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The 'placebo effect' in the conservative treatment of plantar fasciitis: a systematic review and meta-analysis

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- *Purpose:* The study of the placebo effect is key to elucidate the 'real effect' of conservative interventions for plantar fasciitis. The aim of this meta-analysis was to quantify the impact of placebo in the different conservative treatments of plantar fasciitis.
- *Methods:* A systematic literature review was performed on double-blind placebo-controlled trials (RCTs) according to PRISMA guidelines on PubMed, Embase, and Web of Science. The meta-analysis primary outcome was the 0–10 pain variation after placebo treatments analyzed at 1 week, 1, 3, 6, and 12 months. The risk of bias was assessed using the RoB 2.0 tool, while the overall quality of evidence was graded according to the GRADE guidelines.
- *Results:* The placebo effect for conservative treatments was studied in 42 double-blind RCTs on 1724 patients. The meta-analysis of VAS pain showed a statistically significant improvement after placebo administration of 2.13/10 points ($P < 0.001$), being highest at 12 months with 2.79/10 points ($P < 0.001$). The improvement of the placebo groups was higher in the extracorporeal shock wave therapy studies compared to the injection studies (2.59 vs 1.78; $P = 0.05$). Eight studies had a low risk of bias, 23 studies had 'some concerns,' and 4 studies had a high risk of bias. The GRADE evaluation showed an overall high quality of evidence.
- *Conclusion:* This systematic review and meta-analysis demonstrated that the placebo effect represents an important component of all conservative approaches to treat plantar fasciitis. This effect is statistically and clinically significant, increases over time, and depends on the type of conservative treatment applied to address plantar fasciitis.

Keywords

- plantar fasciitis
- placebo
- heel pain
- conservative treatment

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Introduction

Plantar fasciitis is the most common cause of heel pain, affecting up to 10% of the general population during their lifetime and accounting for a considerable amount of health-care costs (1, 2). The underlying pathology is characterized by the degeneration of the plantar fascia at the medial calcaneal tuberosity (3). This process leads to heel pain and tenderness with gradual onset and exacerbated by weight-bearing (4). Conservative treatments for plantar fasciitis include an array of approaches, including nonsteroidal anti-inflammatory drugs (NSAIDs), heel pads or orthoses, physiotherapy, physical therapies such as extracorporeal shock wave therapy (ESWT), ultrasound therapy, or low-level laser therapy, and injections of corticosteroids, botulinum toxin, or platelet-rich plasma (PRP) (5, 6, 7, 8, 9). These strategies have been widely studied in the literature, reporting on one side positive benefits, but on the other side conflicting and inconsistent results when tested in randomized controlled trials (RCTs) in comparison to the inactive treatments implying that their effect, or at least a part of it, may be due to placebo (6).

The impact of the placebo effect has been already investigated in several musculoskeletal diseases (10, 11) Different features of plantar fasciitis make it prone to a placebo-related improvement. In fact, subjective symptoms unrelated to underlying organic diseases, such

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as pain or fatigue (which are also the main symptoms of plantar fasciitis), are considered to be the most likely to have a placebo response (12). Moreover, a beneficial result occurs most often when the treatment is provided by a caregiver who explains that an improvement is expected, in individuals who are highly receptive to suggestion, and when a given medication is thought to be expensive or technologically modern, common characteristics of several conservative approaches to plantar fasciitis (13, 14). Therefore, a deep comprehension of the placebo effect is key to elucidate the 'real effect' of active conservative interventions for plantar fasciitis. However, the magnitude of the placebo effect for the conservative treatment of plantar fasciitis has been scarcely investigated. Understanding the effect of placebo would help to better plan future studies using placebo as a control and to quantify the real effects of conservative treatments.

The aim of this systematic review and meta-analysis was to quantify the impact of placebo effect for the different conservative treatments of patients affected by plantar fasciitis.

Materials and methods

Screening process and study selection

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search on the placebo effect for the conservative treatment for plantar fasciitis was conducted on PubMed (Medline), Embase, and Web of Science on March 21, 2023, and using the following string: (plantar fasciitis OR plantar fasciopathy OR heel pain) AND (placebo OR saline). Duplicates were removed and, subsequently, all records were checked for eligibility by titles and abstracts based on the following inclusion criteria: double-blind RCT with a placebo control group, written in English language, with no time limitation, reporting clinical results of a placebo intervention for the conservative treatment of plantar fasciitis. Exclusion criteria were articles written in other languages, literature reviews, preclinical studies, non-RCT clinical studies, single-blind or unblinded RCT, and trials not reporting clinical results. In the second step, the full texts of the identified articles were screened, with further exclusions according to the previously described criteria. In addition, the reference lists from the selected papers and previously published relevant reviews were also screened. The screening process and article selection were independently performed by two authors (V.V., A.B.), and any discrepancies between them were resolved by discussion and consensus with a third author (F.V.). A flowchart of the study selection is reported in Fig. 1.

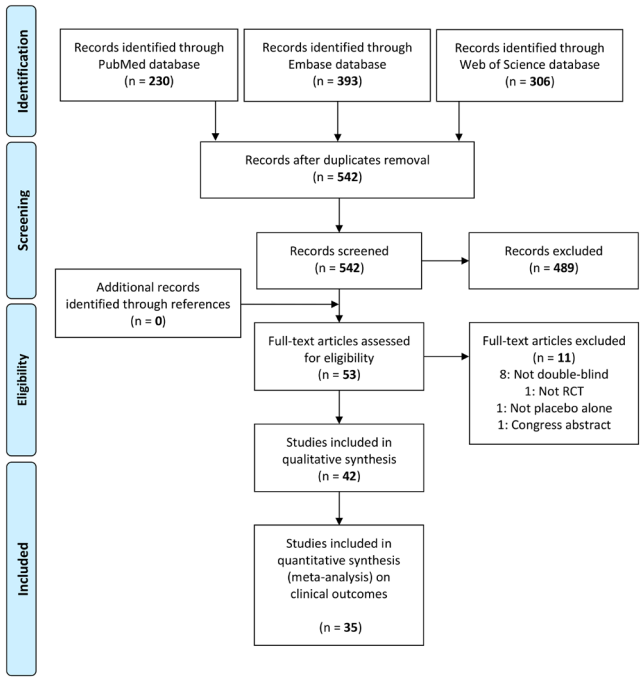

Figure 1
PRISMA flowchart of the study selection process.

Data extraction, outcome measures, and quality assessment

For the included studies, the following information was extracted independently by the two authors (VV and AB): study design, authors, year of publication, inclusion/exclusion criteria, blinding procedure, randomization procedure, follow-up length, and information on the placebo treatment (type, number of administrations, timing) and experimental treatment tested. Moreover, the following data on the study population were extracted: number of patients screened, included, and lost to follow-up; sex, age, body mass index (BMI), associated lesions, previous treatments, symptoms duration, main results, and adverse events. These data were then inserted in a database to be analyzed for the purposes of this study.

The meta-analysis primary outcome was the 0–10 pain variation after placebo treatments. Five different follow-up time points were analyzed: 1 week, 1 month, 3 months, 6 months, and 12 months. Moreover, pooled analyses of other patient reported outcome measurements (PROMs) were not possible due to the heterogeneity of data. In addition, the influence of possible influencing factors on the placebo effects was tested, including age, BMI, sex, length of symptoms, intensity of symptoms at baseline, total length of follow-up, publication year, type of experimental treatment, and improvement in the experimental group.

The risk of bias of the included studies was assessed using the Cochrane Collaboration Risk of Bias 2.0 (RoB

2.0) tool (15), while the overall quality of evidence for each outcome was graded as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. The risk of bias and quality assessment were performed by two separate authors (VV, AB), and discrepancies were resolved through discussion and consensus with a third author (DP).

Statistical analysis

The magnitude of placebo effect in terms of 0–10 VAS pain was evaluated with a meta-analysis grouping the results of the placebo arms of the included studies. An overall analysis was performed computing the results of the longest follow-up of each study. Subanalysis based on specific follow-ups were performed (1 week, 1 month, 3 months, 6 months, 12 months). The studies were grouped based on the type of placebo administered. The placebo effect was expressed as the mean of the improvements from baseline to the different follow-ups. Considering the heterogeneity of the included trials the random effect model was used. Possible influencing factors were analyzed using separate linear meta-regressions. In the meta-regression the influence of the experimental treatment results was computed using the reported Cohen's effect size of the experimental group of the included studies. A multiple meta-regression was not feasible due to the low number of included studies (16). A *P*-value of 0.05 was set as the level of significance. The statistical analysis was performed with meta (v4.9-7, Schwarzer G, 2007) and metafor (v2.1-0, Viechtbauer, W, 2010) packages in RStudio (v1.2.5019; 250 Northern Ave, Boston, MA, USA).

Results

Article selection and characteristics

The initial search resulted in 929 titles from the included databases: among these, 387 were removed because they were duplicate references. Of the remaining 542 articles, 489 were excluded according to the eligibility criteria. Fifty-three articles were assessed for eligibility, but 11 study were excluded because eight were not double-blind RCTs, one was not an RCT study, one did not include a placebo alone arm, and one was a congress abstract. Thus, 42 double-blind placebo-controlled RCTs on the conservative treatment for plantar fasciitis were included in the qualitative data synthesis and their details are reported in Table 1. Since the first reports in 1996, the publication trend increased over time, with a peak of 13 articles published between 2016 and 2020, although only one study has been published in the last 2 years, as shown in Fig. 2.

The 42 articles included in the systematic review evaluated the placebo effect for different conservative treatments for plantar fasciitis: 14 studies focused on ESWT (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30), 13 studies on injective treatments (five on botulinum toxin injection (4, 5, 31, 32, 33), 2 on steroid injection (34, 35), two on PRP versus steroids injection (36, 37), one on PRP injection (38), one on HA injection (39), one on prolotherapy (40), and one on polydeoxyribonucleotide injection (41), three studies on low-level laser therapy (42, 43, 44), two on ultrasound treatment (45, 46), two on iontophoresis (47, 48), two on oral administration therapy with individualized homeopathic medicines (49) or oral NSAIDs (50), one on pulsed radiofrequency electromagnetic field therapy (51), one on intracorporeal pneumatic shock therapy (52), one on electrolysis therapy (53), one on topical wheatgrass cream (54), one on local heating administration (55), and one study on magnetized insoles (56). A total of 1724 patients were included in the placebo arms: 1037 received placebo ESWT, 329 placebo injections, 62 placebo low-level laser therapy, and the other 296 received other placebo treatments. The final follow-up of the included studies ranged from 4 h to 24 months (median: 3 months) after treatment.

The most commonly used score was VAS for pain, evaluated in all studies excepted one. Other considered scores were: the Roles and Maudsley score (RMS) in 11 articles, the American orthopedic foot and ankle score (AOFAS) in four articles, the SF12 in three studies, the foot and ankle ability measure (FAAM) score in two studies, the foot function index (FFI) score in two studies, the Maryland Foot Score (MFS) in two studies, the foot and ankle computerized adaptive test (CAT) in one study, the Manchester-Oxford Foot Questionnaire (MOXF-Q) score in one study, and the Short Form (SF-36) Health Survey score in one study. Safety was documented by 26 out of 42 studies, with no severe adverse events during the follow-up periods in all treatment and control groups. No adverse reactions were documented in 16 studies, while 10 studies reported mild to moderate adverse reactions as pain, skin reddening, or swelling at the site of application therapies such as injection or extracorporeal shock waves, which spontaneously resolved. The other 16 studies did not report whether complications or adverse reactions occurred.

Quantitative analysis of the placebo effect

Out of 42 studies, 35 were included for the meta-analysis. VAS pain was the only score analyzed since the other scores were heterogeneously reported hindering the possibility to perform a meta-analysis. The overall meta-analysis, including all the 35 studies which reported VAS

Table 1 Characteristics of the included studies.

Reference	Placebo type	Experimental product	Patients on placebo,*n*	FU length	Scales used	Results
Abbasian *et al.* (31)	Injective	BTA injection	16	12 months	AOFAS, VAS	BTA injection provided a significant functional and subjective improvement compared with the placebo group at 1 year.
Ahmad *et al.* (5)	Injective	BTA injection	25	12 months	FAAM, VAS	Patients treated with BTA injection had significant better results at 12 months than those who received saline.
Babcock *et al.* (4)	Injective	BTA injection	21	2 months	MFS, PR-VAS, VAS	BTA injection yielded significant improvements in pain relief and overall foot function at both 3 and 8 weeks after treatment.
Ball *et al.* (34)	Injective	Methylprednisolone injection	21	3 months	VAS	Steroid injection showed a clear benefit over placebo at 6 weeks and this difference was maintained at 12 weeks.
Basford *et al.* (42)	Laser therapy	Low-intensity laser	15	2 months	VAS	Low-intensity laser irradiation appears safe but, at least within the parameters of this study, is not beneficial in the treatment of plantar fasciitis.
Brook *et al.* (51)	PRFT	PRF	28	1 week	VAS	PRFT appeared to offer a simple, drug-free, noninvasive therapy to reduce the pain associated with plantar fasciitis.
Buchbinder *et al.* (17)	ESWT	ESW	85	3 months	MFS, SF-36, VAS	No evidence to support a beneficial effect on pain, function, and quality of life of ultrasound-guided ESWT over placebo in patients
Crawford & Snaith (45)	US therapy	US	10	1 month	VAS	Therapeutic US is no more effective than placebo in the treatment of plantar heel pain.
Dogramaci *et al.* (52)	IPST	Pneumatic lithotripter	25	6 months	VAS	This study shows that the intracorporeal mechanical shock therapy is effective in treating chronic plantar fasciitis.
Donley *et al.* (50)	Oral therapy	NSAIDs	17	6 months	FFI	The use of an NSAID may increase pain relief and decrease disability in patients with plantar fasciitis.
Fernández-Rodríguez *et al.* (53)	Electrolysis therapy	Percutaneous needle electrolysis	33	6 months	FAAM, NPRS	Percutaneous needle electrolysis improved pain and function with better results compared with the control group.
Gerdesmeyer *et al.* (18)	ESWT	ESW	122	12 months	VAS	Radial ESWT significantly improves pain, function, and quality of life compared with placebo.
Gerdesmeyer *et al.* (30)	ESWT	ESW	53	1.5 months	RMS, VAS	Change scores of pain ratings were significantly higher in the blinded placebo group than in the unblinded placebo group.
Gollwitzer *et al.* (19)	ESWT	ESW	20	3 months	RMS, VAS	ESWT displayed relative superiority in comparison with the sham intervention.
Gollwitzer *et al.* (20)	ESWT	ESW	124	3 months	RMS, VAS	The present study confirmed both significant and clinically relevant superiority of ESWT compared with the placebo.
Gudeman *et al.* (48)	Iontophoresis	Iontophoresis of dexamethasone	20	1 month	MFS	Patients who underwent iontophoresis experienced greater immediate relief of symptoms than those treated with traditional modalities alone.
Haake *et al.* (21)	ESWT	ESW	137	12 months	RMS	No clinically relevant difference was found in success rates between therapy and placebo up to 1 year.
Huang *et al.* (32)	Injective	BTA injection	25	3 months	VAS	BTA is effective in the treatment of foot pain associated with plantar fasciitis.
Ibrahim *et al.* (23)	ESWT	ESW	25	6 months	RMS, VAS	ESWT was a safe, effective, and easy treatment for patients with chronic plantar fasciitis.
Ibrahim *et al.* (22)	ESWT	ESW	25	24 months	RMS, VAS	The use of ESWT is effective and safe, leading to a significant, long-term reduction in pain, without adverse effects.
Johnson-Lynn *et al.* (38)	Injective	PRP injection	14	12 months	VAS	This pilot study has not produced evidence of significant benefit for the use of PRP, over normal saline, in the treatment of plantar fasciitis.
Katzap *et al.* (46)	US therapy	US	26	1 month	Foot and Ankle, CAT, NPRS	Contrary to our hypothesis, the addition of active therapeutic US therapy does not improve the efficacy of plantar fasciitis treatment.
Kim *et al.* (41)	Injective	PDRN injection	20	3 months	MOXFQ, VAS	PDRN injection is an efficient and safe therapeutic option for the treatment of chronic plantar fasciitis.
Kiritsi *et al.* (43)	Laser therapy	Low-intensity laser	15	1.2 months	VAS	Laser therapy may contribute to plantar fasciitis healing and pain reduction.
Kudo *et al.* (24)	ESWT	ESW	56	3 months	AOFAS, MRS, SF12, VAS	ESWT is a safe and effective treatment for patients who have failed previous conservative nonsurgical treatments for chronic plantar fasciitis.
Kumai *et al.* (39)	Injective	HA injection	59	1.2 months	RMS, VAS	HA injections contributed to alleviation of pain in patients with plantar fasciopathy and improvement in their activities of daily living.

(*Continued*)

Table 1. Continued.

Reference	Placebo type	Experimental product	Patients on placebo,*n*	FU length	Scales used	Results
Macias *et al.* (44)	Laser therapy	Low-intensity laser	32	2 months	FFI, VAS	These data have demonstrated that low-level laser therapy is a promising treatment of plantar fasciitis.
Mahindra *et al.* (37)	Injective	PRP or steroid injection	25	3 months	AOFAS, VAS	PRP and corticosteroid injections were effective at 3 weeks and 3 months of follow-up, with significant clinical improvement.
Malay *et al.* (25)	ESWT	ESW	57	3 months	VAS	Greater qualitative improvements in activity and function in the ESWT group were observed compared with the placebo group.
Mansiz-Kaplan *et al.* (40)	Injective	Dextrose injection	33	3 months	FFI, VAS-Activity, VAS-Rest	Dextrose prolotherapy has efficacy up to 15 weeks and can be used as an alternative method in the treatment of chronic resistant plantar fasciitis.
Marks *et al.* (26)	ESWT	ESW	9	6 months	RMS, VAS	There was lack of evidence for the efficacy of ESWT when compared to sham therapy.
McMillan *et al.* (35)	Injective	Dexamethasone injection	41	3 months	FHSQ	A single dexamethasone injection is a safe and effective short-term treatment for plantar fasciitis, providing better pain relief than placebo.
Ogden *et al.* (27)	ESWT	ESW	126	3 months	VAS	The success rate in subjects who received active treatment at 12 weeks was 56% higher than the success rate for patients who received placebo treatment.
Ogden *et al.* (28)	ESWT	ESW	145	12 months	VAS	There is ample evidence that ESWT is an effective treatment of chronic plantar fasciitis when compared with placebo.
Osborne *et al.* (47)	Iontophoresis	Iontophoresis of dexamethasone or acetic acid	10	4 months	VAS	This study found that a protocol of six treatments of acetic acid iontophoresis combined with taping provides greatest relief of the stiffness symptoms.
Peterlein *et al.* (33)	Injective	BTA injection	20	4.5 months	VAS	No statistically significant differences were observed between BTA injection and placebo group in patients with refractory plantar fasciitis.
Petrofsky *et al.* (55)	Local heating	Heat	10	4 h	VAS	Continuous heat on the trigger points to the foot resulted in significant pain relief.
Shahid *et al.* (49)	Oral therapy	Homeopathic drugs	38	3 months	FFI	Homeopathic medicine acted significantly better than placebo in the treatment of plantar fasciitis.
Shetty *et al.* (36)	Injective	PRP or steroid injection	30	18 months	RMS, SF-12, VAS	Both PRP and steroids significantly improved the clinical scores versus placebo treatment in the short and long term.
Theodore *et al.* (29)	ESWT	ESW	74	3 months	AOFAS, RMS, SF12, VAS	ESWT represents a safe treatment option for chronic proximal plantar fasciitis.
Winemiller *et al.* (56)	Insoles	Magnetic insole	44	2 months	VAS	Static magnetic insoles were ineffective in the treatment of plantar heel pain.
Young *et al.* (54)	Topical application	Wheatgrass cream	38	3 months	VAS	Topical wheatgrass cream is no more effective than a placebo cream for the treatment of chronic plantar fasciitis.

AOFAS, American Orthopaedic Foot & Ankle Society; BTA, botulinum toxin A; ESWT, extracorporeal shock wave therapy; FAAM, Foot and Ankle Ability Measure; FFI, Foot Function Index; FHSQ, Foot Health Status Questionnaire; FU, follow-up; HA, hyaluronic acid; IPST, intracorporeal pneumatic shock therapy; MOXFQ, Manchester – Oxford Foot Questionnaire; NPRS, Numeric Pain Rating Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; PDRN, polydeoxyribonucleotide; PRFT, pulsed radiofrequency therapy; PRP, platelet-rich plasma; RMS, root mean square; Short Form Survey, SF-12; US, ultrasound; VAS, Visual Analog Scale.

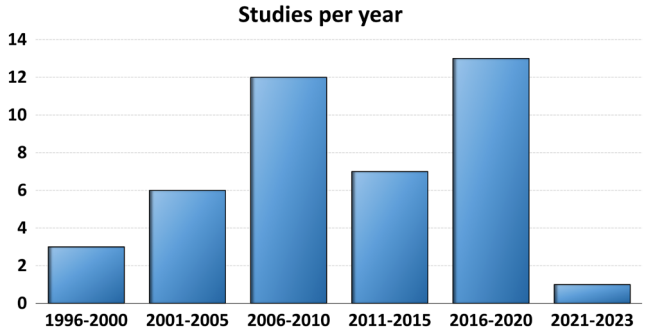

Figure 2
Double-blind placebo-controlled RCTs on the conservative treatment for plantar fasciitis published over the years.

pain, showed a statistically significant improvement after placebo administration of 2.13/10 points ($P < 0.001$). All the subanalyses based on the length of follow-up showed a significant improvement after placebo administration.

The subanalysis at 1 week included six trials and showed an improvement of 0.84/10 points ($P = 0.005$), the subanalysis at 1 month included 21 trials and showed an improvement of 1.55/10 points ($P < 0.001$), the subanalysis at 3 months included 23 trials and showed an improvement of 2.03/10 points ($P < 0.001$), the subanalysis at 6 months included eight trials and showed an improvement of 1.96/10 points ($P < 0.001$), the subanalysis at 12 months included eight trials and showed an improvement of 2.79/10 points ($P < 0.001$) (Figs 3 and 4).

The improvement of the placebo groups was higher in the ESWT studies compared to the injection studies (2.59 vs 1.78; $P = 0.05$); the other treatments were not directly compared due to the number of trials in which they were analyzed. Age, BMI, sex, length of symptoms, intensity of symptoms at baseline, improvement in the experimental group, and year of publication did not significantly influence the magnitude of placebo effect.

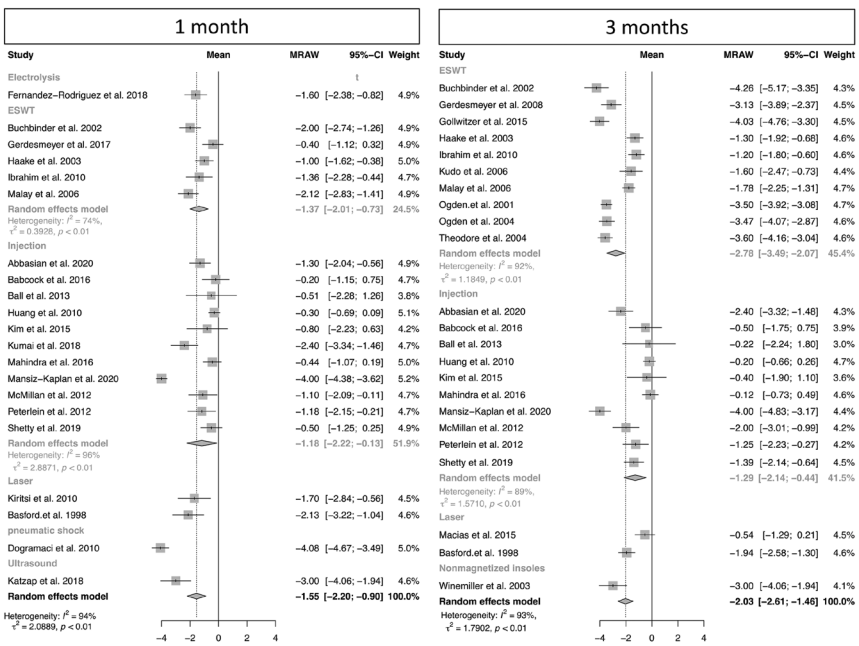

Figure 3
Meta-analysis of the placebo effect at 1 month (left) and 3 months (right).

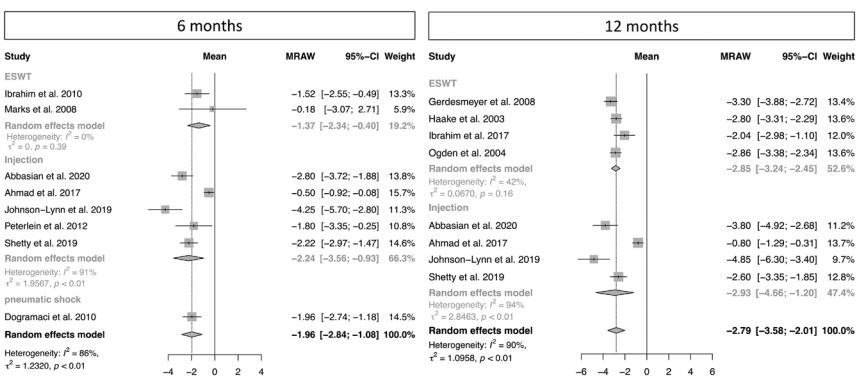

Figure 4
Meta-analysis of the placebo effect at 6 months (left) and 12 months (right).

Risk of bias of the included studies

A summary of the risk of bias assessment of the included studies in the meta-analysis is illustrated in Fig. 5. Eight studies had a low risk of bias, 23 studies had 'some concerns,' and 4 studies had a high risk of bias. The GRADE evaluation showed that the quality of evidence was high for VAS overall, moderate for VAS at 1, 3, and 12 months, low for VAS at 6 months, and very low for VAS at 1 week (Table 2).

Discussion

The main finding of this systematic review and meta-analysis is that the placebo effect represents an important component of the conservative options for the treatment of plantar fasciitis. This effect is statistically significant, increases over time, and depends on the type of treatment being greater for ESWT therapy.

Conservative treatments are considered the first line approach to address symptoms of plantar fasciitis with a growing interest for new approaches, as shown by the large number of studies conducted in the last years, with over 40 published double-blind RCTs. This confirms that plantar fasciitis research is very active for the identification of new effective solutions, being this disease very common and debilitating, involving both athletes and the general population (1, 2). Recently, an increasing number of systematic reviews and meta-analyses investigated the efficacy of different conservative options, reporting overall positive outcomes for these treatments (9, 57, 58, 59). Nevertheless, the results of these studies are often conflicting or inconsistent, making it a challenge for physicians to apply their findings to select the treatment approach in the clinical setting (6). An important aspect that could explain the heterogeneous reported results is the presence of placebo effect, which affects differently the results of the analyzed conservative treatments.

The results of this meta-analysis demonstrated that placebo has a crucial role in the conservative treatment of patients with plantar fasciitis. The contribution of placebo effect in terms of pain relief is highly relevant, being not only statistically but also clinically significant. In fact, the overall benefit ascribable to the placebo effect exceed the minimal clinically important difference of 1.8 previously reported for the 0–10 VAS for foot problems (60, 61). This finding is of high clinical relevance and questions the real efficacy of the conservative treatments used for the management of plantar fasciitis. In fact, an improvement reported after a hypothetically effective treatment, even if statistically and clinically significant, could be attributable also to the placebo effect. Therefore, the results of this meta-analysis, quantifying the large placebo component of conservative therapies, underline the importance of placebo-controlled trials to establish the real effectiveness of an experimental treatment for patients with plantar fasciitis. Only conservative options that exceed statistically and clinically the placebo effect should be considered relevant for the clinical practice.

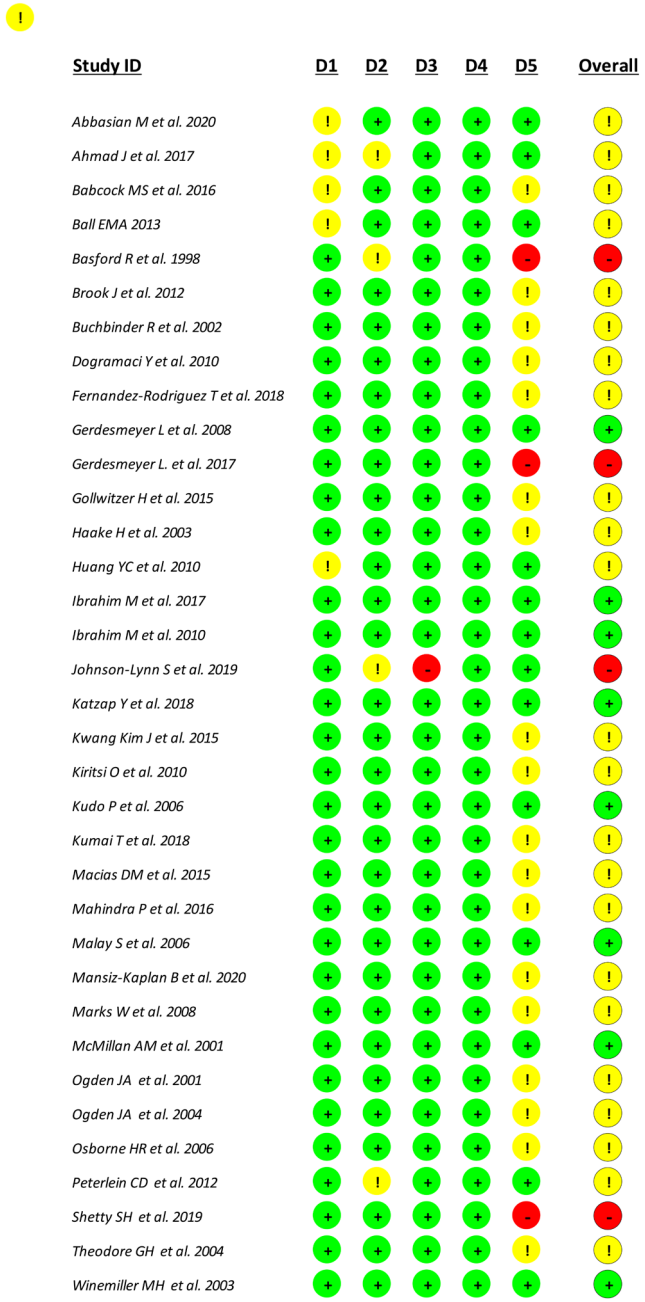

Figure 5
Assessment of risk of bias for randomized controlled trials. Green and red colors correspond to low and high risk of bias, respectively. Yellow represents some concerns. D1, Randomization process; D2, Deviations from the intended interventions; D3, Missing outcome data; D4, Measurement of the outcome; D5, Selection of the reported result.

Table 2 Grade evaluation for VAS pain.

VAS	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrades	Level of evidence
Overall	No	Yes	No	No	No	No	High
1 week	Yes	Yes	No	Yes	No	No	Very low
1 month	No	Yes	No	No	No	No	Moderate
3 months	No	Yes	No	No	No	No	Moderate
6 months	Yes	Yes	No	No	No	No	Low
12 months	No	Yes	No	No	No	No	Moderate

VAS, Visual Analog Scale.

Further insights are offered by the subanalysis based on the length of follow-up, which documented an increasing placebo effect over time, with the highest improvement in VAS pain after placebo treatment found at 12 months. An explanation for this finding may be sought in the natural history of plantar fasciitis. In fact, this disease is often self-limiting with over than 80% of affected patients gaining complete resolution within 12 months (62, 63). In this scenario, the natural history of plantar fasciitis and the frequent spontaneous symptom improvement may be important confounder factors in determining the efficacy of a specific treatment over time, as well as the magnitude of the placebo effect related to that treatment (64). Therefore, the higher placebo effect observed at longer follow-up is not only attributable to placebo but also to the characteristics of the plantar fasciitis disease. Another factor that could affect the clinical response to placebo treatment over time is the so-called Hawthorne-like effect (65). In fact, it has been demonstrated that patients included in clinical trials modify their behaviors to more appropriate habits, thus reporting progressive symptoms benefits not only due the treatment or the placebo effects (65).

Even though the natural history of the disease and the potential 'Hawthorne-like effect' suggest the presence of a 'perceived' placebo effect instead of a 'real' placebo effect, at the same time, an influence of the type of placebo administered was documented. According to the result of this meta-analysis, the placebo effect seems to be affected by the type of treatment, with ESWT having a larger placebo effect. This is possibly due to the fact that patients perceive this procedure as technologically more advanced than other conservative measures and thus potentially more effective, hence developing greater expectations of relief (66, 67), a typical feature of a 'real' placebo effect. This finding further underlines the importance of double-blind placebo-controlled trials in the evaluation of the real effectiveness of new appealing therapeutic approaches.

Injection therapies also presented a high benefit in placebo control groups. Beside 'perceived' and 'true' placebo effects, it has also been suggested that saline, which is commonly used in control groups of placebo-controlled trials on injective procedures, could provide disease-modifying effects on the plantar fascia tissue. Chiavaras *et al.* suggested that the chronic degenerative process characterizing plantar fasciitis might be disrupted by the mechanical injury of the needle and saline solution, which can produce localized bleeding and fibroblastic proliferation (68). Cagnie *et al.* reported that needling induced the release of vasoactive substances, which cause vasodilatation of small vessels, increasing blood flow and oxygenation in the application area (69). In this light, at least part of the effect of saline injections could not be due to placebo effect but to an active effect of the procedure itself. A recent systematic review and meta-analysis questioned the possible disease-modifying effects of this procedure in patients with plantar fasciitis, demonstrating that, beside the beneficial effect on pain and function, saline injections did not lead to a significant objective effect on plantar fascia thickness (70). While interesting, these findings could be prone to bias due to the inclusion in the evaluation also of the results of unblinded RCTs, a key factor in the evaluation of placebo effect. Regardless of being due to placebo or an active effect, the results of the present systematic review and meta-analysis confirm the beneficial effect of saline injections, underlining their statistical and clinical significance. Moreover, the subanalyses based on the type of placebo showed that improvement after placebo administration is present not only for saline injections but also for other types of placebo and is even significantly higher for placebo ESWT.

In addition to length of follow-up and type of placebo treatment, other factors could be at play. Previous studies investigated other possible factors influencing the placebo effect. Weimer *et al.* (71) suggested that both disease-specific as well as disease-unspecific factors can influence the response to placebo treatment in RCTs. In particular, the most predictive individual factor for a higher placebo response was a low symptom severity at baseline (72). This finding was not confirmed in the present study, where, according to the meta-regression performed, factors related to patients and trials characteristics such as age, BMI, gender, length of symptoms, intensity of symptoms at baseline, and improvement in the experimental group did not significantly influence the magnitude of the placebo effect. Future studies should investigate the

role of influencing factors on the placebo response to treatment to better understand its role in the conservative treatment of plantar fasciitis since the results of the meta-regression could be limited due to the heterogeneity of the included trials.

The heterogeneity of the included studies, with different placebo treatments analyzed and differences also within studies with the same placebo treatment in terms of administration protocols, is the main limitation of this systematic review and meta-analysis. Nevertheless, the inclusion of double-blind RCTs produced strong evidence supporting the magnitude and clinical relevance of the placebo effect for the conservative treatment of plantar fasciitis. Moreover, the included studies used different scores with a different length of follow-up. This hindered the possibility to perform a subanalysis on specific functional scores, even though the meta-analysis on VAS for pain could be performed providing important information on placebo effect regarding pain, the most representative symptom of plantar fasciitis. Another limitation of this study is the difficulty in accounting for factors such as the study context, physician attitude, and patient mood, that play a key role in determining the placebo effect. The influence of these factors on the magnitude of placebo effect and their potential benefit in increasing the effectiveness of active treatment needs further insights. Despite the aforementioned limitations, this meta-analysis documented and quantified the placebo effect in terms of pain relief for the conservative treatment of plantar fasciitis, as well important influencing factors. While the mechanism and the determinants of this effect remain uncertain, the placebo effect has shown to be clinically relevant and persistent over time when treating patients affected by plantar fasciitis.

Conclusions

This systematic review and meta-analysis demonstrated that the placebo effect represents an important component of all conservative approaches to treat plantar fasciitis. This effect is statistically and clinically significant, increases over time, and depends on the type of conservative treatment applied to address plantar fasciitis.

ICMJE conflict of interest statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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