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Infrared Thermography in The Diagnosis of Myofascial Trigger Points: A Comprehensive Review of Emerging Techniques and Challenges

Miyofasiyal Tetik Noktaların Teşhisinde İnfrared Termografi: Yeni Geliştirilen Tekniklerin ve Zorlukların Kapsamlı Derlemesi

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Abstract

Myofascial pain syndrome (MPS) poses diagnostic challenges due to the absence of a universally accepted gold standard. Myofascial trigger points (MTrPs), characterized by palpable nodules within taut muscle bands, contribute to widespread chronic musculoskeletal pain. This article reviews alternative diagnostic methods, focusing on the potential role of infrared thermography (IRT) in identifying MTrPs. Traditional manual palpation, although widely used, faces reliability concerns. IRT, offering non-invasive real-time insights into microcirculation dynamics, presents a promising adjunct for MTrPs assessment. However, studies comparing thermography with manual identification reveal conflicting results, emphasizing the need for further investigation. Additionally, the review discusses the integration of thermography with pressure algometry, ultrasound, needle electromyography and biomarker assessment for a comprehensive understanding of MPS. Patient characteristics, such as age, gender, and body mass index, influence thermographic readings, necessitating cautious interpretation. Despite challenges, thermography demonstrates utility in short-term evaluation and treatment monitoring. Standardizing protocols and embracing an evidence-based, integrated diagnostic approach may enhance the accuracy of MTrPs identification in MPS, fostering collaborative efforts and ongoing research for improved patient outcomes.

Key Words: Myofascial trigger points, myofascial pain syndrome, musculoskeletal pain, thermography

Özet

Miyofasiyal ağrı sendromu (MAS), evrensel olarak kabul edilmiş bir altın standardın bulunmaması nedeniyle tanısal zorluklar teşkil etmektedir. Gergin kas bantları içinde palpe edilebilen nodüllerle karakterize miyofasiyal tetik noktalar (MTN) yaygın muskuloskeletal ağrıya katkıda bulunmaktadır. Bu makale, infrared termografinin (IRT) MTN belirlenmesindeki potansiyel rolüne odaklanarak alternatif tanı yöntemlerini incelemektedir. Yaygın olarak kullanılmasına rağmen geleneksel manuel palpasyonun güvenirlik sorunları bulunmaktadır. Mikrosirkülasyon dinamikleri hakkında non-invaziv gerçek zamanlı bilgiler sunan IRT, MTN değerlendirmesi için umut verici bir yardımcıdır. Bununla birlikte, termografi ile manuel tanımlamayı karşılaştıran çalışmaların çelişkili sonuçlar ortaya koyması, daha fazla araştırmaya duyulan ihtiyacı vurgulamaktadır. MAS'ın kapsamlı bir şekilde anlaşılması için derleme ayrıca termografinin; basınç algometrisi, ultrason, iğne elektromiyografisi ve biyobelirteç değerlendirmesi ile entegrasyonunu tartışmaktadır. Yaş, cinsiyet ve vücut kitle indeksi gibi hasta özellikleri termografik okumaları etkileyerek dikkatli bir yorumlama gerektirmektedir. Zorluklara rağmen termografi, kısa-dönem değerlendirme ve tedavi izleminde fayda sağlamaktadır. Protokollerin standartlaştırılması ve kanıta dayalı, entegre bir tanı yaklaşımının benimsenmesi, MAS'ta MTN tanımlanmasının doğruluğunu artırabilir böylece hasta sonuçlarının iyileştirilmesi için iş birliğine dayalı çabaları ve devam eden araştırmaları teşvik edebilir.

Anahtar Kelimeler: Miyofasiyal tetik noktalar, miyofasiyal ağrı sendromu, muskuloskeletal ağrı, termografi

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1. Introduction

Myofascial pain syndrome (MPS) is a chronic musculoskeletal pain condition (Srbely et al., 2016), affecting 85% of individuals at some point with a 15% prevalence in general medical clinics (Duarte et al., 2021). Though the mechanism of MPS is not well understood, it is marked by myofascial trigger points (MTrPs) - hard, palpable nodules within taut muscle bands that cause pain when palpated (Srbely, 2010). MTrPs often occur in the neck, shoulder, and pelvic muscles, such as the trapezius, scalene, and quadratus lumborum (Diep et al., 2021). While manual palpation is the primary diagnostic approach, studies suggest it lacks reliability (Elbarbary et al., 2022), prompting research into alternative methods like thermography, pressure algometry, ultrasonography, electromyography (EMG), and biomarkers. Infrared thermography (IRT) records body surface heat and is promising as a diagnostic tool for MTrPs, especially in masticatory muscles (Haddad et al., 2012). Ultrasound (US), although less commonly used, offers detailed imaging of soft tissues and may assist in diagnosis of MTrPs (Srbely et al., 2016). Combining palpation and biomarker assessment could enhance MPS diagnosis, but further research is needed on inflammation in MPS to utilize biomarkers effectively (Grosman-Rimon et al., 2016). Studies confirm the reliability of algometry in assessing pressure pain threshold for trigger points in neck pain patients (Oliveira et al., 2021). This review examines thermography's effectiveness in MTrPs detection and evaluates various diagnostic tools to enhance diagnosis of MTrPs.

2. Pathogenesis

MPS is likely a pain phenomenon, results from the activation of latent MTrPs triggered by certain predisposing factors as chronic repetitive minor muscle strain, poor posture, systemic illnesses, or neuro-musculoskeletal lesions (Hong & Simons, 1998; Hong, 2004). These triggering lesions are usually away from latent MTrPs sites (Chen et al., 2000; Kawakita et al., 2008). MTrPs have different biomedical and electrical characteristics that can explain pain sensed at their sites. Exploration of MTrP with needle EMG shows spontaneous electrical activity generated by trigger points (Simons et al., 1997) that will disappear together with pain after local phentolamine infusion suggesting adrenergic dependency (Rivner, 2001; Hubbard & Berkoff, 1993). Recent studies have clarified nature of MTrPs (Kumbhare et al., 2020; Shah et al., 2005). Multiple hyperirritable MTrPs regions are found with sensory and motor components. The sensory components of the MTrPs regions are due to sensitized nociceptors responsible for mediating pain, referred pain, and local twitch responses. The concentrations of pain mediators as bradykinin, lactic acid, calcitonin gene-related peptide, substance P, TNF-α, IL-1β, serotonin, and norepinephrine are high in the MTrPs region. The motor components are dysfunctional endplates focal muscle contraction (mini cramps) responsible for taut band formation resulting from excessive acetylcholine leakage. It has been hypothesized that excessive acetylcholine release, sarcomere shortening, and release of the above-mentioned substances are three essential features that relate and interact with one another in a positive feedback cycle creating a vicious circle. It has been

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shown that referred pain is mediated via a spinal cord mechanism and that the elicited referred pain is due to unmasking of formerly ineffective synaptic connections among neurons corresponding to different receptive fields (Hong & Simons, 1998; Mense et al., 2001; Wytrążek et al., 2015).

3. The Role of Thermography in Trigger Points

IRT might be a valuable tool to early diagnose neuromusculoskeletal problems linked to changes in tissue temperature and monitor their dynamics. It has been demonstrated that there is a strong association between temperature variations and pressure pain threshold in MPS, therefore a high IRT reliability for muscle assessment (Skorupska et al., 2015). Infrared pictures can be assessed qualitatively, meaning a qualified examiner will judge based on visual analysis and numerically, whereby particular software is used to assess body skin areas of interest (Dibai-Filho et al., 2015).

IRT is a touchless imaging method working by mapping surface isotherms of a selected area or an entire object, owing to the detection and registration of infrared emissions (Hildebrandt et al., 2012). In contrast to other imaging techniques, IRT is completely passive and non-hazardous technique (Cojocaru et al., 2015). Human skin is a black-body radiator with an emissivity factor of 0.97–0.99 (Cojocaru et al., 2015), thus is a perfect emitter of infrared radiation at room temperature. The skin microcirculatory flow determines amount of infrared irradiation emitted from the human surface, therefore skin temperature. There is a complex relationship between skin, metabolism of internal tissues, especially skeletal muscles, and functions of local vessels. Postganglionic neurons of the sympathetic nervous system innervate the target organs, together with blood vessels, sweat glands by passing with the peripheral nerves or sympathetic plexuses around blood vessels regulating blood flow in skin microcirculation. For this reason, symphatetic nervous system is the most important regulator of human body temperature. (Steketee et al., 1973). The skin is a tightly controlled “heat radiator” system, and over 60% of total lost heat of the naked human occurs as infrared radiation through the skin (Merla & Romani, 2006). Temperature of different body areas is attributed to anatomical variation between body segments in the amount of subcutaneous tissue and its ratio with the overlying skin, as well as innervation and blood supply.

There are two types of thermography used in medicine: static thermography and active dynamic thermography. Static thermography is a qualitative method for visual analysis of a single image mainly based on the confirmation of some asymmetric temperature changes reflected on skin of the pathological region. Thermal asymmetries greater than 0.5–0.7°C are usually associated with a dysfunction of the musculoskeletal system (Vardasca et al., 2012) as it occurs in case of MTrPs. Based on asymmetric thermal patterns, MTrPs and their referral areas can be localized as shown in Figure1. Trigger points can be activated by a variety of neuromusculoskeletal conditions, including arthrosis, enthesopathy, bursitis, spinal disc lesion, and strains. Regarding the identification and monitoring of the trigger sites' thermal patterns, IRT demonstrates encouraging findings and can be a valuable adjunct instrument. However, some authors consider that localizing a hot spot in the skin is not satisfactory to identify MTrPs and this may be attributed to multiple limitation associated with IRT imaging as will be discussed below.

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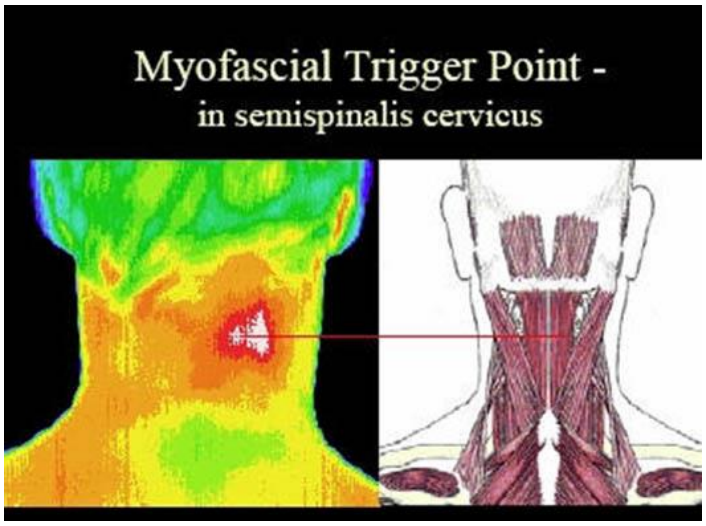

Figure 1.*Trigger points appear as a red hot spot in skin over affected muscles (Adapted from dv-2.com)*

Active dynamic thermography is a modern quantitative diagnostic method using external thermal stimuli, exercise, or pressure excitation to provoke a transient, amplified autonomic nervous system response. It provides a more visible image contrast allowing a more precise analysis of pathological skin microcirculation (Vardasca et al., 2012). Active dynamic thermography protocols are highly recommended to support the diagnosis of breast tumor, Raynaud's disease, burn wounds, or pain states (Gulyaev et al., 1995). In pain medicine, the active dynamic thermography utility has been indicated for neural diseases, musculoskeletal diseases, inflammatory diseases, and vascular diseases. High IRT reliability has also been confirmed for muscle examination (Hakgüder et al., 2003; Ismail & Merla, 2017; James et al., 2014).

4. Limitations

In the context of medicine, thermal imaging has its limits that may decrease its sensitivity as a diagnostic test and increase the fallacies. There are many conditions for the technical and interpretative correctness of thermal imaging studies (environmental, individual, and technical). The most important are the research room's conditions, the patient preparation and pre-examination acclimatization period, the adjustment equipment, and size and position of the regions of interest (ROI). These standard conditions have been developed by thermographic associations such as the American Academy of Thermology, the European Thermological Society, and the Polish Society of Thermographic Diagnostics in Medicine including the following: (a) The acclimatization duration for IRT studies ranged from 5 to 20 minutes; (b) The temperature of the surroundings controlled between 18 and 25°C; (c) It should take patients 8-16 minutes to acclimatize (Sancibrian et al., 2019). Particularly when sympathetic nervous system activity is present; (d) An infrared thermography camera can objectively help the diagnosis of pain sufferers.

5. The Role of Manual Identification in Trigger Point Diagnosis

MPS is a common musculoskeletal disorder that can afflict all types of populations, particularly athletes and old-age. For efficient MPS treatment, it is crucial to precisely identify and deactivate the

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trigger points (Mayoral del Moral et al., 2018). There are no studies investigating the sensitivity and/or specificity of manual palpation for detecting MTrPs. Despite this, manual palpation is the most used clinical method to detect MTrPs. A physical examination can confirm MTRP's diagnosis, which is made using a palpation procedure that includes manual palpation and the patient's responses to specific questions about painful symptoms. Proper palpation technique gives essential information such as bone location, tissue temperature, and texture. Specific palpation techniques are frequently employed to elicit pain by applying pressure to afflicted anatomical regions. These techniques are essential for clinical decision-making and manual therapy treatments. currently, there is no gold standard that enables health care providers to accurately diagnose MTrPs (Xiaoqiang et al., 2014). However, it has been found that the most applied criteria in the research included: (a) Tender point within a taut band of a skeletal muscle; (b) The patient's pain recognition; (c) A predictable pain referral pattern (Figure 2); (d) Local twitch responses (Barbero et al., 2012). These criteria were defined initially (Tough et al., 2007) but as the research has evolved it has proven that it is problematic, it has become clear that their application is problematic, with fewer criteria now considered diagnostically meaningful. Implementing modern technology to measure trigger point characteristics and to establish standardized diagnostic criteria, as given in Table 1, shows promising potential (Travell & Simons, 1992).

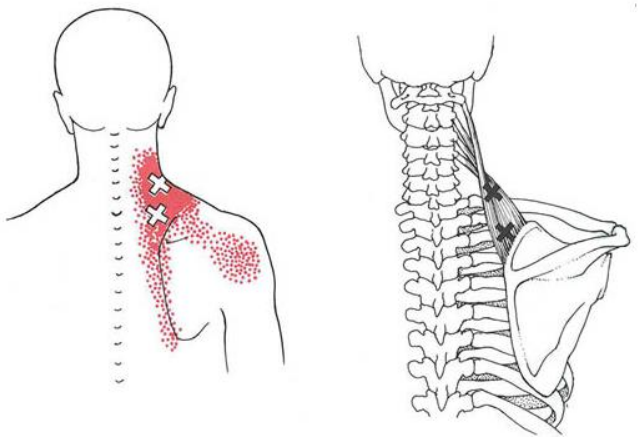

Figure 2. *Typical referral pain pattern (the spillover pain pattern is illustrated by stippled red) referred from trigger points (Xs) regions in the right levator scapulae muscle (Adapted from Simons et al; 1999)*

6. Comparing Thermography with Manual Identification in Trigger Point Diagnosis

The manual examination is considered as the current standard for diagnosing trigger points and determining their location (Myburgh et al., 2008). However, this method presents a challenge, as it requires a skilled examiner (Mazza et al., 2021). The detection of the trigger points by palpation is considered unreliable, but there are no other tests that can take its place (Lucas et al., 2009). Multiple

elements may have caused this unreliability, especially the disagreement between clinicians about the diagnostic criteria. It has been found challenging to perform when MTrPs are deeply located within tissue, or minor (Kumbhare et al., 2016). Accordingly, future research should concentrate on more reliable methods to accurately diagnose MTrPs (Magalhães et al., 2015).

To the best of our knowledge, there is no study directly comparing the manual examination and

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thermography, except for one study published by Swerdlow and Dieter (1992), which included 365 participants divided into two groups based on the presence or absence of MTrPs. In that study, three different protocols of thermography were applied to determine the locations of hot spots, which were assumed to be the same as trigger points' sites previously identified through physical examination. The result of thermography showed a very low specificity and sensitivity. Only half of the participants with trigger points show hot spots, and over 60% of those without trigger points had hot spots. Most of these hot spots did not correlate with the sites of the trigger points (Lucas et al., 2009). Despite these limitations and considering the advantages of thermography and the disadvantages of manual examination, it is possible to recommend the use of thermography as an additional test for diagnosing trigger points (Swerdlow & Dieter, 1992).

Table 1. Proposed Diagnostic Criteria for Identifying Myofascial Trigger Points (Adapted from Simons et al; 1999)

Criterion	Description
Essential Clinical Criteria	**1. Palpable spot** within a taut band of accessible skeletal muscle. **2. Spot tenderness** on pressure or palpation. **3. The patient pain recognition:** Pressure on tender nodule induces pain that patient recognizes as an experienced pain pattern (if positive, indicates active tender point)**.** **4. Painful limitation** to full passive range of motion for affected muscle.
Confirmatory findings	**1. Local twitch responses:** Manual or visual identification of local twitch response (snipping palpation of a trigger point elicits brisk contraction of the taut band) **2.** Imaging of a local twitch response induced by needle penetration of tender nodule. **3. Predictable referral pattern:** Pain or altered sensation (in the distribution expected from trigger point in that muscle) on compression of the tender nodule. **4. Needle Electromyography (EMG):** EMG demonstration of spontaneous electrical activity characteristic of active loci (low voltage noise activity in tender nodule of the taut band) **5. Ultrasonography:** Regions of interest as blobs, local binary patterns **6. Infrared thermography:** Asymmetrical thermal patterns that appears as hot spots on the skin over the site of trigger points. **7. Biomarkers:** Elevated inflammatory and pain mediators

7. Comparing Thermography with Other Diagnostic Techniques for Trigger Points

Thermography and Algometry / Needle EMG

Algometry: Pressure algometry is commonly used to examine both localized or diffuse musculoskeletal pain, such as MPS, (Barbosa et al., 2020) which represents a convenient and budget-friendly method for diagnosis (Linde et al., 2018). It relies on measuring pain pressure threshold, the lowest amount of

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force that causes pain during MTrPs evaluation and is used to numerically assess the sensitivity of MTrPs. Pain pressure threshold is assessed using an algometer by applying pressure to the affected area until the patient reported a shift in sensation from pressure to pain. Therefore, the relationship between rate of application and pain pressure threshold is very crucial. Linde et al. (2018) have found a robust, linear correlation during algometer application on the infraspinatus muscle. It has been shown that algometry is more efficient in detecting trigger points than manual palpation. On the other hand, it can generally detect MTrPs, but it cannot distinguish between active and latent ones (Pöntinen, 1998). Algometry can be used to evaluate the therapeutic efficacy of several MTrPs modalities (Wytrążek et al., 2015). Through evaluation of MTrPs, a positive and significant correlation has been found between thermography and algometry. Thus, algometry can be considered a consistent tool for detecting MTrPs (Hong, 1998).

Needle EMG: EMG is a technique for evaluating and recording the electrical activity produced by skeletal muscles (Delaney & McKee, 1993; Robertson et al., 2013). It is performed using an electromyograph to produce a record of electrical potential and activity generated by muscle cells either spontaneously generated or elicited by electrical or neuronal stimulation. EMG results can reveal nerve dysfunction, muscle dysfunction or problems with nerve-to-muscle signal transmission. Needle EMG is a method of EMG in which a needle is inserted directly into a muscle to records the electrical activity spontaneously generated in that muscle. Needle EMG detects the presence of spontaneous low voltage motor endplate noise activity, as well as the high voltage spike activity that is highly characteristic, but not pathognomonic, of MTrPs (Simons et al., 1997; Paoletti et al., 2020) (Figure 3).

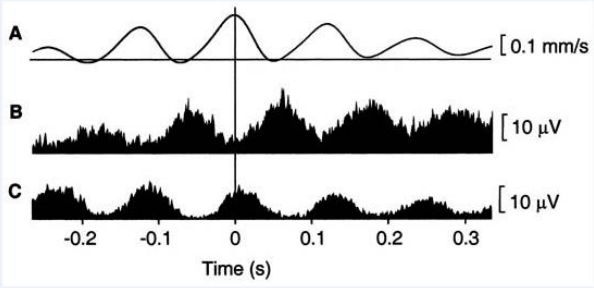

Figure 3. *Electromyography of myofascial trigger points showing spontaneous low voltage noise activity (Adapted from Proceedings of the National Academy of Sciences)*

Thermography and US

Diagnostic US has been suggested as a method to enhance the reliability of MTrPs detection. Diagnostic ultrasonography uses waveform frequencies ranging from 1 to 30 mHz, reflecting off tissues to varying degrees forming high-resolution images. US is used intensively in musculoskeletal imaging as a safe, non-ionizing, and portable tool (Liang et al., 2021). An additional advantage of US is the interactive and

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dynamic process of picture capturing. This allows the clinician to gain insights into various anatomical areas (Hubbard & Berkoff, 1993). Several studies have established the utility of diagnostic US imaging in differentiating between active and latent MTrPs and have found that the most employed diagnostic US methods were conventional B-mode sonography and vibration Sono elastography (Myburgh et al., 2008). Using diagnostic US, it has been observed that MTrPs look like nodules ranging from 0.05 to 0.5 cm^2 in size and showing different levels of hypo-echogenicity. Elbarbary et al. (2022) found that diagnostic US is valuable in ruling out the existence of MTrPs due to high positive predictive value and specificity. Currently, the most widely accepted treatment technique for MPS is the deactivation of active trigger points and the easing of taut bands (Shankar & Cummings, 2013). Therefore, correct localization of MTrPs is the first step in effective treatment. Diagnostic US can increase diagnostic accuracy by preventing mistakes, providing accurate needle placement, since it has been observed that ultrasound guidance during treatment led to an increase in pain alleviation and a decrease in the average number of needling and treatment sessions. Diagnostic US can also guide injection in obese patients where manual detection of MTrPs is challenging (Takla & Rezk-Allah, 2018). Integration between shear wave elastography and contrast-enhanced US can offer a quantitative and highly-reliable diagnostic method for identifying MTrPs in trapezius muscle as shear wave elastography could detect the elastic modulus of trigger points (Liang et al., 2021). This new US technique can also guide an accurate and effective acupuncture as it identifies the proper depth for inserting the needle and performs an impartial assessment of dry needling and laser acupuncture (Kumbhare et al., 2016). However, the advantages of diagnostic ultrasound, more studies are needed to measure its accuracy in detecting MTrPs as a reliable diagnostic technique (Elbarbary et al., 2022).

Thermography and Biomarkers

The use of US and biomarkers improves the detection of MTrPs (Srbely et al., 2016). A comparison between the trapezius muscle, with active MTrPs, and a healthy gastrocnemius muscle has revealed a distinct biochemical milieu of substances associated with pain and inflammation, such as high concentrations of protons, substance P, calcitonin gene-related peptide, bradykinin, TNF- α, lL-1, IL-6, IL-8, 5-HT, and norepinephrine, nearly from active sites. These chemical substances differ numerically between the two muscles, but high levels of inflammatory mediators, neuropeptides, catecholamines, and cytokines have also been found in the gastrocnemius muscle, which hypnotized that the increase in biochemicals is not restricted to the localized MTrPs area (Kumbhare et al., 2020). It has revealed

that patients with MPS have notably higher serum levels of inflammatory biomarkers and growth factors compared to healthy controls (Grosman-Rimon et al., 2016). The current data indicates that inflammatory biomarkers and growth factors may be helpful for both the diagnosis and treatment of

MPS. Examining biomarkers concurrently with manual palpation may help emergency physicians identify MPS more precisely (Shah et al., 2008). Even though biomarkers and US offer a significant additional objective insight for assessing and detecting MTrPs, they cannot replace manual palpation and can only serve as an aid.

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8. Influence of Patient Characteristics on the Validity of Thermography

The accuracy and reliability of thermographic readings is influenced by various patient characteristics, leading to diagnostic variability. For instance, ageing can reduce overall skin temperature due to decreased core temperature caused by altered metabolic processes and changes in heat dissipation through the skin (Moraska et al., 2013). Body mass index was found to influence skin temperature. It has been shown that women have different thermal responses to heat load compared to men, likely due to differences in body surface-to-mass ratio, subcutaneous fat content, exercise capacity, and metabolic rate. Men, on the other hand, generally have higher muscle mass and lower body fat percentage (Hernandes Júnior & Sardeli, 2021).

Wilson et al. (2022) have found that gender significantly affects thermographic temperature, which varied by anatomical site. However, no significant differences in thermographic temperature were observed based on race (Neves et al., 2017). Thermal imaging encounters certain limitations in its application within medical practice. The technique is confined to capturing only skin temperature and, when used independently, it lacks reliability. To illustrate, a similar thermal pattern may be observed in cases of localized skin infections, underscoring the significance of the manual identification (Cojocaru et al., 2015).

9. Clinical Utility and Practical Application of Thermography

Thermography, specifically IRT, has been explored as a potential method for evaluating subjects with MPS (Wilson et al., 2022). While some studies have recognized its utility for monitoring neuromusculoskeletal alterations and short-term evaluation of MTrP interventions, there remains a lack of standardization in the method of infrared image analysis (Hakgüder et al., 2003). Additionally, studies testing the ability of IRT to identify trigger points have yielded contradictory results. Zhang et al. (2009) found no difference in temperature over the forearms with latent MTrPs compared to those without them, while increased temperatures over MTrPs were detected (Gabrhel et al., 2013; Haddad et al., 2012). Despite these discrepancies, there have been instances of successful use of IRT to examine the effects of various treatments on temperature over or near MTrPs. (Magalhães et al, 2015). A significant increase was observed in areas of higher temperature in MTrPs-positive patients undergoing dry-needling treatment (Sancibrian et al., 2019).

Despite the potential benefits of thermography in assessing MTrPs, there are challenges to its widespread implementation. The literature documents a lack of good evidence for thermography as a valuable tool for detecting long-term MTrPs in the region of interest. Moreover, The complicated agreement on skin temperature patterns in the presence of trigger points further complicates its diagnostic accuracy and reliability (Gabrhel et al., 2013). Despite these challenges, there is promise for IRT in the evaluation of various musculoskeletal conditions. Potential of thermography to quantify and identify MTrPs, especially when used in conjunction with physical assessment, may enhance diagnostic accuracy in clinical practice (Dibai-Filho & de Jesus Guirro, 2015).

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10. Conclusion

In summary, this review underscores the difficulties associated with diagnosing MPS and MTrPs. The absence of a universally accepted gold standard for diagnosis of MTrPs has led to the exploration of alternative methods. While concerns about the reliability of manual palpation persist, IRT emerges as a promising supplementary tool, providing real-time insights into microcirculation dynamics. Despite the potential advantages, questions remain regarding the specificity and sensitivity of thermography. The integration of other diagnostic approaches, such as pressure algometry, US, and biomarker assessment, offers a more comprehensive view of MPS. Standardizing protocols and continually exploring innovative technologies are crucial to address diagnostic uncertainties. Furthermore, an evidence-based and integrated approach that combines various diagnostic modalities holds the potential for more accurate identification and management of MTrPs in the context of MPS. Collaborative efforts and ongoing research are required to refine diagnostic strategies and enhance outcomes in the challenging landscape of MPS.

Authors Contributions

Topic Selection: IAI, TG, AMH, AH, AMS, BN; Design: IAI, TG, AMH; Planning: IAI, AH, AMS; Manuscript writing: IAI, AH, AMS, BN; Critical review: IAI, BN.

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Conflict of Interest

All authors report no conflict of interest.

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