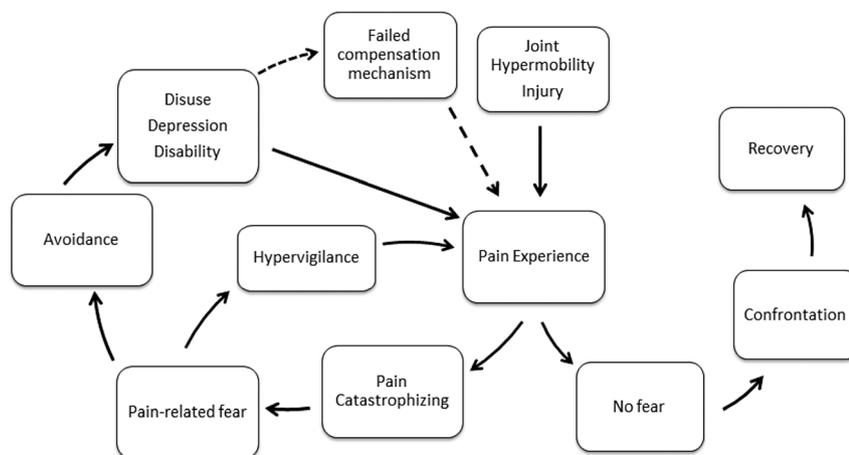


Figure 3: The fear-avoidance model applied to adolescents with G-HSD/hEDS.

headedness were significantly more common in patients with G-HSD/hEDS [71]. In addition, in adults with G-HSD/hEDS anxiety sensitivity is strongly associated with fearful appraisals of pain [72]. Furthermore, a recent study in 9-year old children with asymptomatic GJH showed that high symptoms of GJH were associated with higher scores in anxiety symptoms [73]. *In conclusion, heightened pain-related fear and more generalized anxiety is common in individuals with G-HSD/hEDS. This might represent a general vulnerability for the cascade of cognitive/affective responses in the FAM.*

It is now proposed that this vulnerability for heightened pain-related fear and anxiety causes avoidance behaviour. This avoidance behaviour seems to be a coping strategy to avoid (re)injury and to prevent musculoskeletal complaints. As a result, avoidance behaviour may lead to disability, depression and disuse and eventually to physical deconditioning, further fueling the vicious circle of CMP. It is hypothesized that physical deconditioning has additional negative consequences in individuals with G-HSD/hEDS. Their compensation mechanism, essential for joint stability to compensate for joint laxity, might fail. As a result of the failed compensation mechanism proprioception [48, 74–76] and balance [44, 77] can be impaired, which negatively influences body posture. An affected body posture, proprioceptive impairment and decreased balance may lead to an increased risk for injury and affect gait patterns [77, 78]. This FAM applied to G-HSD/hEDS, describing a vulnerability for heightened pain-related fear and anxiety, might explain the higher prevalence of GJH in adolescents with functionally disabling CMP compared to the general population.

Currently there is some support in the literature for components of this hypothesized model, but are cross-sectional in nature, with only few evaluating more than one aspect of the FAM. We proposed that, both joint hypermobility and pain-related fear are important factors in the development and maintenance of CMP leading to disabling pain in adolescents with G-HSD/hEDS. Therefore, in explaining disability, it is important to focus on both the physical components related to joint hypermobility, in tandem with the psychological components such as pain-related fear, catastrophizing thoughts and generalized anxiety in individuals with G-HSD/hEDS.

Future studies should further focus on identifying the underlying mechanism that causes functional impairment in adolescents with G-HSD/hEDS. A recent study already showed that children with G-HSD/hEDS who are severely affected have a high incidence of multi-systemic

complaints, in addition to high pain levels, fatigue and poor postural control [61]. Furthermore, there is a growing evidence of autonomic nervous system dysfunction in G-HSD/hEDS, including symptoms such as hypotension, orthostatic intolerance, presyncope, palpitations, postural orthostatic tachycardia, gastrointestinal dysfunction, and disturbed bladder function [71, 79–82]. Autonomic dysfunction contributes to disability and decreased quality of life in G-HSD/hEDS [79, 81]. In addition, increased autonomic dysfunctions were related to higher pain severity [82, 83] and autonomic dysfunction may result in increased interoceptive sensitivity [84]. Higher pain severity in combination with increased interoceptive sensitivity may have additional emotional consequences such as anxiety and fear, which also may contribute to higher disability levels. Furthermore, recent studies showed the potential role of neurodiversity, such as Attention-deficit/hyperactivity disorder (ADHD) and Autism Spectrum Disorders (ASD) in G-HSD/hEDS [85, 86]. The potential connection between these psychiatric disorders and G-HSD/hEDS can be useful in clinical practice since it allows to better identify patients with ASD or ADHD who may be vulnerable for disabling pain. However, the causality between these disorders and G-HSD/hEDS remains questionable, due to the design of the studies. Despite the highly variable clinical presentation of G-HSD/hEDS the diagnosis is frequently overlooked and misdiagnosed [87]. Therefore, in clinical practice and future studies these factors are important factors to take into account.

Furthermore, it is suggested to perform studies that evaluate the specific impact of hypermobility on catastrophizing, pain-related fear, hypervigilance and avoidance behaviour, to further unravel the vulnerability for heightened pain-related fear and generalized anxiety. In addition, an experimental study may contribute to unravel the influence of both physiological (deconditioning) and psychological factors (pain-related fear) on physical performance in adolescents with G-HSD/hEDS. Verbunt et al. [88] used an interpolated twitch technique during muscle testing. This technique alongside with surface EMG may distinguish the influence of both physiological and psychological factors during performance testing to confirm whether deconditioning or submaximal performance will influence physical test outcomes. Furthermore, it is important to examine associations over time, regarding physical and psychological functioning, in children with GJH before the onset of CMP to unravel the influence of GJH, physical and psychological functioning in children who will or will not develop CMP.

Conclusion

This topical review integrates knowledge from different research fields of expertise in CMP, hypermobility related disorders and rehabilitation medicine by presenting a FAM applied to adolescents with G-HSD/hEDS. It is proposed that both GJH and pain-related fear are important factors in the development and maintenance of CMP leading to disabling pain in adolescents with G-HSD/hEDS. Although scientific confirmation of this FAM applied to G-HSD/hEDS seems warranted, many studies are cross-sectional and therefore the suggested mechanism should be interpreted with caution. Longitudinal studies are necessary to further unravel the mechanism of disabling G-HSD/hEDS.

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