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REVIEW

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Chronic Pain and Joint Hypermobility: A Brief Diagnostic Review for Clinicians and the Potential Application of Infrared Thermography in Screening Hypermobile Inflamed Joints

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Joint hypermobility syndromes, particularly chronic pain associated with this condition, including Hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorders (HSD), present diagnostic challenges due to their multifactorial origins and remain poorly understood from biomechanical and genomic-molecular perspectives. Recent diagnostic guidelines have differentiated hEDS, HSD, and benign joint hypermobility, providing a more objective diagnostic framework. However, incorrect diagnoses and underdiagnoses persist, leading to prolonged journeys for affected individuals. Musculoskeletal manifestations, chronic pain, dysautonomia, and gastrointestinal symptoms illustrate the multifactorial impact of these conditions, affecting both the physical and emotional well-being of affected individuals. Infrared thermography (IRT) emerges as a promising tool for joint assessment, especially in detecting inflammatory processes. Thermal distribution patterns offer valuable insights into joint dysfunctions, although the direct correlation between pain and inflammation remains challenging. The prevalence of neuropathies among hypermobile individuals accentuates the discordance between pain perception and thermographic findings, further complicating diagnosis and management. Despite its potential, the clinical integration of IRT faces challenges, with conflicting evidence hindering its adoption. However, studies demonstrate objective temperature disparities between healthy and diseased joints, especially under dynamic thermography, suggesting its potential utility in clinical practice. Future research focused on refining diagnostic criteria and elucidating the underlying mechanisms of hypermobility syndromes will be essential to improve diagnostic accuracy and enhance patient care in this complex and multidimensional context.

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Abbreviations: JH, Joint Hypermobility; GJH, Generalized Joint Hypermobility; JHS, Joint Hypermobility Syndrome; HCTD, Hereditary Connective Tissue Disorders; hEDS, Hypermobility Type of Ehlers-Danlos Syndrome; HSD, Hypermobility Spectrum Disorders; gHSD, Generalized Hypermobility Spectrum Disorders; pHSD, Peripheral Hypermobility Spectrum Disorders; lHSD, Localized Hypermobility Spectrum Disorders; hHSD, Historical Hypermobility Spectrum Disorders; BS, Beighton Score; 5PQ, The five-part questionnaire for identifying hypermobility; CS, Central Sensitization; CNS, Central Nervous System; IRT, Infrared Thermography; TI, Thermographic Index; HDI, Heat Distribution Index; ROI, Region of Interest; CRP, C-Reactive Protein; VAS, Visual Analog Scale; MRI, Magnetic Resonance Imaging; SDright, Standard Deviation Right; SDleft, Standard Deviation Left

Keywords: joint hypermobility, chronic pain, musculoskeletal pain, Ehlers-Danlos syndrome, fibromyalgia, missed diagnosis, thermography

INTRODUCTION

Hippocrates was the first to describe joints with excessive mobility in a tribe located south of Russia. However, the term "hypermobility" was first used only in the 19th century to explain marfanoid joint characteristics [1,2]. Joint Hypermobility (JH) is a term given to joints whose range of motion exceeds what is considered normal for that joint, taking into account the individual's age, sex, and ethnicity [3], commonly referred to as "loose joints," "double-jointed," or even used synonymously with "loose ligaments" [4]. It is a relatively common condition and can confer greater flexibility abilities to the joints of healthy individuals, acrobats, gymnasts, and dancers, and should not be considered a pathological condition or disease in these cases [5-7]. Some studies conducted with school-age children suggested a prevalence of JH in the general population ranging from 30% to 50% [8,9], reaching up to 64.6% in the age group accumulated up to 15 years old and declining over time, possibly affecting about 20% of the adult population [10-12].

GENERAL OVERVIEW OF JOINT HYPERMOBILITY

When JH involves multiple joints (ideally involving limbs and axial skeleton), it is characterized as Generalized Joint Hypermobility (GJH) [4] – a state that can be symptomatic or asymptomatic. The presence of symptoms such as pain and instability, among others, characterizes Joint Hypermobility Syndrome (JHS) [13]. Joint stability primarily depends on ligaments, muscles, tendons, joint capsule, and surrounding soft tissues, and hypermobility can result from the failure of one or more of these structures [14], which can cause stretching, tension, muscle spasm, tendinitis, and/or pain. JH can lead to biomechanical modifications caused by compensatory adjustments in other regions of the body, increasing musculoskeletal overload. An example of this is the presence of flexible flat feet, which can lead to pronation and valgus of the heel, potentially resulting in gait impairment, lower limb joint issues, and dorsalgia [4,15-17].

CURRENT OVERVIEW

It is now recognized that individuals diagnosed with JHS may also present with a spectrum of additional conditions, encompassing joint instability (such as subluxations/dislocations), temporomandibular joint disorders, localized and diffuse chronic pain (including periarticular pain, chronic pelvic pain, and headaches), ecchymoses, fatigue, dysautonomia (manifesting as hypotension and postural dizziness), mood psychiatric disorders (anxiety and depression), as well as genitourinary and gastrointestinal manifestations (such as menstrual irregularities, endometriosis, pelvic and vulvar varices, abdominal distension, loose stools, or constipation) [12,18-25]. With this wide variation in both type and severity of symptoms and the significant syndromic overlap observed over time, it has been noted that differentiating between JHS and other Hereditary Connective Tissue Disorders (HCTDs) would become a significant challenge, especially when compared to the Hypermobility Type of Ehlers-Danlos Syndrome (hEDS). An international group of experts even suggested that JHS and hEDS should be recognized as two synonymous disorders, corroborating this substantial clinical similarity [19,26]. However, in 2017, with the aim of resolving the conflict of definitions, Castori et al. [18] consensually began employing the term Hypermobility Spectrum Disorders (HSDs), making it possible to differentiate individuals with JH from those with JHS and carriers of hEDS, allowing for the creation of broader criteria for EDS [27,28]. Thus, if an individual meets the criteria for JH, but does not meet the criteria for an hEDS diagnosis, for example, the patient is diagnosed as having Generalized HSD (gHSD) – one of the four forms of HSD: generalized (gHSD), peripheral (pHSD), localized (lHSD), and historical (hHSD). In other words, it is now clear that it is possible to have JH (which can be asymptomatic as in a ballet dancer or gymnast), without necessarily having HSD and even, according to the most recent scientific knowledge, without being a carrier of hEDS [4,18].

CURRENT DIAGNOSIS

Thus far, the diagnosis of JH, HSD, and hEDS is primarily clinical and supported by a set of scientifically based criteria from questionnaires and physical examinations, accepted alongside the exclusion of pertinent overlapping conditions related to other HCTDs [29,30]. Assessment of GJH is directly conducted using the Beighton Score (BS), a 9-point assessment [31]. A positive BS is any score equal to or greater than 5/9 points in adults, 6/9 points in children (pre-puberty), and 4/9 points in adults over 50 years old [12,32]. However, it is possible for an individual to exhibit hypermobility in other joints besides those covered by the BS, such as hypermobility in the temporomandibular joint, for instance. In these cases, classification for GJH is also applicable. In 2003, aiming to minimize the risk of false negatives in the diagnosis of GJH, Hakim and Grahame [33] developed "The five-part questionnaire for identifying hypermobility" (5PQ). This instrument was devised using the BS as a reference and consists of 5 items, each worth 1 point. Positive responses to 2 or more questions on the questionnaire suggest GJH. Should the BS result in a score 1 point below the cutoff and the 5PQ remain positive, the diagnosis of GJH can

Table 1. Two Main Diagnostic Criteria for Generalized Joint Hypermobility

BS (Beighton Score)	9-point assessment	A positive BS is any score equal to or greater than 5/9 points in adults, 6/9 points in children (pre-puberty), and 4/9 points in adults over 50 years old
5PQ (Five-part questionnaire for identifying hypermobility)	5-point assessment	Positive responses to 2 or more questions on the 5PQ suggest Generalized Joint Hypermobility

still be made [34] (Table 1). The sensitivity and specificity for the 5PQ and the BS were, respectively, 71–84% and 77–89% [33-35]. In a systematic literature review involving individuals with and without joint hypermobility, the BS was found to be a highly reliable clinical tool, demonstrating substantial to excellent consistency both inter-rater and intra-rater, even among assessors from different backgrounds and with varying levels of experience. Despite significant variation in the individual components of risk of bias across studies, most items were rated from adequate to very good [36]. The 5PQ, although showing some discrepancies in results across different nationalities and populations studied in validations for other languages, was found to be a valid and reliable instrument for screening or identifying GJH [37-39].

CHRONIC PAIN IN JOINT HYPERMOBILITY

Notably, occasional and recurrent musculoskeletal pain is a common symptom among individuals with GJH, HSD, and hEDS given their natural history – likely as a consequence of long-term predisposition to recurring microtraumas [18]. It is believed that generalized hyperalgesia in individuals with GJH can be traced through three phases, following a comprehensive logic [40]. The first decade of symptom onset (first phase) would be characterized by acute and localized pain resulting from persistent microtraumas of joints and soft tissues, primarily of nociceptive etiology [3]; that is, pain resulting from the activation of nociceptors (pain receptors, present in nerve endings), due to actual or potential tissue damage [41]. In the second – perhaps even the third – decade of symptom evolution (second phase), Central Sensitization (CS) processes due to acute and/or prolonged peripheral painful stimuli [40] would promote a picture of diffuse musculoskeletal pain with eventual involvement of myofascial structures [4]. CS is a generic term encompassing various central mechanisms worsening pain, originating from neuronal signaling amplification in the Central Nervous System (CNS) leading to hyperalgesia [41]. Here, it is important to highlight the neuropathic bases of pain maintenance [3] by injury or disease of the somatosensory nervous system [41]. By the third or fourth decade of its natural evolution associated with various symptoms (third phase), it is observed that the condition of chronic pain, already well established, can lead to mental and cognitive impairment, with more defined states of catastrophizing and fear of pain [40,42]. This is characterized by nociplastic pain, ie, the painful condition originating from altered nociception, even though there is no clear evidence of actual or threatened tissue damage causing activation of peripheral nociceptors or evidence of disease or injury of the somatosensory system causing pain [41]. In this latter phase, there is considerable overlap of diverse signs and symptoms, and often, many individuals with HSD, in the absence of an explanation for the variety of symptoms, are diagnosed as having fibromyalgia and/or some psychiatric disorder, often missing out on care and guidance tailored to the needs of individuals with JHS, as well as those with HSD and hEDS [43,44].

HYPERMOBILITY AND INFLAMMATION

The specific underlying causes and mechanisms responsible for the reported chronic musculoskeletal pain in patients with HSD still require further extensive investigation [45]. Current theories emphasize biomechanical overload and chronic soft tissue injuries due to joint laxity and instability [27], which are responsible for soft tissue injuries manifesting as localized arthralgias (nociceptive pain) and, in some cases, over time, non-localized musculoskeletal pain (central sensitization) [46]. However, Rodgers et al. (2017) [47], in a study involving 379 individuals with hEDS, identified a higher prevalence of concomitant inflammatory rheumatologic conditions than in the general population. Considering the similarity of biomechanical and molecular triggers for both conditions, it is still not possible to rule out potential correlations between HSD and hEDS with inflammatory rheumatologic mechanisms. This is important to consider given that the implementation of analgesic therapy can differ significantly, for example, when considering nociceptive (inflammatory-based) and neuropathic pain, requiring accurate diagnosis to increase the chances of therapeutic success [48]. Given this peculiarity, a model capable of identifying inflammatory signatures in the joints of individuals with HSD and hEDS could enhance the therapeutic strategy to be implemented.

INFRARED THERMOGRAPHY AND INFLAMMATION

IRT, known since the 1970s in rheumatology for its potential capacity to evaluate inflamed joints [49-53], quantifies the infrared radiation from the surface of a body through sensors called bolometers, expressing it in terms of temperature and creating a digital image based on a color scale called a thermogram [54]. Since Horvath & Hollander (1949) measured intra-articular temperature in patients with rheumatoid arthritis and observed that it could be used as a guide for the intensity of inflammation [55], the search for methodologies to evaluate and quantify inflammation in the joints has progressed over time. In recent decades, IRT has been viewed by researchers and enthusiasts as an efficient method for studying diseases in which skin temperature may reflect the presence of inflammation in underlying tissues, quantifying the information in real-time and distinguishing temperature differences smaller than 0.07ºC in less than 0.03 seconds [56-61].

There are classically two models for the thermological assessment of joint inflammatory processes: the Thermographic Index (TI) developed by Collins & Ring and published in 1974 [62] in a study conducted on arthritic knees, and the Heat Distribution Index (HDI) developed by Salisbury et al. in 1983 [63]. The TI is a multi-isothermal analysis method obtained by subtracting the average temperature value of the region of interest (ROI) from a constant 26ºC, with prior acclimatization of the patients in a room at 20ºC. Studies published by Ring (1975) [64] and Collins (1976) [65] revealed that the group of affected joints in patients with rheumatoid arthritis showed a higher TI, with an average of 3.96. The HDI, on the other hand, reflects the relative distribution of temperature frequencies and is defined as the mean relative frequency ± standard deviation over a joint, showing an approximately linear relationship between the HDI and clinical assessment [63]. In fact, research has demonstrated greater sensitivity and higher correlation of the HDI with clinical findings aggravating the affected joint than the TI [66,67]. However, according to an extensive literature review published by Ammer (2012) [68], the absolute values for the HDI of normal and inflamed knees were not reported by the author. Conversely, Spalding et al. (2008) [69] proposed that 2 standard deviations of the ROI be equal to the HDI, noting that thermograms of the joints were obtained laterally and, as with the TI, also previously acclimatized in an environment at 20ºC.

Subsequent studies obtained relevant findings, reinforcing the potential of IRT to identify inflamed joints and to monitor therapeutic outcomes in patients with inflammatory rheumatological diseases. In 1985, a publication by Devereaux et al. [70] showed the results of a 12-month follow-up of seropositive rheumatoid arthritis patients with significant clinical correlation of multiple joints. The researchers identified a high correlation between HDI, Ritchie Articular Index, Mallya Score, grip strength, morning stiffness, ESR (Erythrocyte Sedimentation Rate), CRP (C-Reactive Protein), and pain via Visual Analog Scale (VAS) ($p < 0.001$). It is important to note that these researchers and subsequent studies have shown that HDI is reproducible, sensitive, quantifiable, and not subject to patient's circadian thermoregulatory variation or interobserver error [70,71]. Another study demonstrated the correlation between decrease in TI and inhibition of leukocyte migration, providing potential molecular and cellular bases for these findings [72].

CASE SERIES AND THERMOGRAPHIC ANALYSIS OF A REGION OF INTEREST

The following report illustrates cases of three patients with the syndromic presentation of joint hypermobility who sought outpatient care for the management of pain due to refractory chronic musculoskeletal pain. All participants, whose clinical-epidemiological data and thermal images are presented here, signed a formal document authorizing their use in medical-scientific studies, provided that the confidentiality of their identities is maintained. As this report is expressly authorized by all participants, the authors of this report waived the review by an ethics committee, given that the ethical principles established by the Helsinki Declaration were adhered to.

Participant (a): 47 years old, female, sedentary with overweight, additionally complained of symptoms compatible with menopause, especially hot flashes. Reported occasional polyarthralgia in childhood, with doctors telling her she had "loose joints," and stood out for her ability to make extreme joint movements, similar to a contortionist (as highlighted by the participant). At 15 years old, she began to experience persistent musculoskeletal and polyarticular pain. During her consultation, she mentioned spending her entire life without a definitive diagnosis to explain the persistent pain, having been evaluated by multiple medical specialties. Emphasized that she made countless visits throughout her life to various rheumatologists, who "ruled out" inflammatory rheumatic diseases. Also sought help from neurologists, orthopedists, endocrinologists, and general practitioners. Underwent various exams and physical and drug treatments, which she could not recall in detail, but without any improvement in painful symptoms. She said musculoskeletal pain worsened with physical exertion, especially in the hips, without identifying conditions for improvement. On the contrary, she experienced significant worsening of pain with mechanical efforts, which were even recommended by healthcare professionals (physio-

therapists, physical educators, and doctors) with the aim of "strengthening her muscles." The patient emphasized that she could not perform the exercises for "muscle strengthening" because she felt "as if she were tearing" her limbs – in her own words. However, both physical educators and physiotherapists insisted on exercises for "strengthening," telling her that "the presence of pain was normal" – as reported in her own words.

Participant (b): 25 years old, female, sedentary with overweight, complained of persistent musculoskeletal pain for about 5 years. In childhood, she stood out for her greater joint flexibility. She reported that the onset of symptoms was characterized as a sensation of wearing a boot on the left lower limb that lasted about 3 months. Initially sought attention from an orthopedist who requested electromyography of the affected lower limb, with a normal result, according to the volunteer's report. Developed lumbosacral pain and cervicalgia, seeking the attention of a rheumatologist who requested magnetic resonance imaging (MRI) of the lumbar and cervical spines, which did not show abnormalities to justify the condition. She said she sought other professionals during the first year of symptoms when she was advised to seek attention from a neurologist under suspicion of multiple sclerosis. Reported having an MRI of the skull and biochemical tests, including cerebrospinal fluid, for investigation of this condition, which were normal. The following year, she sought an orthopedist specializing in pain medicine, who requested a pelvic MRI that was normal, referring her to physiotherapeutic care. During this period, she began to experience paresthesias in other parts of the body and occasional sensations as if experiencing sudden drops in her blood pressure with palpitations, malaise, weakness, and transient sweating. There was worsening of pain in the lumbar spine and hips. She emphasized that she had always noticed that her hands and feet were always very cold since she was younger, a fact that bothered her a lot. The following year, she sought the attention of a new rheumatologist who diagnosed her with Fibromyalgia Syndrome, initiating drug therapy. The following year, she sought the attention of another rheumatologist who diagnosed "polyneuropathy." However, she said this new specialist did not sufficiently clarify its etiology, initiating drug therapy with non-steroidal anti-inflammatory drugs, anticonvulsants, and muscle relaxants. However, she did not experience relief from the painful condition. She described that in recent years, she had been experiencing headache crises with migrainous characteristics, which worsened over the years. She was also advised several times to start regular physical activity for "strengthening," but she complained of severe low back pain. She said her sister also had marked joint flexibility and also began to complain of musculoskeletal pain.

Participant (c): 42 years old, female, sedentary, overweight, complained of pelvic pain since the age of 12, which over the years, was added to the picture of perineal pain, and more recently, proctalgia. Additionally, she began to experience diffuse polyarthralgia and chronic musculoskeletal pain 14 years ago. Described multiple visits to orthopedists and rheumatologists with countless radiological exams, mostly within normal limits. At the age of 20, she underwent buccomaxillary surgery for restoration of the right temporomandibular joint. During a new investigation of chronic pelvic pain, 3 years ago, performed by a gynecologist, a diagnosis of endometriosis with presence of endometriomas in the pelvic compartment and uterine myomatosis was made – the latter was successfully treated through embolization. During the process of investigating chronic musculoskeletal pain, she was diagnosed with hypothyroidism due to Hashimoto's thyroiditis. After medication, she reported some relief from muscle pain and fatigue, but still with significant symptoms. Over the past 5 years, she underwent various screenings for inflammatory rheumatic diseases, all negative. Reported persistent gastrointestinal disorders over the years, with constipation and minor anorectal bleeding – investigated with colonoscopy, detecting perianal fissures and no inflammatory or neoplastic disease. Due to persistent anal pain, she also received a diagnosis of chronic proctalgia. More recently, pelvic pain and low back pain stood out in her most relevant complaints, leading her to seek specialized pain management services.

All three participants responded to two questionnaires for screening for joint hypermobility: the BS [31] and the 5PQ proposed by Hakim and Grahame [33]. They underwent a detailed clinical examination and Total Body Infrared Thermography during routine procedures at the pain management outpatient clinic. At the time of the thermographic examination, none of the patients exhibited joint abnormalities suggesting an active inflammatory mechanism, such as edema, hyperemia, or localized hyperthermia or joint stiffness, except for the presence of pain as indicated on the pain map. In the illustration below (Figure 1), there are full-body thermographic images of the front and back, with the respective pain maps filled in by the three participants who were diagnosed with JH. In these representative maps of their bodies, the participants drew the areas where they feel persistent pain, and next to them, the respective scores/results obtained from the questionnaire responses.

All examinations were conducted in a controlled environment using a FLIR T430sc infrared sensor (FLIR® Inc., Sweden), with a thermal resolution of 320x240 pixels, focal length of 0mm, thermal sensitivity of 30mK, and exposure time of 1/59 s. All images were thermally enhanced using the UltraMax™ tool provided by FLIR TOOLS+ software (FLIR®, FLIR Tools+, version 5.13.180312002, FLIR® Inc.), generating a thermal

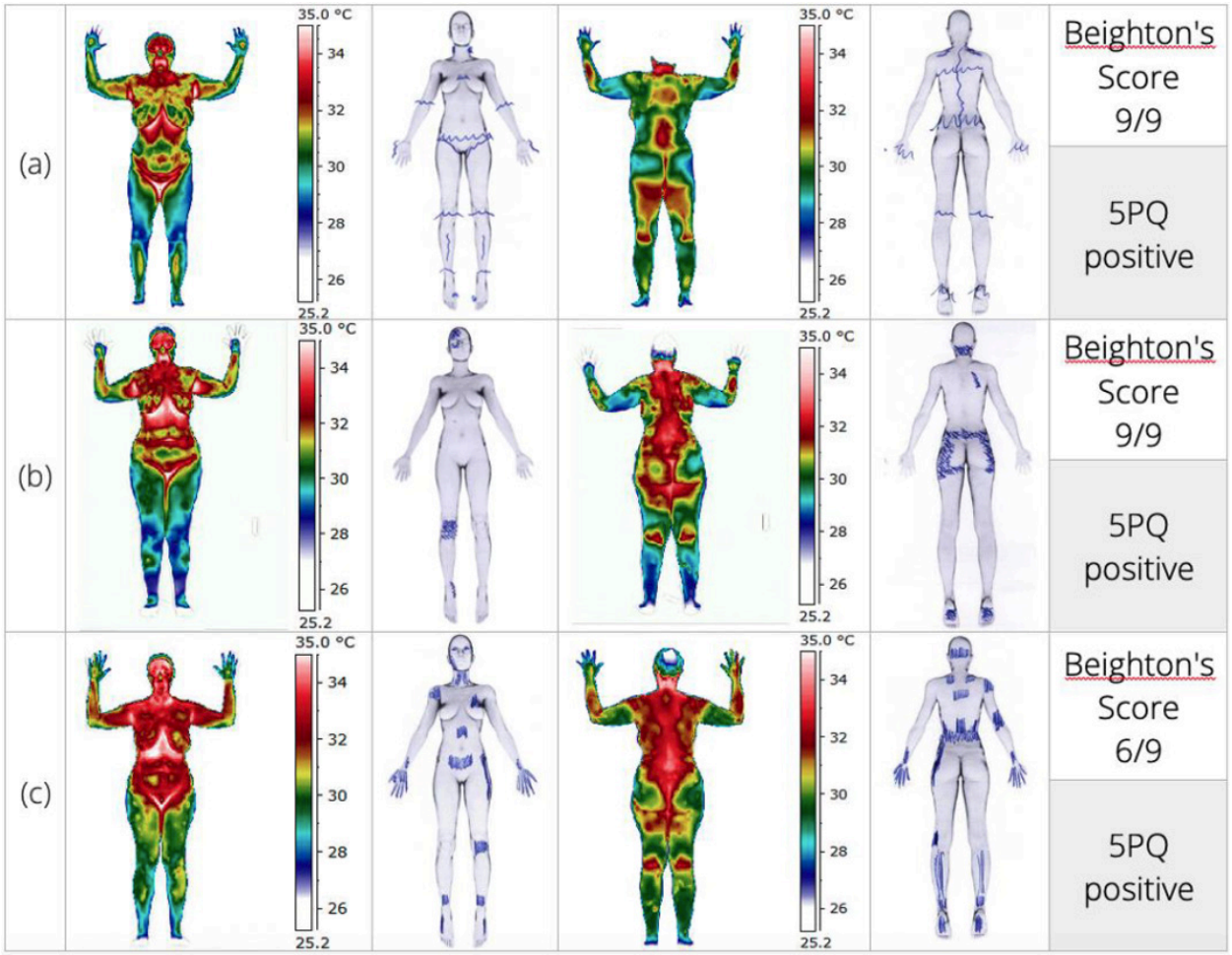

Figure 1. **Infrared images front and back** with respective pain maps and values obtained from the Beighton Score and The Five-Part Questionnaire for Identifying Hypermobility.

resolution of 640 x 480 pixels. Each patient remained completely undressed, covered only by a very thin and breathable gown that was not sufficient to retain heat for a period of 15 minutes for the purpose of thermal equilibrium with the environment – an internationally standardized procedure [73-76]. All thermograms were obtained in a temperature-controlled environment at 23.0±1.0ºC [76] – a well-documented measure of thermal comfort in Brazil [77,78], as it is not cold enough to cause shivering or muscle spasms and is well-suited to the population – as recommended by researchers in the field of medical thermography in this country. There was minimal air convection (0.2 m/s), and a thermo-hygrometer ensured monitoring of ambient temperature and relative humidity below 60% [74]. The images obtained were subsequently analyzed using FLIR TOOLS+ software.

For illustrative purposes, segments were extracted from the infrared images obtained at knee height, with an identically sized ROI determined in each, providing matrices with 999 temperature measurements (Figure 2). In this manner, the aim is to present a model for the collection of multiple simultaneous measurements of skin surface temperature and its potential statistical use for the study of hypermobile joints. There was no intention to provide a detailed thermological description of the clinical findings from these images.

Additionally, for comparison purposes, we have included in this case series a 16-year-old participant without pain or any other symptoms in the knees (Figure 3d). The descriptive statistics of her ROIs can be seen in Table 2.

Using FLIR TOOLS+ software, thermal matrices were extracted from each ROI so that the set of temperature measurements could be statistically analyzed. Next to each thermogram is a graph comparing the temperature distribution of the thermal matrix contained in each ROI (right and left) as well as the respective standard deviations of such distributions in each ROI (Figure 3). Graphs, data manipulation, descriptive and analytical statistics were obtained using statistical and data visualization packages employing the Python programming language [79].

Table 2 presents the descriptive statistics of the data-

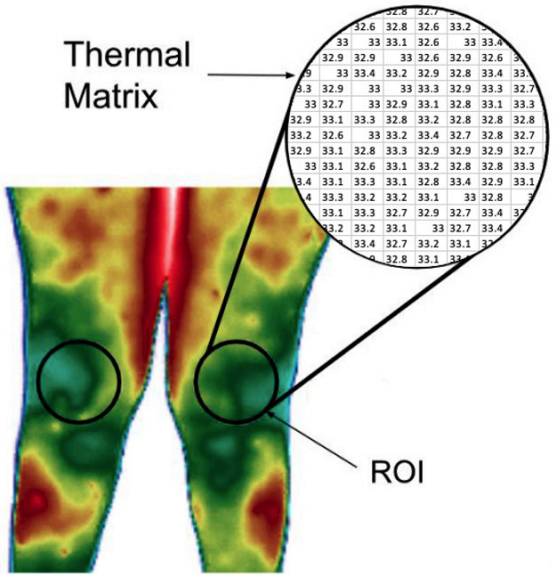

Figure 2. **Representation of the region of interest (ROI)** and how the thermal matrix is obtained. It is not intended for thermographic interpretation and, therefore, does not contain more specific data.

sets obtained from the respective ROIs on the right and left knees, complementary to the graph presented in Figure 3, displaying the thermal distribution behavior of the areas extracted from the respective thermograms.

DISCUSSION

The hypermobile syndromes, whether hEDs or HSD, constitute a group of complex conditions with multifactorial origins that remain poorly understood from both biomechanical and genomic-molecular perspectives [45]. These conditions have undergone several conceptual, semiological, and diagnostic revisions over the past decades. However, it was only in 2017 that hEDS, HSD, and benign hypermobility itself were objectively distinguished, creating a diagnostic logic for each condition based on the most current evidence [80].

Nonetheless, despite efforts to create a model that sheds light on diagnosis and, consequently, the implementation of more precise therapies and guidance, several variables related to joint hypermobility still remain underdiagnosed or inadequately diagnosed [43]. Halverson et al. used the term "diagnostic odyssey" to refer to the extensive journey that hEDS patients must undergo before receiving a definitive diagnosis, with approximately 10 misdiagnoses (on average) along the way. Indeed, previous studies have shown that hEDS patients take an average of 5 years to be correctly diagnosed [43,81]. In a survey conducted by Donohue et al. (2018), for example, it was observed that hEDS patients are frequently misdiagnosed as having fibromyalgia. This is likely due to the similarity of signs and symptoms between this disease and those manifested in hEDS and HSD, both in terms of musculoskeletal pain and the inherent dysautonomic states [82]. This underscores the complexity of the syndromic entanglement that can make the definitive diagnosis of conditions related to joint hypermobility a significant challenge.

Both HSD and hEDS affect their carriers in a multidimensional and varied manner, encompassing physical (biological) and psychological (emotional) aspects [83]. Notably, musculoskeletal conditions, especially those related to joint instability phenomena (sprains, dislocations, and subluxations, for example), and chronic pain stand out among the others, causing significant losses to affected individuals [83,84]. However, headache, dizziness, persistent fatigue, and gastrointestinal symptoms, along with mental disorders such as anxiety, depression, persistent feelings of distress, and catastrophizing, are also commonly present in the daily lives of these patients [84].

History and clinical examination remain fundamental for the diagnosis of syndromic conditions related to hypermobility and cannot be underestimated. Additionally, questionnaires contribute to standardizing the diagnosis of hypermobile joints, a key point for the diagnostic hypothesis [85]. Their aim is to objectively identify JH, determine the extent of the disease, and help exclude other connective tissue diseases characterized by JH [82]. This is particularly important considering a possible connection between syndromes related to JH and some rheumatologic diseases, as noted by Rodgers et al. (2017) in cases of hEDS [47].

With the popularization and increased accessibility of infrared imaging devices, it is possible that the use of this technology could become an ally in joint assessment

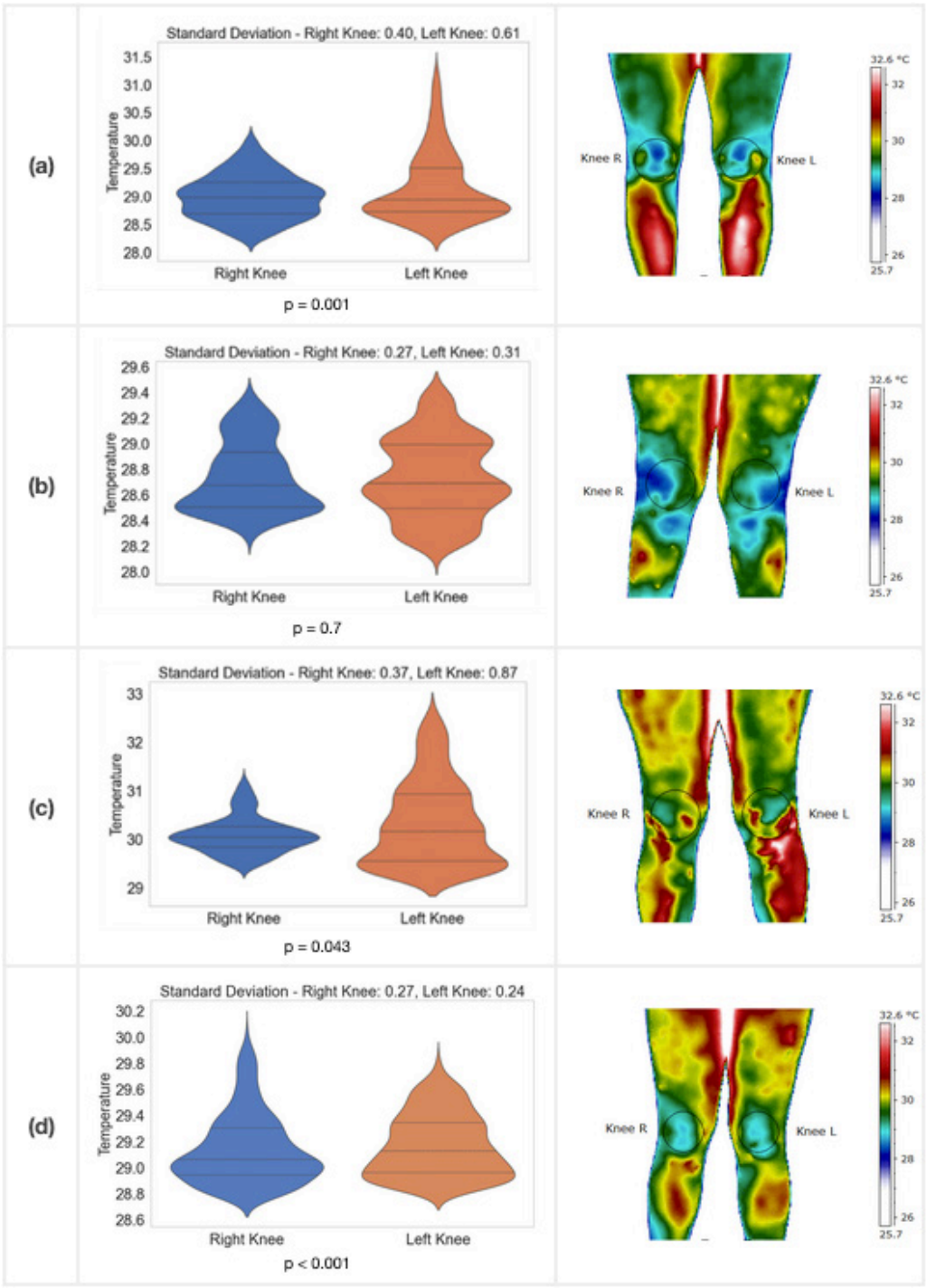

Figure 3. **Comparative graphs of heat distribution** in the respective ROIs obtained from the thermal matrices of each knee (right and left) and thermal images showing the topographies of the data sources of each participant (**a**, **b**, **c**, and **d**). Legend: knee R = right knee; knee L = left knee.

Table 2. Descriptive Statistics of the Temperature Sets Contained in the Respective Thermal Matrices of the ROIs

	(a) p = 0.001		**(b)** p = 0.7		**(c)** p = 0.043		**(d)** p < 0.001	
	knee R	**knee L**	**knee R**	**knee L**	**knee R**	**knee L**	**knee R**	**knee L**
MEAN	29.00	29.16	28.74	28.73	30.08	30.33	29.14	29.17
SD	0.39	0.61	0.27	0.31	0.37	0.87	0.27	0.24
MIN	28.21	28.34	28.27	28.13	29.39	29.27	28.76	28.80
MAX	30.06	31.27	29.37	29.40	31.27	32.59	30.06	29.84
ΔT(max-min)	1.85	2.93	1.1	1.27	1.88	3.32	1.3	1.04

MEAN = mean of the temperature sets of the ROIs; SD = standard deviation; MIN = minimum temperature of the dataset; MAX = maximum temperature of the dataset; ΔT(max-min) = difference between the maximum and minimum temperatures of each dataset; knee R = right knee; knee L = left knee.

of individuals with syndromes related to hypermobile joints, especially regarding joint inflammatory processes. Heat, redness, swelling, and pain are cardinal clinical features of joint inflammation [86]. However, clinicians face a challenge in unequivocally diagnosing inflamed joints when there is inflammatory arthralgia in a characteristically subclinical presentation [87]. The inflammatory response is typically attributed to elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) [88], individually or synergistically involved in many other pathological processes [89,90]. Dysfunctions in microvascular homeostasis are primary components in these processes [91,92] and may be crucial for assessing subclinical inflammatory signs. IRT would be a tool for addressing these abnormalities by early and indirectly detecting microvascular dysfunctions before typical clinical inflammatory manifestations occur [93,94].

In light of the case series presented here, some authors [63,95,96] have described, for example, that the thermal distribution of normal knee surfaces corresponds to a central hypo-radiant zone (relative to the patellar contour) with a progressive increase in infrared radiation towards its periphery – but this is not a universal rule. According to Marziani et al. (2023) [97], the normal anterior knee has been previously described by other authors [51,98] as exhibiting symmetry in the image of both knees, with an oval isothermal area showing a lower temperature corresponding to the patella – possibly due to the fact that the skin in this region is cooler over tendons and bones than over muscles [93]. The temperature of the skin over the knee may indicate the presence of an inflammatory process within the joint. This process is marked by heightened vascularity of the synovial membrane and can be readily observed in regions where there is no underlying bone [97]. Inflammation-generated heat distorts the thermal gradient, and the normal thermal pattern is lost [63].

Comparing the Pain Maps, infrared images, and comparative thermal distribution graphs, it is possible to observe that there may not always be a direct relationship between the presence of pain and potentially inflammatory mechanisms observable through IRT. In Figure 3, the participant (a) reports pain in both knees. The regions of interest (ROI), centered on the patella, suggest apparent points of asymmetry in infrared radiation on the Rainbow Hi Contrast (rainbowHC) color scale, with greater asymmetry on the left compared to the contralateral knee. However, according to Ammer's study (2012) [68], based on 566 thermal images from healthy individuals, the average temperature of the normal (asymptomatic) anterior knee was 29.5 ± 1.6°C (95% CI: 28.5 to 30.5°C). Thus, the ROIs of participant (a) in this example appear thermometrically normal. However, upon evaluating the temperature distribution (Figure 3), we can observe an asymmetry regarding the extreme temperatures between the right and left sides, with the presence of more extreme temperatures on the left (Table 2).

Additionally, the thermal matrix distribution graph is more leptokurtic on the right in relation to the contralateral knee, following a non-parametric distribution (Shapiro-Wilk: $p<0.001$) with a statistically significant difference more relevant on the left (SDright = 0.4; SDleft = 0.61; Mann-Whitney: p = 0.001). Salisbury et al. (1983) [63], following series of individuals with "arthritic" knees under anti-inflammatory therapy, observed a gradual transition from an irregular thermal gradient with marked thermal outliers in inflamed joints to a leptokurtic distribution, ie, increasingly narrow and symmetrical, typically observed in "normal" knees. It is worth noting that in their study, thermograms were collected from knees laterally under acclimatization at 20ºC. In this case, although both knees present a loss of the so-called normal thermal grid, the left side appears to be more affected from a thermological point of view than the right. On the other hand, participant (b) indicates the right knee as painful, with both joints showing an apparent loss of the gradual transition of the thermal gradient – suggestive of dysfunction in thermological studies – with no statistically relevant thermal differences between them (SDright = 0.27; SDleft =

0.31; Shapiro-Wilk: p<0.001; Mann-Whitney: p = 0.7), with both graphs showing a wide (graphical) distribution of temperatures in an approximately symmetrical manner visually. However, even though visual symmetry is present, the left knee has a greater variation in temperatures compared to the contralateral knee. Participant (c) reports the left knee as painful again, with both knees showing a presumed loss of the normal thermal gradient. However, in this case, a more leptokurtic distribution is observed on the right, along with a statistically significant increase in thermal distribution to the left (SDright = 0.37; SDleft = 0.87; Shapiro-Wilk: p<0.001; Mann-Whitney: p = 0.043). The participant who does not present any symptoms in the knees (d), included here as a supposedly healthy control without joint hypermobility, showed a statistically significant difference between the temperature sets – higher on the right (SDright = 0.27; SDleft = 0.24; Shapiro-Wilk: p<0.001; Mann-Whitney: p<0.001) – and presented a more leptokurtic curve on the left. All these results may reinforce the potential influence of musculoskeletal pain mechanisms of neuropathic origin previously reported and common to individuals with joint hypermobility, which may be the source of pain without a necessary thermographic correspondence, as well as the subclinical inflammatory processes that can compromise the clinical assessment of joints, even those that are asymptomatic. Indeed, Fernandez et al. (2022) [99] in a retrospective study with 79 volunteers with hEDS and HSD (71% with hEDS) reported dysfunction of small fibers in 70% of those evaluated, as well as a structural deficit based on intraepidermal nerve fiber density in 78% of cases. Small fiber neuropathies consist of dysfunction of A-delta and C fibers that transmit thermal, nociceptive, and autonomic information and have already been suggested in previous cases in individuals with hEDS/HSD [100-102]. Consequently, frequent burning sensations, hypoesthesia, and allodynia [103] are commonly reported by individuals with these conditions.

It is worth noting that, although there is considerable evidence in favor of the use of IRT in the analysis of arthritic joints [104-108], its use in clinical practice still does not seem to be well established, especially due to the persistence of some discrepancies among the various findings and respective conclusions [109,110]. However, several studies have verified objective temperature differences between diseased and healthy joints, especially when performed under ROI cooling (dynamic/functional thermography), creating greater enhancement between areas of higher and lower infrared radiation [111,112].

CONCLUSION

Conditions associated with hypermobile joints, whether the hEDS or HSD, are multifactorial entities and are often confused with other diseases present in various other conditions. Not infrequently, this leads affected individuals to a long search for a diagnosis that justifies such heterogeneous signs and symptoms and often not even being included in the differential diagnosis for painful musculoskeletal syndromes. The development of diagnostic criteria segments these diseases more clearly and contributes both to therapeutic and scientific efforts. IRT, although lacking consensus for its use in clinical practice, can be an ally in identifying inflamed or dysfunctional joints. However, even though showing evidence that is capable of identifying dysfunctional joint patterns, further studies are needed to correlate a dysfunctional or arthritic joint with painful symptoms. Once this goal is achieved IRT may enable professionals involved in the care of these individuals to develop therapeutic strategies that take into account the neuropathic and nociceptive components of chronic musculoskeletal pain and, perhaps, achieve better therapeutic outcomes.

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