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Effectiveness of Relaxation and Hypnosis Interventions in Distressed Patients With Chronic Diabetic Foot Ulcers: A Longitudinal Pilot Randomised Controlled Trial

M. Graça Pereira[1] | Margarida Vilaça[1] | Susana Pedras[2] | André Carvalho[3] | Kavita Vedhara[4] | M. Jesus Dantas[5] | Alberto Lopes[6] | Susana Faria[7]

[1]Psychology Research Center (CIPsi), School of Psychology, University of Minho, Braga, Portugal | [2]Angiology & Vascular Surgery Department, Centro Hospitalar Universitário Porto (CHUP), Porto, Portugal | [3]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Centro Hospitalar Universitário do Porto (CHUP), Porto, Portugal | [4]Division of Primary Care, University of Nottingham, Nottingham, UK | [5]Department of Surgery, Centro Hospitalar Tâmega e Sousa, Penafiel, Portugal | [6]Portuguese Association of Clinical Hypnosis and Hypnoanalysis (APHCH), Porto, Portugal | [7]Department of Mathematics, Centre of Mathematics (CMAT), Minho University, Guimarães, Portugal

Correspondence: M. Graça Pereira (gracep@psi.uminho.pt)

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ABSTRACT

Diabetic foot ulcer (DFU) healing is a complex and slow process that depends on several factors such as the patient's physical health. However, psychological factors such as distress, which are commonly reported by patients with DFU, may also influence DFU development and recurrence. This pilot randomised control trial (RCT) assesses the effectiveness of progressive muscle relaxation and hypnosis on DFU healing and quality of life (QoL) in distressed patients. Sixty-nine patients who received standard care treatment were randomly assigned to one of four groups: muscle relaxation (TG1), hypnosis (TG2), neutral sessions (active control: ACG), and no intervention (passive control: PCG). Primary outcomes were both DFU healing and QoL. Secondary outcomes were perceived stress, psychological morbidity, and illness (DFU) representations. Patients were assessed at baseline (T0), 2 months after the baseline (T1), and 4 months later (T2). Regarding primary outcomes, comparisons between groups showed significant differences only in DFU healing: TG1, TG2, and ACG reported more improvements than PCG at T1, while TG1 showed more improvements than TG2 and PCG at T2. Results for secondary outcomes revealed less threatening DFU representations in TG1 compared to TG2 and ACG, and more psychological morbidity in TG2 than TG1, both at T1. Within-group analysis in primary outcomes showed DFU healing and physical QoL improvement in all groups, DFU-related QoL improvement in all groups except PCG, and an increase in mental QoL only in TG2 and ACG. Regarding secondary outcomes, results showed a decrease in DFU's representations only in TG1, and a significant decrease in stress and psychological morbidity in TG1, TG2, and ACG. Results suggest that both stress-reduction interventions should be included in the multidisciplinary treatment and rehabilitation plan for distressed patients with DFU(s).

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1 | Introduction

Diabetic foot ulcers (DFU(s)) are one of the most serious complications of diabetes, associated with amputation (Shin et al. 2017), and increased morbidity and mortality (Renner and Erfurt-Berge 2017). It is estimated that 15%–25% of all patients with diabetes mellitus (DM) may develop a foot ulcer (Yazdanpanah et al. 2015), which is more common in patients with type 2 DM (T2DM) (Zhang et al. 2017).

DFU healing is a complex and slow process depending on several factors such as the patient's health condition. However, psychological factors such as distress may also influence DFU development and recurrence (Jiang et al. 2022; Walburn et al. 2009; Westby et al. 2020). There is strong evidence suggesting that individuals with DM are more likely to suffer from anxiety and depression symptoms compared to the general population (Khan et al. 2019), with patients with DFU(s) experiencing moderate anxiety and depression (Polikandrioti et al. 2020). Additionally, psychological morbidity may lead to poor adherence to treatment and self-care behaviours, complicating the healing process (Polikandrioti et al. 2020).

One of the consequences of DFU is the loss of mobility and, consequently, the inability to perform activities of daily living (Renner and Erfurt-Berge 2017), which contributes to impaired quality of life (QoL). In addition, the stress resulting from hard-to-heal or recurrent ulcers, together with the stress related to financial strain, social isolation, daily self-care, and fear of foot amputation, is associated with poorer QoL (Alosaimi et al. 2019; Pedras et al. 2016; Polikandrioti et al. 2020; Wukich et al. 2018).

Illness perceptions also play a crucial role in patients' emotional and behavioural responses when facing a health problem (Leventhal et al. 2020). In patients with DM, illness perceptions are related to adherence to treatment, foot care behaviours, metabolic control, and prognosis (Almeida et al. 2023; Broadbent et al. 2011; Pereira et al. 2018; Vedhara et al. 2016). According to Vedhara et al. (2016), worse DFU perceptions predict poorer health outcomes and higher mortality rates.

Considering that psychological variables such as stress, psychological morbidity, and illness representations impair patients' QoL and DFU healing, there is an urgent need for robust evidence on the effectiveness of psychological interventions in this area (Norman et al. 2020; van Netten et al. 2016). Also, given that most studies are focused on DFU prevention, effectiveness studies on DFU healing and QoL are required (McGloin et al. 2021; Norman et al. 2020).

Over the past years, the effects of specific interventions to reduce psychological distress on health outcomes have been addressed in the literature, particularly relaxation interventions (Robinson et al. 2017). According to a study conducted with 70 patients, eight weekly relaxation sessions reduced psychological morbidity (i.e., anxiety, depression, and stress) and blood glucose levels in patients diagnosed with T2DM (Ebrahem and Masry 2017). A randomised study with 32 patients with type 1 (T1DM) and T2DM, with non-healing DFU(s), concluded that one single session of biofeedback-assisted relaxation contributed to wound healing (Rice et al. 2001) with 87.5% of individuals from the experimental group having their DFU healed compared to 43.8% of patients from the control group. Along with relaxation, hypnosis has also shown promising results in reducing stress, decreasing blood sugar levels, and managing neuropathic pain in patients with DM (Deswita et al. 2019; Kubra et al. 2023; Pereira 2017). However, as far as the authors are aware, no study has previously focused on the impact of hypnosis on chronic wounds such as DFU(s).

Although stress-reduction interventions as adjuvant therapies are known to improve DFU healing (Pombeiro et al. 2022; Rice et al. 2001) and QoL (Ebrahem and Masry 2017), previous literature on the effectiveness of stress-reduction interventions, such as muscular relaxation and hypnosis, in patients with diabetes or DFU, is scarce. Therefore, more studies on the effectiveness of such interventions on patients' QoL and chronic wounds are needed, specifically randomised clinical trials (RCTs) since these are the most appropriate designs to assess treatment effectiveness (Hariton and Locascio 2018).

Given previous evidence showing the benefits of relaxation and hypnosis on clinical and psychological outcomes in individuals with diabetes, a four-armed pilot RCT to compare the effectiveness of two stress-reduction interventions, progressive muscle relaxation, and hypnosis, on DFU healing and QoL, in distressed patients with one or two DFU(s) was designed. This pilot RCT aimed to assess the effectiveness of a muscle relaxation intervention with guided imagery (treatment group 1: TG1) compared to hypnosis with guided imagery (treatment group 2: TG2) versus two control groups—neutral guided imagery placebo (active control group: ACG) and a group that does not receive any psychological intervention (passive control group: PCG)—on DFU healing, QoL, psychological distress, and illness representations. Specifically, the aim was to assess differences between and within groups regarding patients' DFU healing and QoL, over time. The secondary objective aimed to assess differences between and within groups regarding patients' perceived stress, psychological morbidity, and illness representations, over time.

2 | Methods

2.1 | Study Design

This is a longitudinal, multicenter, participant-masked, sham-controlled pilot RCT with a 1:1:1:1 allocation ratio. Although the initial goal was to conduct a full-scale pre-registered RCT, the COVID-19 pandemic confinement compromised the sample collection. Therefore, the initial proposal was adapted and transformed into a pilot RCT. Thus, the pilot trial resulted from an adaptation of the design and methodology planned for the definitive RCT, which was originally registered at ClinicalTrials.gov (NCT02003261). For a more detailed presentation of the design and methodology of the large RCT, please refer to the study protocol publication (Pereira et al. 2022).

2.2 | Ethical Considerations

The study was conducted by the Declaration of Helsinki (World Medical Association 2013).

2.3 | Setting and Participants

All eligible patients with one or two chronic DFU(s) being treated for the first time in the diabetic foot outpatient clinic of one of the three major public central hospitals in northern Portugal, between March 2019 and September 2021, were consecutively enrolled in this study. The diabetic foot consultations were performed by a multidisciplinary team that included physicians (endocrinology, general and vascular surgery, orthopedics), nurses, and podiatrists, with no costs for patients as they were fully covered by the national healthcare system.

Participants were distressed patients, 18 years old and above, with one or two chronic DFU(s) at the baseline assessment, who provided written informed consent. Chronicity was defined as active ulcers lasting more than 6 weeks but < 14 weeks, based on literature showing that non-healing ulcers as those that fail to heal after 6 weeks of conservative therapy (Rabba Tabassum et al. 2022), and those that remained unhealed at 14 weeks (Ince et al. 2007). Distress was assessed through the Perceived Stress Scale (PSS) (Trigo et al. 2010) and the Hospital Anxiety and Depression Scale (HADS) (Pais-Ribeiro et al. 2007), with scores equal to or > 13 (male patients) or 17 (female patients) on PSS, or equal to or > 11 on the HADS subscales, indicating distress.

Exclusion criteria were: having recurrent DFU(s), i.e., ulcer resurgent at the same location within < 6 months of complete healing; having more than two active DFU(s); showing no distress; having undergone an organ transplant; undergoing hemodialysis/stage 5 of chronic kidney disease (CKD); having an active cancer diagnosis; having a diagnosis of a psychotic disorder or dementia (recorded in the patient's medical records); and receiving psychological support.

2.4 | Interventions

All participants received standard medical/nursing care for DFU, according to the guidelines of the Portuguese General Health Direction and the International Working Group on the Diabetic Foot. The standard DFU care included pressure relief at the ulcer site, debridement, control of infection and inflammation, and revascularisation when appropriate.

Participants in the intervention groups received progressive muscle relaxation (TG1) or hypnosis (TG2) sessions with guided imagery. The protocol for both interventions included four individual scripted sessions, each one with approximately 45 min. Sessions were delivered every 2 weeks, resulting in approximately a 2-month treatment course.

Muscle relaxation consisted of alternately tensing and relaxing muscle groups throughout the body. Relaxation began with diaphragmatic breathing, followed by progressive muscle relaxation, a technique initially developed by Jacobson in the 1930s involving the contraction and subsequent relaxation of different muscle groups (Payne and Donaghy 2010). Guided imagery was focused on the DFU healing following the muscle relaxation exercises, during which the patient was asked to imagine the DFU and the foot being healed. Hypnosis was conducted by two qualified hypnotherapists Each session followed the hypnotic protocol, specifically tailored to reduce stress, based on the following stages: presentation of the session goals and a call for change (pre-talk); capturing patients' attention to absorb the sensations from the surrounding environment and/or the body (absorption); the use of direct and indirect hypnotic suggestions (ratification); providing patients evidence that the hypnotic mindset was occurring at the moment (aliciation); activating patients' unconscious responses through hypnotic language and guided imagery (dissociation); and, finally, the patients' awakening from the hypnotic mindset (awakening). The hypnosis protocol included guided imagery with patients being specifically asked to focus on healing metaphors regarding DFU healing.

Patients allocated to the ACG received neutral sessions with guided imagery with the sole purpose of controlling the attention effect received from health psychologists and hypnotherapists towards those patients allocated to the treatment groups. Neutral sessions were conducted by health psychologists and were focused on the patients' daily life before the DFU (e.g., 'Please, try to remember how your daily routine was on regular working days before the DFU. Can you describe those memories?'). As in the treatment groups, ACG sessions followed a scripted protocol that included four sessions of approximately 45 min every 2 weeks, each one dedicated to a different topic (family, work, friends, and leisure). The purpose of including a comparable attention placebo control activity, with similar contact time with the health psychologist, intended to enhance the study's credibility in ACG participants (Aycock et al. 2018).

The PCG did not receive any intervention besides the standard medical/nursing DFU treatment.

2.5 | Randomisation

Eligible participants were randomised into one of the four groups, in varying size blocks. An independent researcher unaware of the numeric coding for each group, created the randomisation sequence using an online random number generator with a 1:1:1:1 allocation, using block sizes of 12. The sequence was stored in a secure and password-protected database, only accessible by the independent researcher.

Participants' randomisation was stratified according to (i) data collection site, (ii) chronic kidney disease (CKD) and the disease stages (without CKD/CKD stage 1, and 2; CKD stage 3, and 4), and (iii) peripheral arterial disease (PAD) (without PAD; with PAD), in a total of 12 possible strata. Participants were masked throughout the conduct of the trial, whereas researchers were aware of the allocation since they were responsible for the TG1, TG2, and ACG sessions. The envelopes containing the group assignment were sealed, numbered sequentially, and were opened only after patients' baseline assessment, thus ensuring that the allocation process was concealed from both participants and researchers.

2.6 | Procedures

Participants in the intervention and control groups were assessed at the pre-intervention baseline (T0), at the end of the intervention (T0 + 2 months: T1), and 6 months after T0 (T0 + 6 months/T1 + 4 months: T2). Patients' demographic information (e.g., sex, age, education) was gathered at the baseline. Data was collected through face-to-face interviews conducted by researchers (health psychologists).

2.7 | Outcomes

The primary outcomes in this study were the DFU healing, and the impact of DFU on QoL, and on physical and mental QoL. Secondary outcomes included perceived stress, psychological morbidity, and illness representations.

2.8 | Measures

2.8.1 | Clinic Questionnaire

This questionnaire was created by the research team (health psychologists and physicians) to gather patients' relevant medical information (e.g., DM duration, diabetic foot type, HbA1c). The patient's physician or nurse completed this questionnaire.

2.8.2 | RESVECH 2.0-PT (Marques 2016)

This scale monitors chronic wound healing progression, from its emergence to complete healing, and has been widely used among Hispanic and Latin American populations. It includes six dimensions (size of the wound, depth/tissue concerned, edges, type of tissue in the wound bed, exudate, and infection/inflammation), with total scores ranging from 0 (healed wound) to 35 (worst possible lesion). RESVECH was used in this study to evaluate DFU healing, with higher scores indicating the worst progression regarding wound healing. The Cronbach's alpha of the Portuguese version was 0.79, and in this study, the Cronbach's alpha was 0.66. Since the questionnaire has a small number of items and the average inter-item correlation (0.24) falls in the range of 0.15–0.50, as recommended by Clark and Watson (2019), internal consistency reliability was considered adequate. This questionnaire was completed by the patient's physician or nurse.

2.8.3 | Diabetic Foot Ulcer Scale-Short Form (DFS-SF; Bann et al. 2003; Pereira et al. 2024)

The Portuguese validation of DFS-SF assesses the impact of the DFU on patients' general QoL through 26 items grouped into six subscales: leisure, physical health, dependence/daily life, negative emotions, worried about ulcers/feet, and bothered by ulcer care. Items are rated on a five-point Likert scale, with higher scores indicating higher QoL. In this study, only the total scale was used, with a Cronbach's alpha of 0.92.

2.8.4 | Short-Form Health Survey (SF-36; Ferreira et al. 2012)

SF-36 measures physical and mental health-related QoL through eight health dimensions: physical function, physical performance, bodily pain, general health perceptions, vitality, social function, emotional performance, and mental health. SF-36 provides physical (PSM) and mental (MSM) summary measures with higher scores indicating better health-related QoL. Items are answered using a Likert scale with three, five, and six options. Internal consistency for the Portuguese version was good (PSM: $\alpha = 0.86$; MSM: $\alpha = 0.87$). In this study, Cronbach's alphas for PSM and MSM were 0.79 and 0.88, respectively.

2.8.5 | Illness Perception Questionnaire-Brief (IPQ-B; Figueiras et al. 2010)

This instrument is an eight-item scale that assesses illness representations through three dimensions: cognitive representations (five items) that include identity, duration, personal control, treatment control, and consequences; emotional representations (two items) that include concern and emotional responses; and comprehensibility consisting of a single item. IPQ-B uses a 0–10 visual analogue scale, and higher scores indicate more threatening illness representations. In this study, IPQ-B was used to assess DFU representations. Since each item represents a subscale, neither the original nor the Portuguese version presents internal consistency coefficients. More recently, Broadbent et al. (2015) have suggested a single coefficient for the global scale. In this study, Cronbach's alpha for the global scale was 0.57. Given that this scale measures a broad construct such as illness representations, includes a small number of items, and presents an average inter-item correlation of 0.18, included in Clark and Watson's criteria for valid scales (between 0.15 and 0.50), (Clark and Watson 2019), the total score was used.

2.8.6 | Perceived Stress Scale (PSS; Trigo et al. 2010)

This instrument consists of 10 items to evaluate perceived stress during the previous month. Items are answered on a five-point Likert scale, and higher scores indicate higher levels of perceived stress. Internal consistency for the Portuguese version was 0.87. In this study, Cronbach's alpha was 0.74.

2.8.7 | Hospital Anxiety and Depression Scale (HADS; Pais-Ribeiro et al. 2007)

This 14-item scale assesses psychological morbidity. HADS includes two subscales: depression (7 items) and anxiety (7 items). Items are rated on a four-point scale, with higher scores indicating higher levels of psychological morbidity (scale), depression, and anxiety (subscales). The Portuguese version presented Cronbach's alphas of 0.81 for depression and 0.76 for anxiety. This study used the global scale, with a Cronbach's alpha of 0.78.

2.9 | Sample Size Calculation

According to Cocks and Torgerson (2013), sample size calculation for pilot studies with continuous outcome measures, assuming the average effect size of 0.50, statistical power of 0.80, and a statistical significance level of 0.05, requires 48 participants i.e., 12 participants per arm. Considering that RCTs involving chronic patients and multiple evaluation moments often report attrition rates from 20% to 30% (Hui et al. 2013), the calculated sample size was increased by 30%, resulting in a sample of 69 participants at baseline.

2.10 | Statistical Analysis

Frequencies, means, and standard deviations were used to describe demographic, clinical, and psychological data. Comparisons between groups and within groups, over time, were performed using mixed general linear models of analysis of variance for repeated measures, and assuming an intention-to-treat approach. Time (T0/T1/T2) and group (TG1/ACG/PCG/TG2), as well as their interaction, were defined as fixed effects, taking TG1 and baseline (T0) as reference. Comparative analyses were carried out controlling for (i) the number of sessions received (0/1/2/3/4), with patients from the PCG receiving zero intervention sessions; (ii) sex (male/female) and (iii) residential area (rural/urban). A p value lower than 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS Statistics software (version 28, IBM Corp., NY, USA) and Rstudio, (version 3.6.2, R Core Team, Vienna, Austria).

3 | Results

3.1 | Sample Characteristics

A sample of 153 patients with one or two chronic DFU(s) was assessed. However, 84 patients did not report significant distress and were not included in the study. A total of 69 distressed patients with T2DM were randomly allocated to one of four groups (Figure 1).

Baseline participants' characteristics are shown in Table 1. DFU healing and psychological descriptive statistics for each group in T0, T1, and T2 are shown in Table S1.

3.2 | Differences Between Groups Across Time Controlling for the Number of Sessions, Sex, and Residential Area

3.2.1 | Primary Outcomes

Significant differences between groups over time were only found in DFU healing (Figure 2). TG1 ($\beta = 4.54$, $p = 0.02$), TG2 ($\beta = 4.30$, $p = 0.03$), and ACG ($\beta = 4.19$, $p = 0.03$) showed more significant improvements than PCG after sessions (T1). During the follow-up period (T2), TG1 revealed more healing improvements than TG2 ($\beta = 3.68$, $p = 0.04$) and PCG ($\beta = 4.30$, $p = 0.03$).

3.2.2 | Secondary Outcomes

Only DFU representations and psychological morbidity showed significant changes between groups across time (Figure 2). DFU representations showed significant differences between intervention groups in T1, with TG1 reporting less threatening DFU representations than TG2 ($\beta = 14.26$, $p = 0.01$). TG1 also showed less threatening DFU representations than ACG in T1 ($\beta = 11.44$, $p = 0.04$). Regarding psychological morbidity, there were also significant differences between intervention groups, with TG2 reporting more psychological morbidity in T1 ($\beta = 5.02$, $p = 0.04$).

3.3 | Differences Within Groups Across Time Controlling for the Number of Sessions, Sex, and Residential Area

Results for primary and secondary outcomes, taking TG1 and T0 as reference, may be found in Tables 2 and 3.

3.3.1 | Primary Outcomes

3.3.1.1 | DFU Healing. Significant improvements were found between T0 and T1 for TG1 ($\beta = -5.88$, $p < 0.001$), TG2 ($\beta = -4.04$, $p < 0.01$), ACG ($\beta = -6.29$, $p < 0.001$), and PCG ($\beta = -3.19$, $p = 0.01$). There were also significant improvements between T0 and T2, in TG1 ($\beta = -8.39$, $p < 0.001$), ACG ($\beta = -8.70$, $p < 0.001$), and PCG ($\beta = -5.95$, $p < 0.001$).

3.3.1.2 | DFU-Related QoL. QoL improved significantly between T0 and T1 in TG1 ($\beta = 15.61$, $p < 0.01$), TG2 ($\beta = 19.41$, $p < 0.01$), and ACG ($\beta = 17.05$, $p < 0.01$). TG1 ($\beta = 17.02$, $p < 0.01$), TG2 ($\beta = 20.80$, $p = 0.02$), and ACG ($\beta = 19.13$, $p = 0.02$) also improved between T0 and T2.

3.3.1.3 | Physical QoL. TG1 ($\beta = 8.17$, $p = 0.04$), TG2 ($\beta = 13.31$, $p < 0.01$), and ACG ($\beta = 14.68$, $p < 0.01$) showed significant improvements from T0 to T1, while all groups showed significant improvements between T0 and T2 (TG1: $\beta = 12.34$, $p < 0.01$; TG2: $\beta = 14.43$, $p = 0.03$; ACG: $\beta = 12.58$, $p = 0.01$; PCG: $\beta = 14.52$, $p = 0.01$). Only PCG improved significantly from T1 to T2 ($\beta = 11.97$, $p = 0.02$).

3.3.1.4 | Mental QoL. TG2 showed a significant improvement from T0 to T1 ($\beta = 12.98$, $p = 0.01$), while ACG showed significant improvements from T0 to T1 ($\beta = 11.87$, $p = 0.02$), and from T0 to T2 ($\beta = 11.68$, $p = 0.04$).

3.3.2 | Secondary Outcomes

3.3.2.1 | DFU Representations. TG1 showed a significant decrease from T0 to T1 ($\beta = -12.84$, $p < 0.01$), with an increase from T1 to T2 ($\beta = 14.06$, $p < 0.01$).

3.3.2.2 | Perceived Stress. TG1, TG2, and ACG showed a significant decrease between T0 and T1 (TG1: $\beta = -5.25$, $p < 0.01$; TG2: $\beta = -7.59$, $p < 0.001$; ACG: $\beta = -7.12$, $p < 0.001$),

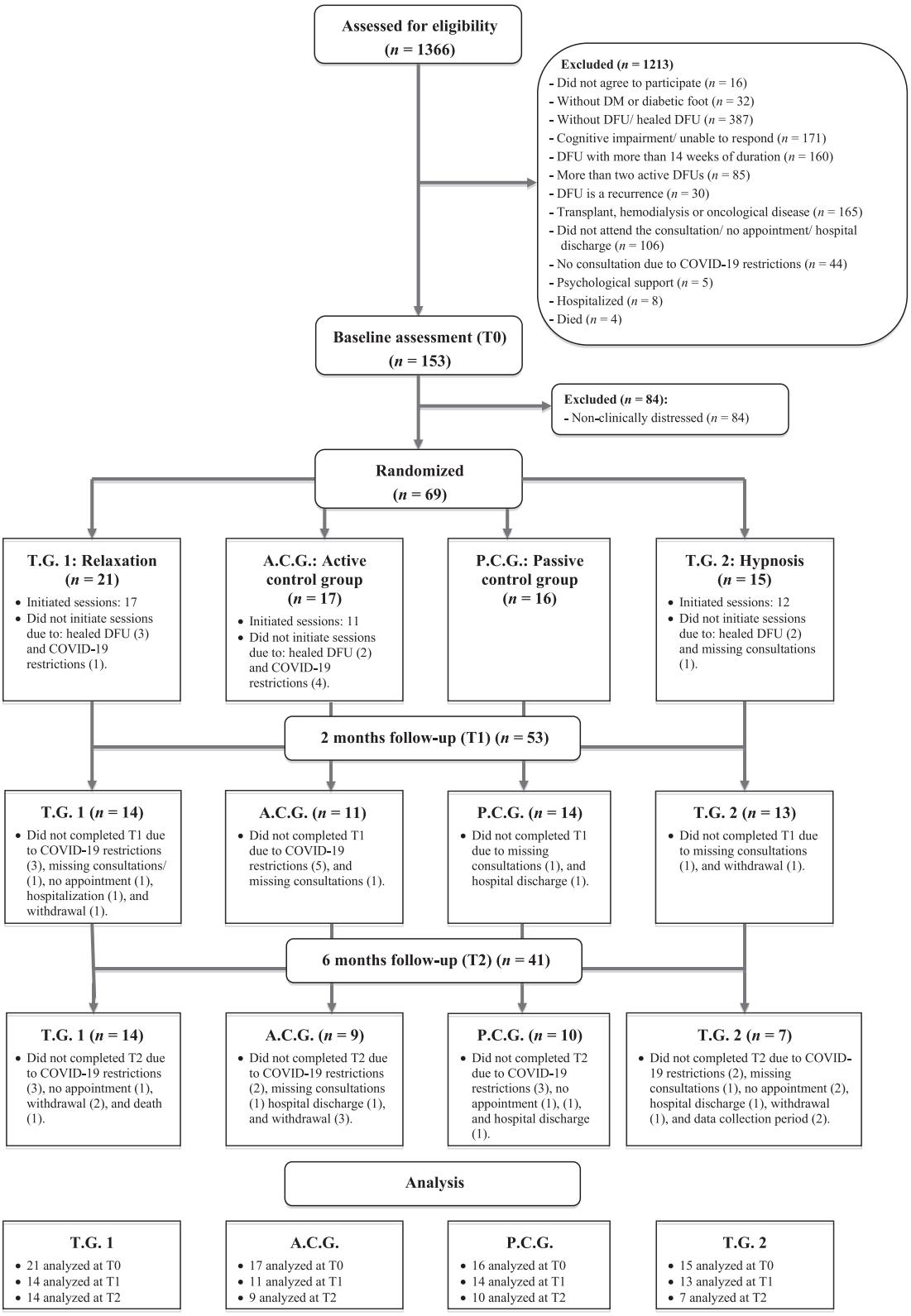


FIGURE 1 | CONSORT flow diagram.

and between T0 and T2 (TG1: $\beta = -4.26$, $p = 0.02$; TG2: $\beta = -10.18$, $p < 0.001$; ACG: $\beta = -8.25$, $p < 0.001$).

3.3.2.3 | Psychological Morbidity. TG1 showed a significant decrease between T0 and T1 ($\beta = -7.45$, $p < 0.001$), and between T0 and T2 ($\beta = -4.18$, $p = 0.04$), while TG2 only decreased significantly between T0 and T2 ($\beta = -7.06$, $p = 0.01$). ACG showed a significant decrease between T0 and T1 ($\beta = -5.68$, $p < 0.01$).

Several models were constructed to test whether the relationship between time and outcome, or between groups and

TABLE 1 | Demographic and clinical characteristics of participants by groups at baseline assessment (T0).

	Total ($n = 69$)	TG1 ($n = 21$)	TG2 ($n = 15$)	ACG ($n = 17$)	PCG ($n = 16$)
			n (%)/M ± SD		
Demographic variables					
Sex					
Female	17 (24.60)	5 (23.8)	7 (46.70)	4 (23.50)	1 (6.30)
Male	52 (75.40)	16 (76.2)	8 (53.30)	13 (76.50)	15 (93.80)
Age (years)	62.14 ± 9.02	62.86 ± 9.66	58.33 ± 10.08	62.71 ± 8.77	64.19 ± 6.90
(min.–max.)	41–80	48–80	41–75	46–73	55–78
≤ 60	30 (43.50)	9 (42.90)	9 (60.00)	6 (35.30)	6 (37.50)
> 60	39 (56.50)	12 (57.10)	6 (40.00)	11 (64.70)	10 (62.50)
Residential area					
Rural	44 (63.80)	16 (76.20)	11 (73.30)	10 (58.80)	7 (43.80)
Urban	25 (36.20)	5 (23.80)	4 (26.70)	7 (41.20)	9 (56.30)
Marital status					
Single/divorced/widowed	21 (30.40)	4 (19.00)	7 (46.70)	5 (29.40)	5 (31.30)
Married	48 (69.60)	17 (81.00)	8 (53.30)	12 (70.60)	11 (68.80)
Education					
≤ Primary	37 (53.60)	12 (57.10)	6 (40.00)	10 (58.80)	9 (56.30)
≤ Secondary	30 (43.50)	8 (38.10)	9 (60.00)	7 (41.20)	6 (37.50)
≤ University	1 (1.40)	1 (4.80)	0 (0.00)	0 (0.00)	0 (0.00)
Professional activity					
Active	15 (21.70)	5 (23.80)	3 (20.00)	3 (17.60)	4 (25.00)
Inactive	54 (78.3)	16 (76.20)	12 (80.00)	14 (82.40)	12 (75.00)
Health literacy					
Adequate	17 (24.60)	5 (23.80)	3 (20.00)	6 (35.30)	3 (18.80)
Inadequate	52 (75.40)	16 (76.20)	12 (80.00)	11 (64.70)	13 (81.30)
Clinical variables					
Diabetes duration (years)	18.33 ± 8.54	19.60 ± 8.77	16.80 ± 7.17	18.94 ± 9.08	17.47 ± 9.38
(min.–max.)	1–42	7–38	5–30	1–30	7–42
Comorbidities	5.01 ± 1.74	5.14 ± 1.59	5.00 ± 1.36	5.06 ± 2.02	4.81 ± 2.04
HbA1c	8.33 ± 2.01	8.20 ± 1.70	9.13 ± 2.42	7.96 ± 1.80	8.11 ± 2.19
(min.–max.)	5.00–14.00	5.00–11.10	6.30–14.00	5.30–11.70	5.50–13.50
Type of diabetic foot					
Neuropathic	40 (58.00)	10 (47.60)	10 (66.70)	11 (64.70)	9 (56.30)
Neuroischemic	29 (42.00)	11 (52.40)	5 (33.30)	6 (35.30)	7 (43.80)
DFU duration (weeks)	8.57 ± 2.57	8.91 ± 2.81	8.07 ± 2.52	9.12 ± 2.74	8.00 ± 2.10
(min.–max.)	6–14	6–14	6–13	6–14	6–13
DFU area	4.13 ± 8.12	3.42 ± 4.17	2.31 ± 4.64	7.63 ± 13.73	3.05 ± 5.98
(min.–max.)	0.01–42.00	0.04–12.21	0.04–18.00	0.04–42.00	0.01–24.00
First DFU in clinical history					
Yes	23 (33.30)	6 (28.60)	6 (40.00)	7 (41.20)	4 (25.00)
No	46 (66.70)	15 (71.40)	9 (60.00)	10 (58.80)	12 (75.00)

(Continues)

TABLE 1 | (Continued)

	Total ($n = 69$)	TG1 ($n = 21$)	TG2 ($n = 15$)	ACG ($n = 17$)	PCG ($n = 16$)
			n (%)/M ± SD		
Previous lower limb amputation					
Yes	52 (75.4)	4 (19.00)	5 (33.30)	5 (29.40)	3 (18.80)
No	17 (24.6)	17 (81.00)	10 (66.70)	12 (70.60)	13 (81.30)

Abbreviations: ACG, active control group; *M*, mean; PCG, passive control group; SD, standard deviation; TG1, treatment group 1 (muscle relaxation); TG2, treatment group 2 (hypnosis).

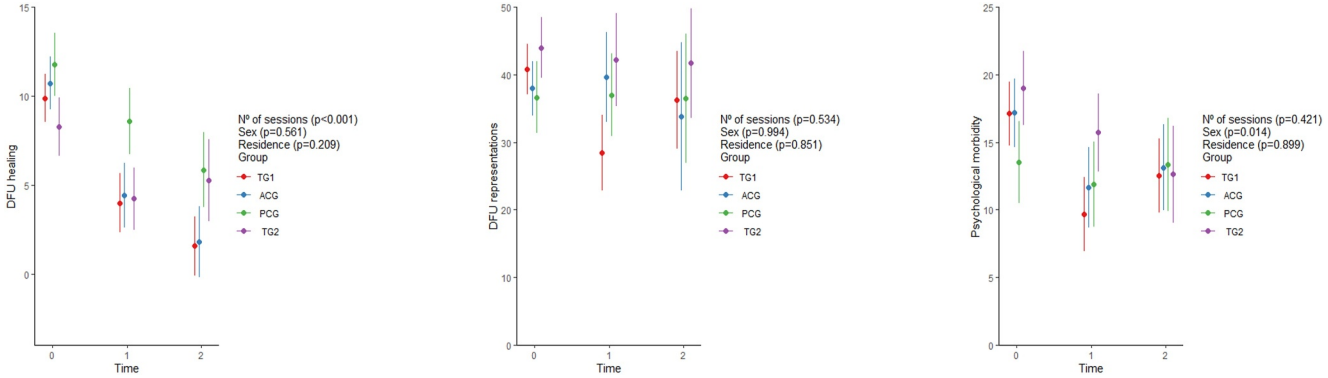


FIGURE 2 | Graphical representations of statistically significant differences between groups across time (estimated means with 95% confidence intervals) for DFU healing scores (RESVECH 2.0-PT) (left), DFU representations (IPQ-B) (middle), and psychological morbidity (HADS) (right).

TABLE 2 | Regression coefficients estimates for the linear mixed-effects model for primary outcomes controlling for number of sessions, sex, and residential area.

	Outcome variables			
	DFU healing (Resvech 2.0) β (SE)	DFU-related QoL (DFS-SF) β (SE)	Physical QoL (SF-36) β (SE)	Mental QoL (SF-36) β (SE)
Intercept	6.703 (1.305)***	64.447 (7.324)***	48.557 (5.973)***	61.117 (7.024)***
T1	−5.879 (1.271)***	15.604 (5.600)*	8.166 (3.830)*	6.210 (4.648)
T2	−8.394 (1.339)***	17.015 (6.314)*	12.339 (4.648)*	0.976 (5.145)
ACG	0.756 (1.393)	−2.527 (7.456)	2.091 (5.936)	0.297 (6.996)
PCG	1.857 (1.641)	1.098 (9.030)	−1.284 (7.300)	−2.495 (8.579)
TG2	−1.603 (1.442)	−2.677 (7.710)	−0.552 (6.138)	−3.123 (7.223)
Nr. of sessions	1.326 (0.280)***	−3.520 (1.645)	−2.901 (1.369)	−2.520 (1.616)
Sex	0.626 (1.075)	−13.441 (6.186)*	−11.047 (5.089)*	13.857 (5.979)*
Residence	1.047 (0.829)	−5.737 (4.908)	1.347 (4.100)	0.980 (4.840)
T1 × ACG	−0.411 (1.902)	1.449 (8.394)	6.513 (5.733)	5.666 (6.969)
T2 × ACG	−0.301 (2.074)	2.118 (9.732)	0.241 (7.075)	10.710 (7.974)
T1 × PCG	2.680 (1.834)	−7.422 (8.046)	−5.824 (5.522)	−2.366 (6.665)
T2 × PCG	2.442 (2.063)	−4.210 (9.805)	1.863 (7.254)	5.046 (7.977)
T1 × TG2	1.840 (1.865)	3.807 (8.175)	5.149 (5.592)	6.770 (6.770)
T2 × TG2	5.278 (2.235)*	3.788 (10.592)	2.093 (7.733)	12.070 (8.657)

Note: Reference group: β-, unstandardised estimates; ACG, active control group; PCG, passive control group; SE, standard error; TG1, treatment group 1 (muscle relaxation); TG2, treatment group 2 (hypnosis).
*$p < 0.05$.
**$p < 0.005$.
***$p < 0.001$.

TABLE 3 | Regression coefficients' estimates for the linear mixed-effects model for secondary outcomes controlling for number of sessions, sex, and residence area.

	Outcome variables		
	DFU representations (IPQ-b) β (SE)	**Perceived stress (PSS) β (SE)**	**Psychological morbidity (HADS) β (SE)**
Intercept	39.577 (3.885)***	16.159 (2.133)***	14.809 (2.329)***
T1	−12.835 (3.757)**	−5.253 (1.648)**	−7.449 (1.634)***
T2	1.228 (5.740)	−4.259 (1.911)*	−4.176 (1.976)*
ACG	−2.584 (3.780)	2.236 (2.172)	0.568 (2.342)
PCG	−4.204 (4.478)	1.587 (2.632)	−1.378 (2.861)
TG2	3.315 (3.923)	3.753 (2.248)	0.854 (2.424)
Nr. of sessions	0.589 (0.943)	1.002 (0.477)	0.426 (0.527)
Sex	0.022 (3.155)	3.011 (1.798)	4.905 (1.976)*
Residence	−0.477 (2.528)	0.340 (1.427)	−0.199 (1.576)
T1 × ACG	14.025 (5.719)*	−1.867 (2.465)	1.761 (2.445)
T2 × ACG	−3.634 (9.292)	−3.987 (2.916)	0.375 (3.003)
T1 × PCG	13.241 (5.157)*	4.940 (2.384)*	5.911 (2.359)*
T2 × PCG	−2.249 (8.443)	0.868 (2.961)	4.094 (3.080)
T1 × TG2	10.496 (5.824)	−2.339 (2.415)	4.158 (2.389)
T2 × TG2	−4.582 (8.442)	−5.922 (3.159)	−2.887 (3.278)

Note: Reference group: β, unstandardised estimates; ACG, active control group; PCG, passive control group; SE, standard error; TG1, treatment group 1 (muscle relaxation); TG2, treatment group 2 (hypnosis).
*$p < 0.05$.
**$p < 0.005$.
***$p < 0.001$.

outcome, changed depending on the number of sessions, sex, and residential area. The results indicated that there was no significant effect of the number of sessions, sex, or residential area in the relationship between time and outcome, or between groups and outcome. However, regarding sex, women showed lower DFU-related QoL ($p = 0.03$), lower physical QoL ($p = 0.03$), more psychological morbidity ($p = 0.01$), and better mental QoL ($p = 0.02$) than men.

4 | Discussion

This pilot RCT aimed to analyse the effectiveness of two stress-reduction interventions in distressed patients with a DFU on a comparative, participant-masked, sham-controlled basis. Participants were mainly older men, all diagnosed with T2DM, which is in line with other studies (Zhang et al. 2017). Almost half of the initial sample (45%) reported significant distress, as expected, considering the prevalence of depression and anxiety among patients with DFU(s) (Jiang et al. 2022; Udovichenko et al. 2017).

Both interventions and active control groups reported more DFU healing improvements than the passive control group after the completion of sessions. However, in the long term, muscle relaxation seemed to be more effective than hypnosis and the active control intervention. Although previous research has shown the effectiveness of relaxation and hypnosis in DM (Deswita et al. 2019; Ebrahem and Masry 2017; Paschali et al. 2020; Pombeiro et al. 2022; Rice et al. 2001), the comparison between both interventions, in patients with DF, had not been previously studied. Within-group analysis showed that both interventions improved DFU healing, DFU-related QoL, and physical QoL. Although few studies have addressed the effects of psychological interventions on nonsurgical wound healing, there is evidence showing promising results regarding the impact of psychological interventions on the reduction of blood glucose and glycated hemoglobin levels in patients with DM (Najafi Ghezeljeh et al. 2017; Paschali et al. 2020; Xu and Cardeña 2008), DFU wound healing (Pombeiro et al. 2022; Rice et al. 2001), and increasing QoL (Ebrahem and Masry 2017; Najafi Ghezeljeh et al. 2017).

Interestingly, only patients who received hypnosis reported improvements in mental QoL. Similar data have been found in studies focused on other chronic diseases (e.g., irritable bowel syndrome, oncological disease, dementia) (Grégoire et al. 2018; Wawrziczny et al. 2021), however, to the best of our knowledge, this is the first RCT study suggesting improvements in mental QoL after hypnosis, in patients with DFU(s).

Muscle relaxation patients reported less threatening DFU representations than hypnosis and active control patients, at T1, which underlies the potential positive effect of relaxation on DFU representations. These results are in line with previous

research indicating that less stressed patients may perceive their health condition more positively and feel more in control of their health, resulting in less threatening DFU representations (Martinez et al. 2018). Patients who received hypnosis showed more psychological morbidity than those who received muscle relaxation at T1, suggesting that muscle relaxation sessions may be effective in reducing psychological morbidity (i.e., depression and stress). According to the findings, one may also hypothesize that four sessions of hypnosis may not have been sufficient to change patients' DFU representations and decrease psychological morbidity. Thus, a future definitive RCT should also assess the optimal number of hypnosis sessions needed for a change to occur when patients with DFU report high psychological morbidity and threatening DFU representations.

According to the within-group analysis, only muscle relaxation showed an impact on DFU representations. In TG1, DFU threatening representations significantly decreased during treatment but increased during follow-up, which may be related to a greater perception of support provided by healthcare professionals, and a perceived internal locus of control during sessions. Although DFU representations were not addressed directly in TG1, the script of muscle relaxation with guided imagery, addressing wound recovery, could have provided patients with a sense of control regarding body healing.

Both intervention groups reported reduced stress perceptions and psychological morbidity. According to previous studies, muscle relaxation sessions can reduce psychological morbidity in patients with DM (Ebrahem and Masry 2017; Paschali et al. 2020), while hypnosis has shown to be effective in reducing general anxiety (Valentine et al. 2019), anxiety associated with cancer, surgery, burns, and a variety of medical/dental procedures (Hammond 2010). Hypnosis has also shown positive effects on stress reduction (Deswita et al. 2019; Fisch et al. 2020), although, due to exploratory designs and the high risk of bias, the effectiveness of hypnosis, in stress reduction, remains equivocal (Fisch et al. 2017).

Patients who received neutral sessions with guided imagery also reported increased DFU healing and QoL, and reduced perceived stress and psychological morbidity, showing similar results to the intervention groups, except for DFU representations. The association between health professionals' empathy, emotional availability, eye contact, and improved health outcomes is well known (Bokhour and Cutrona 2019). Therefore, results suggest that providing time and being emotionally available to listen to patients' personal life narratives (not just DFU narratives) may be important in promoting physical and psychological health outcomes.

Patients from the passive control group showed positive improvements only in DFU healing and physical QoL, in the long-term (between T0 and T2, and between T1 and T2) as expected, due to the standard clinical wound care treatment protocol they received at the hospital (Everett and Mathioudakis 2018). However, the passive control group showed no differences in psychological outcomes emphasising and the importance of the two stress-reduction interventions in DFU patients with DFU(s).

Overall, results suggest that both stress-reduction interventions may be effective in achieving positive changes, although in different ways. Only participants who received muscle relaxation reported significant and sustainable improvements during follow-up, specifically in DFU healing. Also, at T1, muscle relaxation results were more favourable than hypnosis in reducing DFU threatening representations and psychological morbidity. Hypnosis, in turn, was the only stress-reduction intervention that showed improvement in mental QoL. Finally, the neutral intervention (active control group) showed improvements in primary and some secondary outcomes, suggesting the importance of face-to-face contact with a mental health provider (in this case the clinical health psychologist).

This pilot RCT has several limitations such as the modest sample size, particularly at the 6-month follow-up (T2). In fact, the low retention rate at 6-month follow-up (59.4%; $n = 41$) may have reduced the statistical power of analyses. Participants were selected from three of the major hospitals in the northern region of Portugal with a multidisciplinary diabetic foot consultation, which may not represent patients from other regions of the country. Also, the use of multiple strata randomisation with a reduced sample size, as well as the imbalance between male and female patients, may limit the generalisation of the findings. Finally, although linear mixed models help reduce Type I error by incorporating random effects and accounting for within-subject correlations, no formal type I error control was applied in this study.

Definitive RCT studies, using larger samples, should focus on the long-term effects of both interventions, are needed to determine which intervention may be more sustainable in maintaining primary and secondary outcomes, in order to inform healthcare decision-makers about the number of sessions that are needed to ensure the sustainability of outcomes, over time.

5 | Conclusions

In this 6-month trial, both stress-reduction interventions were effective as adjunctive treatments to promote DFU healing and QoL. Muscle relaxation showed a greater impact on DFU healing and DFU representations, while hypnosis showed a greater impact on mental QoL. Patients who received attention from the health psychologist, without any stress-reduction intervention, also reported good outcomes, except on DFU representations, emphasising the importance of psychological interventions, in stress management, regarding changes in DFU representations. Since DFU representations predict mortality in this population (Vedhara et al. 2016), it is important to include stress management techniques in patients' psychological interventions within the multidisciplinary treatment plan for distressed patients with DFU(s). We particularly advocate stress management techniques with a short and long-term impact on different dimensions of QoL, such as the ones tested in the present RCT. Such techniques are very low cost for health institutions and patients may also practice them in between sessions, at their own pace, when needed.

Author Contributions

M.G.P. was responsible for funding acquisition, study conceptualization, and design, supervision, data curation, data interpretation, critical revisions, and editing. M.V. was involved in the literature review, data collection, data interpretation, writing the original draft of the manuscript, and editing. S.P. collaborated in the manuscript writing, data interpretation, and manuscript review. A.C., M.J.D., and A.L. provided input to the trial concept and design, and manuscript review. K.V. was responsible for manuscript review and editing. S.F. was responsible for formal data analyses, data interpretation, and manuscript review. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Tâmega e Sousa Hospital Center (198/2018), the Ethics Committee of the Porto University Hospital Center (2018-205 (180-DEFI/179-CES)), and the Ethics Committee of the Hospital de Braga (20200011_Endocrinologia180620).

Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data presented in this study are available on request from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.