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Efectos del Ejercicio Combinado en la Hipoalgesia y Variables Autonómicas en una Paciente con Síndrome de Ehlers-Danlos Hipermóvil: Un Informe de Caso

Alberto Melis-Romeu[1], Cristian Mendoza-Arranz[1], Alberto Pérez González[1,2]

1. Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, España.
2. Instituto de Rehabilitación Funcional La Salle

Correspondencia:

Alberto Melis Romeu, Msc.
CSEU La Salle. Universidad Autónoma of Madrid.
Calle La Salle, nº 10, 28023 Madrid, España
Teléfono: (+34) 639539151
E-Mail: melisllauri@gmail.com

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RESUMEN

Los síndromes de Ehlers-Danlos (SED) son un grupo heterogéneo de trastornos del tejido conectivo caracterizados por una hipermovilidad articular, hiperextensibilidad de la piel y fragilidad del tejido. Además de sufrir dolor crónico, lesiones musculoesqueléticas y dislocaciones de forma recurrente, su patología suele conllevar síntomas relacionados con disautonomías, los cuales pueden dominar la patología y conllevar una discapacidad muy importante. Este caso es único al explorar los efectos previamente no estudiados del ejercicio sobre la función autonómica y la modulación descendente del dolor en un paciente con síndrome de Ehlers-Danlos hipermóvil.

Mujer de 26 años diagnosticada de SED hipermóvil con dolor crónico y síntomas de disautonomías de 3 años de evolución. Se evaluaron: Umbrales de dolor a la presión, frecuencia cardíaca, temperatura de la piel a nivel periférico y conductancia de la piel durante un Tilt Test y protocolos de Bruce modificados para este estudio.

Se tomaron dos mediciones, una antes y otra después de 7 semanas de tratamiento.

El tratamiento basado en ejercicio cardiovascular de tipo interválico y trabajo de fuerza general produjo cambios importantes en todas las variables mencionadas anteriormente. Se observaron disminuciones en frecuencia cardíaca, temperatura y conductancia de la piel, así como aumento de los umbrales de dolor a la presión en ciertos casos.

Los resultados de este caso podrían indicar que una intervención a base de ejercicio es capaz de producir cambios en variables relacionadas con el sistema nervioso autónomo y los sistemas descendentes de modulación del dolor en una paciente diagnosticada con SED hipermovil.

Palabras clave: Síndrome de Ehlers-Danlos; Umbral de dolor; Disautonomía; Ejercicio; Reporte de caso

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Effects of Combined Exercise on Hypoalgesia and Autonomic Variables in a Patient with Hypermobile Ehlers-Danlos Syndrome: A Case Report

Alberto Melis-Romeu[1], Cristian Mendoza-Arranz[1], Alberto Pérez González[1,2]

1. Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid, España.
2. Instituto de Rehabilitación Funcional La Salle

Correspondence:

Alberto Melis Romeu, Msc.
CSEU La Salle. Universidad Autónoma of Madrid.
Calle La Salle, nº 10, 28023 Madrid, España
Teléfono: (+34) 639539151
E-Mail: melisllauri@gmail.com

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ABSTRACT

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. In addition to experiencing chronic pain, musculoskeletal injuries, and recurrent dislocations, their condition often involves symptoms related to dysautonomia, which can dominate the pathology and lead to significant disability. This case is unique as it explores the previously unstudied effects of exercise on autonomic function and descending pain modulation in a patient with hypermobile Ehlers-Danlos syndrome.

A 26-year-old woman diagnosed with hypermobile EDS with chronic pain and dysautonomia symptoms of 3 years' duration was evaluated. Pain pressure thresholds, heart rate, peripheral skin temperature, and skin conductance were assessed during a Tilt Test and modified Bruce protocols for this study. Two measurements were taken, one before and one after 7 weeks of treatment.

The treatment, based on interval-type cardiovascular exercise and general strength training, produced significant changes in all the variables mentioned above. Decreases in heart rate, temperature, and skin conductance were observed, as well as an increase in pain pressure thresholds in certain cases.

The results of this case may indicate that an exercise-based intervention is capable of producing changes in variables related to the autonomic nervous system and descending pain modulation systems in a patient diagnosed with hypermobile EDS.

Keywords: Ehlers-Danlos Syndrome; Pain Threshold; Dysautonomia; Exercise; Case Report

INTRODUCTION

Ehlers-Danlos syndromes (EDS) comprise a heterogeneous group of connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility (Malfait et al., 2017). The current international EDS consortium proposes a classification recognizing 13 different subtypes, among which the hypermobile type (hEDS) is the most prevalent (>80% of cases) (Reychler et al., 2021). Furthermore, although EDS was traditionally considered a rare condition, affecting 1 in every 5000 births, more recent studies in specific regions indicate that its prevalence is increasing due to the establishment of more specific diagnostic criteria in recent years, providing prevalence data of approximately 1 in every 3100 individuals (Demmler et al., 2019).

Due to this condition, patients often experience chronic pain, musculoskeletal injuries, and recurrent dislocations (Rombaut et al., 2010). However, their pathology typically entails a wide variety of symptoms unrelated to the musculoskeletal condition, such as palpitations, thermoregulation problems, orthostatic intolerance, etc. In fact, in some cases, these types of symptoms can dominate the pathology and lead to significant disability in daily life (De Wandele et al., 2013), similar to other conditions with similar issues such as fibromyalgia or chronic fatigue syndrome. These problems have been associated with underlying dysautonomias (De Wandele et al., 2014; Freeman, 2002; Martínez-Lavín & Hermosillo, 2000), which are related to poor prognosis, decreases in quality of life, and increased morbidity and mortality (De Wandele et al., 2014; Fedorowski & Melander, 2013; Yang et al., 2023).

The pathological mechanisms of these dysautonomias are heterogeneous and related to various factors (Benarroch, 2012), including physical deconditioning, which, although there is controversy regarding whether it can be considered a direct cause of these dysautonomias (van Campen et al., 2021), does seem to exert influence on them, thus being susceptible to improvement (Fu & Levine, 2018; Parsaik et al., 2012).

Current treatment strategies for this condition are based on alleviating symptoms and treating the physical and mental disabilities that arise secondarily (Ra et al., 2022). From a physiotherapy perspective, there are some studies that mainly analyze the effectiveness of different types of interventions (exercise, education, multidisciplinary approaches, etc.) and their effects on pain, functional, and psychological variables (Buryk-Iggers et al., 2022; Reychler et al., 2021). However, no study conducted to date considers the effects of exercise on hypoalgesia and dysautonomias in this type of patients. Therefore, the aim of this study will be to assess whether a training program is capable of producing changes in variables related to the autonomic nervous system (ANS) and descending pain modulation systems in a patient diagnosed with hEDS.

METHODS

Case presentation

The patient is a 26-year-old woman presenting to the clinic with a diagnosis of hypermobile Ehlers-Danlos Syndrome. Since an early age, the patient has experienced subluxations and significant sensations of instability. Additionally, since 2020, she has exhibited alterations due to dysautonomias, Postural Orthostatic Tachycardia Syndrome (POTS), and temperature dysregulation, which hinder her ability to change positions and perform daily activities, as well as to stand for prolonged periods or be in warm environments. Cardiovascular exercise triggers marked autonomic activity dysregulation subsequently, and alterations in ocular accommodation, polycystic ovary, and gastroparesis have also been observed. Regarding pain, the patient reports generalized pain, mainly in the joints, with a minimum score of 4 on the visual analog scale (VAS) at rest and 8 during the most intense moments.

Currently, the patient is undergoing treatment with Midodrine for managing orthostatic hypotension, as well as DAO enzyme for histamine control and lactase for lactose intolerance.

Clinical Findings and Methodology

The methodology of this study is explained in more detail in Annex 2. As outcome measures to assess the potential efficacy of the intervention, two measurements were taken, one prior to the intervention and another after 7 weeks of intervention, evaluating the following aspects:

Pressure Pain Thresholds (PPT): Measured using algometry following a protocol established in other studies (Chesterton et al., 2007).

Skin Conductance: eSense Skin Response (Mindfield Biosystems, Inc., Berlin, Germany) was used. This device has been used to measure autonomic variables in other studies where the feasibility of its use has been demonstrated (Dutkiewicz et al., 2019; Hinrichs et al., 2017).

Peripheral Skin Temperature: eSense Temperature (Mindfield Biosystems, Inc., Berlin, Germany) was used. The data are presented in Table 3 and Figure 3.

Heart Rate and Blood Oxygen Saturation: Measured using pulse oximetry. These are presented in Annex 1 and Figure 1.

The measurement protocol was adapted from a Tilt Test and a modified Bruce protocol (Sarma & Levine, 2016; Sutton et al., 2021), taking into account both the resources available in the clinic and the specific characteristics and needs of the patient, monitoring her at all times through the modified Borg scale (Jakobsen et al., 2014).

Finally, post-intervention, the patient completed the Global Rating of Change (GRoC) scale. Through this self-report measure, general changes in the patient's condition after receiving treatment are evaluated. This aims to quantify the magnitude of change perceived by the subject (Bobos et al., 2020).

Intervention

No interventions with the objectives of this study were reported; therefore, the intervention was decided based on the literature, aiming to achieve effects on pain sensitivity and autonomic variables (Besnier et al., 2017; Roque Marçal et al., 2022; Song et al., 2022), but primarily according to the patient's preferences and needs to achieve maximum treatment adherence (Fogarty, 1997; Loew et al., 2017).

The intervention was based on a 7-week combined exercise and manual therapy protocol, involving supervised exercise by a physiotherapist twice a week,

complemented with home-based work 2/3 times a week.

The first day in the clinic involved global upper limb strength exercises followed by high-intensity interval training (HIIT) with 3 to 4 sets of 3-minute intervals at the maximum intensity tolerated by the patient (140 beats per minute [bpm] correlating with 8/9 on the modified Borg scale) and 3 minutes at moderate intensity equivalent to 65-70% of maximum heart rate, aiming for a range of 122-132 bpm corresponding to 6/7 on the modified Borg scale

(Tanaka et al., 2001). On the second day, strength training of large muscle groups was performed. The work pattern consisted of 3 sets of 3 to 4 superset series (2 upper limb and 2 lower limb), performing 10/12 repetitions at an intensity according to the patient's tolerance and sensations. Additionally, manual therapy was performed before exercising to modify symptoms and better tolerate physical activity.

Home-based work involved performing 3 to 4 sets of 20-minute moderate-intensity interval training (MIIT) on a recumbent bicycle, where the patient performed 3 minutes at low/moderate intensity and 3 minutes at moderate/high intensity.

de media intensidad (MIIT) en bicicleta reclinada donde la paciente realizaba 3 minutos a baja/moderada intensidad y 3 minutos a moderada/alta intensidad.

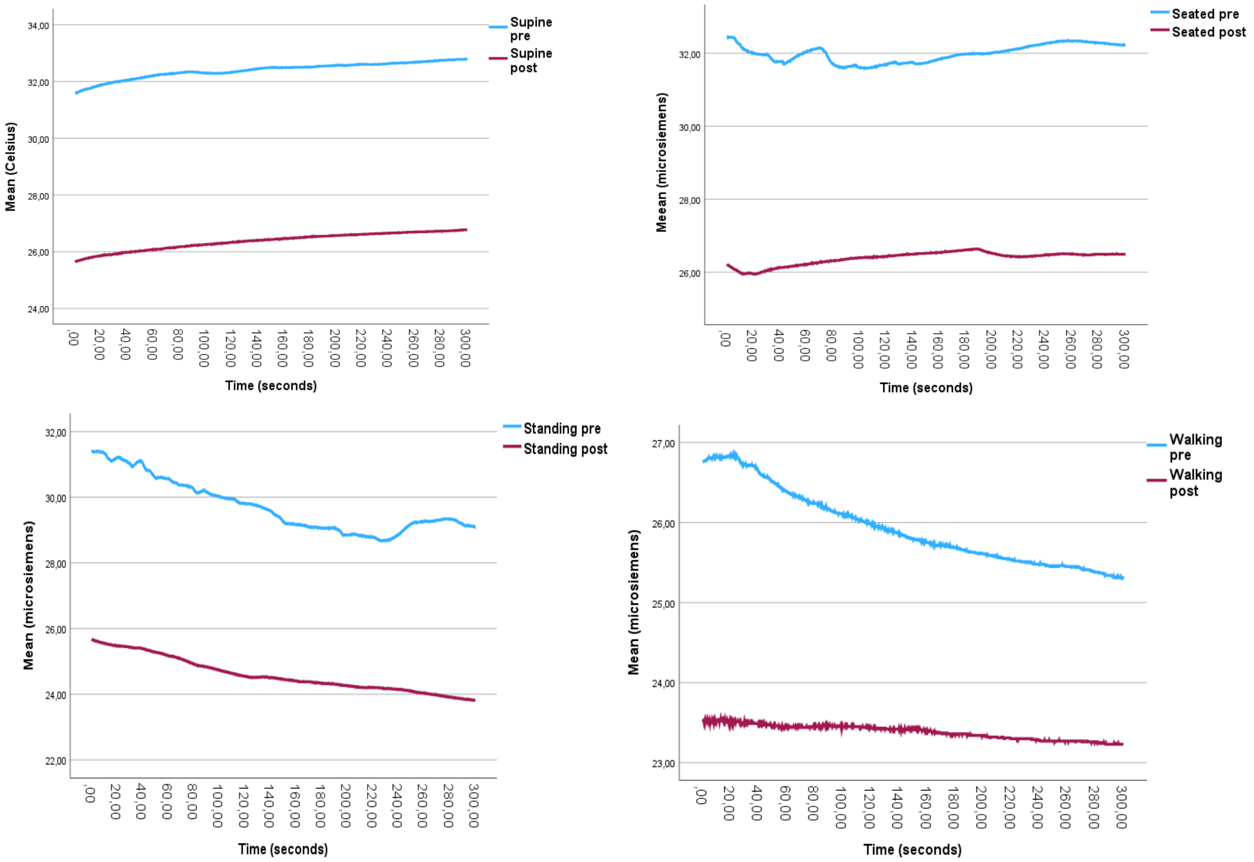
RESULTS

The patient received a total of 14 in-person sessions and between 14 and 21 home exercise sessions.

Heart Rate

Heart rate data are depicted in Figure 1 and numerically detailed in Annex 1. A marked decrease in heart rate is observed in the measurements taken after treatment compared to control measurements. Overall, the heart rate remains below control values, except for a peak occurring at three minutes into the standing measurement, briefly exceeding pre-treatment values. According to Nelson & Petersen (2017), the minimum detectable change for heart rate during walking in other pathological populations is 4.9 beats per minute (bpm). Upon analysis of the results, except for minutes 3 and 5 during standing and minute

Figure 1: Comparison of heart rate data in different positions.



3 during walking, the rest of the data obtained exceed 5 bpm, often surpassing 20 bpm.

Pressure Pain Thresholds

Regarding the data collected on Pressure Pain Thresholds (PPT) as shown in Table 1, there is no clear consistency of hypoalgesia produced by manual therapy or physical activity in the pre-intervention measurements, even showing decreases in thresholds in certain cases. However, upon examining the results of post-intervention measurements, while there is no significant change in baseline thresholds compared to control, we do observe that now manual therapy induces hypoalgesia in some areas such as the radius, fibula, or L5, and these changes persist more consistently after physical activity. Considering that a minimum clinically relevant change is proposed as a 15% increase in thresholds, we can assume that the changes produced in the aforementioned areas could be considered significant (Moss et al., 2007; Vicenzino et al., 1996; Voogt et al., 2015).

Skin Conductance

Table 2 displays clear differences in skin conductance pre- and post-treatment across all considered descriptive statistics. Figure 2 illustrates the comparisons of each measurement in a line chart format, clearly demonstrating a decrease in skin conductance post-intervention in all measurements taken. According to the results, we observe mean differences of over 3.2 microsiemens in standing, for example, and 2.47 during walking. Additionally, variability has also decreased in each of the variables, except in supine position due to the peak occurring around the 4-minute mark.

Temperature

Following the trend of skin conductance, peripheral skin temperature substantially decreased in all analyzed aspects and in all measurements taken, as shown in Table 3 and Figure 3. We observe decreases in the mean greater than 5°C in all analyzed positions

Table 1: Pressure Pain Threshold Measurements Before and After Intervention

PPT MEASUREMENTS		Pre - MT	Post - MT	Post - 5MW
THUMB PRE	Left	0.99	1.25	1.69
	Right	1.31	0.85	1.61
THUMB POST	Left	2.42	1.95	1.99
	Right	1.74	2.14	2.06
RADIUS PRE	Left	1.18	2.10	1.49
	Right	2.04	1.98	1.69
RADIUS POST	Left	0.69	1.66	1.84
	Right	1.09	2.16	2.25
FIBULA PRE	Left	2.46	4.28	1.81
	Right	3.78	1.57	1.7
FIBULA POST	Left	2.08	3.67	3.56
	Right	3.62	4.17	3.32
L5 PRE	N/D	2.11	2.52	1.5
L5 POST	N/D	1.74	3.45	3.10

except during walking, where the decrease was 2.52°C. Furthermore, variability in temperature also decreased.

Self-Reported Measures

Finally, to compare whether changes in the analyzed physiological variables correlated with the subjective perception of changes perceived by the patient, the GRoC scale was administered, the score of which ranges from -7 ("as bad as it could be") to +7 ("as good as it could be"). The patient responded with a +6, indicating "Much Better" (Bobos et al., 2020).

DISCUSSION

This case presents a patient diagnosed with h-SED with chronic pain and symptoms associated with dysautonomia. The main objective of this case is to analyze the effects of a treatment based on strength training and cardiovascular endurance on Exercise-Induced Hypoalgesia (EIH), skin conductance, peripheral skin temperature, and heart rate (HR), intending to evaluate the effectiveness of this treatment in producing changes in the descending pain inhibition systems and autonomic nervous system (ANS) responses. The results obtained showed significant changes in all analyzed variables.

Pressure Pain Thresholds

In recent years, it has been demonstrated that manual therapy decreases pain sensitivity through the activation of descending inhibitory pathways (Skyba et al., 2003). Similarly, exposure to a single session of exercise induces hypoalgesia in healthy individuals, although these effects are inconsistent in patients with pain (Bonello et al., 2021; Wewege & Jones, 2021). This is related to a malfunction of pain inhibitory pathways due to neuroplastic changes that can occur with prolonged pain in conditions such as fibromyalgia (Cagnie et al., 2014; Kosek & Hansson, 1997; Staud & Domingo, 2001). However, some treatments like cognitive therapy have shown the ability to produce neuroplastic changes in the Central Nervous System in such patients, reducing central sensitization components and improving pain modulation (McCrae et al., 2022). Current studies hypothesize that chronic exercise may be capable of inducing similar changes (Song et al., 2022).

Table 2. Data on skin conductance before and after the intervention.

CONDUCTANCE	Supine pre	supine post	seated pre	seated post	Standing pre	Standing post	Walking pre	Walking post
Mean	1.0305	.8847	2.4542	1.1163	5.1427	1.8961	4.5913	2.1210
Range	.33	.56	2.27	.63	3.25	1.30	1.68	.59
Minimum	.91	.62	1.20	.97	3.10	1.42	4.10	1.89
Maximum	1.24	1.18	3.47	1.60	6.35	2.72	5.78	2.48

As seen in the results of our patient, consistent changes were not achieved in baseline hypoalgesia measurements after the intervention, which aligns with some studies conducted on fibromyalgia populations (Assumpção et al., 2018; Schachter et al., 2003). However, upon analyzing changes in PPTs after manual therapy and exercise, post-intervention, there is an observed decrease in pain sensitivity that was not present before. Therefore, we hypothesize that physical exercise could have produced central changes, which in turn have managed to reverse the malfunction of these descending inhibitory pathways, consistent with current studies where patients with fibromyalgia and dysfunctional conditioned pain modulation related to their pathology improved their ability to modulate painful sensations after an exercise session, suggesting activation of these descending inhibitory pathways as a result of treatment (Alsouhibani & Hoeger Bement, 2022).

Skin Conductance

Skin conductance response (SCR) has been used in recent years to measure autonomic dysfunctions in conditions such as Parkinson's disease, Post-

Figure 2: Comparison of Skin Conductance in different positions.

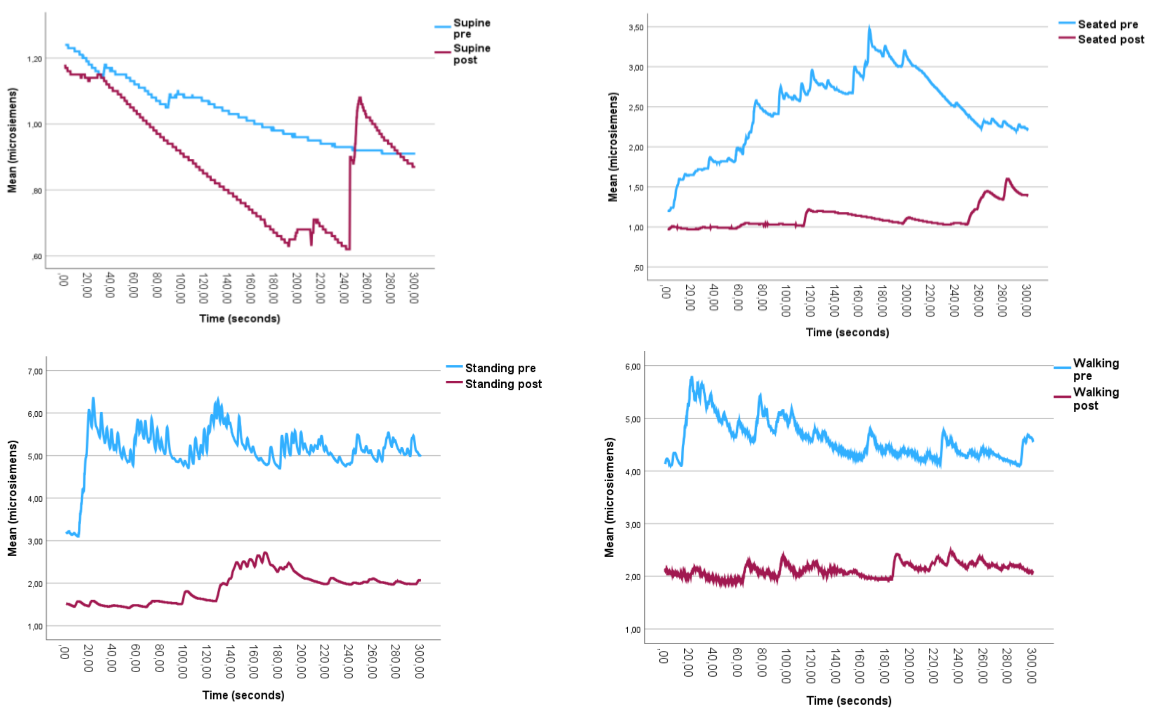


Table 3. Data on temperature before and after the intervention.

TEMPERATURE	supine pre	Supine post	seated pre	Seated post	Standing pre	Standing post	Walking pre	Walking post
Mean	32.3964	26.3686	31.9894	26.3849	29.7218	24.5840	25.9301	23.3848
Range	1.21	1.12	.85	.70	2.73	1.86	1.56	.31
Minimum	31.59	25.65	31.59	25.94	28.67	23.82	25.30	23.23
Maximum	32.80	26.77	32.44	26.64	31.40	25.68	26.86	23.54

Traumatic Stress Disorder, or Stroke (Çakır et al., 2015; Hinrichs et al., 2017; Ke et al., 2017). It is a non-invasive procedure used to assess sympathetic cholinergic pseudomotor function through the detection of the potential generated by sweat glands in the skin and surrounding skin. SCR provides a reliable record of stimulation of efferent sympathetic fibers through electrical stimulation of the posterior tibial or median nerves in their afferent portion (Dutkiewicz et al., 2019).

Consistent with our case, other studies have shown that patients with h-SED exhibit sympathetic nervous system hyperactivity at rest, similar to patients with fibromyalgia and severe heart failure (De Wandele et al., 2014; Martinez-Lavin, 2007; van de Borne et al., 1997). This hyperactivity is common in cardiovascular pathology and is highly related to increased morbidity and mortality (De Wandele et al., 2014). As observed in the results of our patient, the intervention led to a substantial decrease in this sympathetic hyperactivity at rest, as well as during exercise. Studies on the subject suggest that the demands of exercise on the ANS can induce adaptations and neuroplastic changes when occurring recurrently (training) (Martins-Pinge et al., 2005). This leads to adaptations in cardiac autonomic balance, characterized by a greater predominance of the parasympathetic component compared to the sympathetic through modulation of neurons in the dorsal ventrolateral medulla, the main tonic source of supraspinal sympathetic outflow (Martins-Pinge, 2011).

Therefore, we hypothesize that the decreases in SCR and its variability observed in our patient after the intervention could be due to the mechanisms mentioned above, which could imply an ANS adaptation, regulating and decreasing sympathetic hyperactivity. This hypothesis aligns with other studies where similar results were obtained in different pathological populations. Figueroa et al. (2008) found improvements in cardiac autonomic functions after 4 months of strength training in patients with fibromyalgia, while other authors also observed such improvements in patients with metabolic syndrome following 4 months of High-Intensity Interval Training (HIIT) (Ramos et al., 2017). Additionally, other reviews also support the results of training in modulating autonomic variables in patients with heart disease or POTS (Besnier et al., 2017; Fu & Levine, 2018).

Thus, we hypothesize that the significant decrease in HR variables observed could be due to a combination of both peripheral and central mechanisms.

Heart Rate

Various mechanisms may have induced the changes observed in our patient's heart rate (HR). Physical training induces a series of cardiovascular adaptations, including changes in skeletal muscle circulation and modifications in the structure and autonomic control of the heart (Martins-Pinge, 2011).

Individuals who train regularly experience an increase in their maximal oxygen consumption capacity, which is accompanied by additional cardiovascular adaptations. These include faster ventricular filling, an increase in myocardial contractile strength resulting in a greater stroke volume, and enhanced capillary perfusion and vasodilatory response in the arterioles during exercise. These effects allow for greater oxygen extraction by the active muscles. Such adaptations contribute to maintaining an efficient cardiac output with lower energy expenditure, which is reflected in a reduced heart rate (Clausen, 1977).

Furthermore, regular exercise can modify the autonomic balance of the heart by increasing parasympathetic nervous system activity and reducing sympathetic nervous system activity (de Abreu et al., 2009). As previously discussed, we believe this is one of the adaptations that has occurred in our patient. This results in a greater influence of the parasympathetic component in cardiac regulation, contributing to increased stability and adaptability of the cardiovascular system due to training, as has been observed in previous studies on populations also affected by dysautonomias (Figueroa et al., 2008; Fu & Levine, 2018).

Thus, we hypothesize that the significant reduction in HR-related variables observed may be due to a combination of both peripheral and central mechanisms.

Peripheral Skin Temperature

Following the mentioned hypothesis suggesting that the intervention has improved SNS regulation, the decreases in skin temperature at rest and during exercise in our patient could be attributed to the relationships between the SNS and the neuroendocrine system. Temperature regulation is mediated by the neural control of peripheral organs, glands, and non-musculoskeletal tissues, primarily managed by the SNS. Conversely, the endocrine system directly affects these tissues through hormone actions, mediated by neuroendocrine mechanisms originating from the hypothalamic region or through autonomic control. Thus, both systems act together and communicate, especially in the paraventricular nucleus of the hypothalamus due to the proximity of neuroendocrine and autonomic neurons in this area, making it a fundamental pillar in integrating autonomic and neuroendocrine responses in the body (Sladek et al., 2015). This hypothesis aligns with other studies where exercise-based interventions have induced changes in neuroendocrine systems through improvements in hormonal activation and secretion in healthy individuals and the elderly, where these systems begin to decline (Alves et al., 2012; Jackson et al., 2005).

In addition to this mechanism, other related mechanisms could account for the observed results. As discussed in the HR section, regular exercise improves many parameters of the cardiovascular system, leading to increased blood volume, greater capillarization, higher stroke volume, improved hemodynamics, etc. (Clausen, 1977). All of this implies an enhancement in the efficiency of this system, which, through blood flow control, is one of the main thermoregulators of the human body. Therefore, the increased effectiveness of the cardiovascular system could result in a greater capacity to regulate body temperature and improved tolerance to sweating, making it more effective in reducing body temperature (Charkoudian, 2003).

Limitations

There are several limitations to consider in the present case study. Firstly, both Heart Rate (HR) and peripheral skin temperature are not entirely reliable or representative of the intended measurements, as they are highly variable and can be influenced by numerous factors. Therefore, our study only allows for hypotheses regarding the mechanisms involved in the observed changes to be drawn. Secondly, although there were no variations in the patient's medication during or prior to the study, potential interactions with the results obtained are not known. Lastly, a long-term follow-up was not conducted, limiting the consideration of the treatment outcome to the short to medium term.

For future research, it is proposed to analyze Heart Rate Variability (HRV), which is more commonly used in studies of this nature and provides a reliable measure of autonomic cardiac balance. Additionally, echocardiography is suggested to accurately measure the patient's cardiac output, enabling the evaluation of changes at the systolic volume level and analysis of their potential effects on HR. Furthermore, conducting a Randomized Clinical Trial is recommended to confirm that the results of this study are consistent across the majority of the population and therefore applicable in clinical practice.

CONCLUSION

This case study has demonstrated the effectiveness of a combined treatment of physical exercise and manual therapy in improving autonomic variables and increasing pain sensitivity in a patient with h-SED. Furthermore, improvements in the various outcome variables analyzed have been correlated with a significant improvement (+6) in the patient's subjective perception of their condition using the GRoC scale. This indicates that the treatment may have had an impact on their daily activities and quality of life, as observed in other studies involving populations with the same pathology (Buryk-Iggers et al., 2022; Reychler et al., 2021).

HIGHLIGHTS

- Patient diagnosed with h-EDS with chronic pain and dysautonomia for the past three years.
- A 7-week treatment program was implemented, consisting of interval-based cardiovascular exercise and general strength training.
- Reductions in heart rate, peripheral skin temperature, and skin conductance were observed, along with increased pressure pain thresholds in certain cases.
- Results may suggest that an exercise-based intervention can induce changes in variables related to the autonomic nervous system and descending pain modulation systems in a patient diagnosed with hypermobile EDS.

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