





# Therapeutic use of pulsed electromagnetic field therapy reduces prostate volume and lower urinary tract symptoms in benign prostatic hyperplasia

Marta Tenuta<sup>1</sup>  | Maria G. Tarsitano<sup>1</sup> | Paola Mazzotta<sup>1</sup> | Livia Lucchini<sup>1</sup> | Franz Sesti<sup>1</sup> | Giorgio Fattorini<sup>1</sup> | Carlotta Pozza<sup>1</sup> | Valerio Olivieri<sup>1</sup> | Fabio Naro<sup>2</sup> | Daniele Gianfrilli<sup>1</sup>  | Andrea Lenzi<sup>1</sup> | Andrea M. Isidori<sup>1</sup>  | Riccardo Pofi<sup>1</sup> 

<sup>1</sup>Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

<sup>2</sup>Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy

## Correspondence

Andrea M. Isidori, Department of Experimental Medicine, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy.  
Email: andrea.isidori@uniroma1.it

## Funding information

This study was funded by Amico Andrologo Onlus, Italy through a contribution by the Parsemus Foundation, San Francisco, California, USA; "Sapienza" University of Rome, Italy. Open-access publication of this manuscript was funded by the Parsemus Foundation.

## Abstract

**Background:** Benign prostatic hyperplasia (BPH) etiology remains poorly understood, but chronic low-grade inflammation plays a role. Pulsed electromagnetic field therapy (PEMF) (1-50 Hz) is effective in reducing tissue inflammation.

**Objectives:** We designed a pilot study to evaluate the effects of PEMF on prostate volume (PV) in BPH.

**Materials and Methods:** This is a prospective interventional trial on 27 naive patients with BPH and lower urinary tract symptoms (LUTS). At baseline ( $V_0$ ), all patients had blood tests, transrectal ultrasound, and questionnaires (IPSS, IIEF-15) and received a perineal PEMF device (Magcell<sup>®</sup> Microcirc, Physiomed Elektromedizin). PEMF was delivered on perineal area 5 minutes twice daily for 28 days, then ( $V_1$ ) all baseline evaluations were repeated. Afterward, nine patients continued therapy for 3 more months (PT group) and 15 discontinued (FU group). A 4-month evaluation ( $V_2$ ) was performed in both groups.

**Results:** A reduction was observed both at  $V_1$  and at  $V_2$  in PV:  $PV_{V_0}$  44.5 mL (38.0;61.6) vs  $PV_{V_1}$  42.1 mL (33.7;61.5,  $P = .039$ ) vs  $PV_{V_2}$  41.7 mL (32.7;62.8,  $P = .045$ ). IPSS was reduced both at  $V_1$  and at  $V_2$ :  $IPSS_{V_0}$  11 (5.7;23.2) vs  $IPSS_{V_1}$  10 (6;16,  $P = .045$ ) vs  $IPSS_{V_2}$  9 (6;14,  $P = .015$ ). Baseline IPSS was related to IPSS reduction both at  $V_1$  ( $r_s = 0.313$ ;  $P = .003$ ) and at  $V_2$  ( $r_s = 0.664$ ;  $P < .001$ ). PV reduction in patients without metabolic syndrome ( $\Delta PV_{V_1 \text{ in MetS}}$  -4.7 mL, 95%CI -7.3;-2.0) was greater than in affected patients ( $\Delta PV_{V_1 \text{ MetS}}$  1.7 mL, 95%CI -2.69;6.1) ( $P = .017$ , Relative Risk<sub>MetS</sub> = 6). No changes were found in gonadal hormones or sexual function.

**Discussion:** PEMF was able to reduce PV after 28 days of therapy. Symptoms improved in a short time, with high compliance and no effects on hormonal and sexual function or any side effects. Patients with moderate-severe LUTS and without MetS seem to benefit more from this treatment.

Marta Tenuta and Maria Grazia Tarsitano equally contributed to this study.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. Andrology published by Wiley Periodicals, Inc. on behalf of American Society of Andrology and European Academy of Andrology

**Conclusion:** PEMF reduces PV and improves LUTS in a relative short time, in BPH patients. These benefits seem greater in those patients with moderate-severe LUTS but without MetS.

**KEYWORDS**

BPH, LUTS, PEMF, prostate volume, IPSS, inflammation

## 1 | INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prostate volume (PV) enlargement due to a non-malignant cellular proliferation of the parenchyma and stroma of the gland, mainly in the transition area. BPH is a common age-related pathology, often causing lower urinary tract symptoms (LUTS) due to compression of the urethra by the enlarged prostate, which reduces the quality of life of affected patients.<sup>1,2</sup>

The underlying etiology is not completely understood yet. Risk factors include age, diabetes, cardiovascular disease, hypertension, and metabolic syndrome (MetS).<sup>3</sup> Due to the wide expression of androgen receptors (AR), hormonal stimulation of prostate growth may play a role<sup>4</sup>: This is mainly due to dihydrotestosterone (DHT), an active metabolite with a higher affinity for the AR compared with testosterone. However, the most supported etiological hypothesis for BPH identifies inflammatory damage<sup>5,6</sup> as the trigger for subsequent fibrosis and tissue hypoxia resulting in structural changes in the prostate.<sup>7,8</sup> To confirm this, some histological studies have shown intraprostatic inflammatory infiltration in 43%-98% of BPH tissues.<sup>9,10</sup> During inflammation, in fact, mitogen substances (cytokines, growth factors) are released, causing abnormal proliferation of prostatic cells and stroma<sup>11,12</sup> (Figure 1). The net result is the triggering of a vicious cycle of inflammation-fibrosis-hypoxia-inflammation which in turn causes glandular remodeling, alteration of prostatic architecture, and adenoma's growth. This etio-pathogenetic hypothesis represents the rationale of our study.

Pulsed electromagnetic field therapy (PEMF) consists of low-frequency pulsed energy waves (1-50 Hz)<sup>13</sup> that have been employed for many therapeutic purposes mainly because of its anti-inflammatory effect.<sup>14</sup> Moreover, many studies have shown that it is a safe procedure, without side effects.<sup>15</sup>

The biophysical mechanism of PEMF efficacy is likely to involve an electrochemical model of the cell membrane<sup>16</sup> with intracellular pathways that promote angiogenesis, vasodilatation, and tissue remodeling. The overall effect is reduction in tissue hypoxia<sup>17</sup> (Figure 1).

Traditional BPH treatment, together with lifestyle changes,<sup>18</sup> includes medical and surgical therapy.<sup>19,20</sup> However, they are both expensive<sup>21</sup> and can have side effects<sup>22</sup> (anejaculation, erectile dysfunction, surgery risks). These factors have led to a growing interest in alternative, non-invasive procedures for BPH treatment. To date, two studies have used PEMF in BPH treatment, with different in-office devices, study designs, and outcomes.<sup>23,24</sup>

The aim of our study was to evaluate the efficacy of magneto-therapy on BPH using a patient-applied handheld PEMF device: the main outcome measure was PV reduction after 28 consecutive days

of PEMF therapy. Secondary outcomes were changed in PV after 4 months and changed in LUTS during treatment.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

This is a longitudinal, prospective, interventional pilot study performed in Policlinico Umberto I, Rome, Italy.

We selected 27 male Caucasian patients with diagnosis of BPH and/or referring LUTS among those who underwent an andrological examination from April to December 2018 in our Unit. All patients signed a written informed consent before enrollment.

Exclusion criteria were as follows: any medical treatment for LUTS, androgens, gonadotropins, or cortisone therapy; previous prostatic surgery; PSA values > 10 ng/mL,<sup>25</sup> urogenital malformations, genetic syndromes, ongoing tumors, and autoimmune diseases; pacemakers and automatic implantable cardioverter defibrillators.<sup>26</sup>

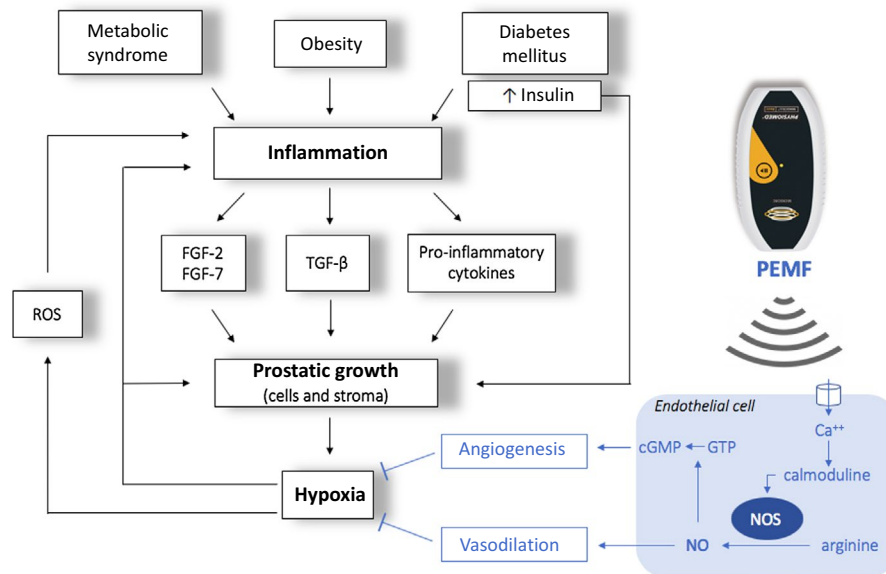
### 2.2 | Sample size

Sample size was calculated with the optimal two-stage design<sup>27</sup>: the null hypothesis that  $P \leq .35$  versus the alternative that  $P \geq .60$  has an expected sample size of 16.04 and a probability of early termination of 0.609. If the therapy is not effective, there is a 0.046 probability of concluding that it is (the target for this value was 0.05). If the therapy is effective, there is a 0.195 probability of concluding that it is not (the target for this value was 0.20). After testing the therapy on nine patients in the first stage, the trial was supposed to be terminated if three or fewer respond. If the trial goes on to the second stage, a total of 27 patients should be studied. If the total number responding is less than or equal to 13, the therapy is rejected.

The first stage was completed in August 2018:six of the first nine patients reported a variable degree of response in terms of PV. Therefore, the second stage started in September 2018. Enrollment was completed in December 2018, and the study ended in April 2019.

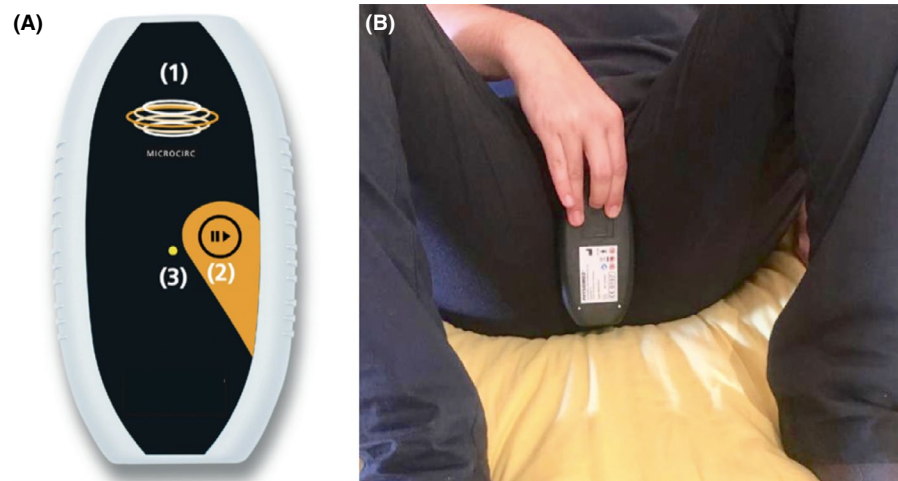
### 2.3 | Study design

The study was structured into three visits: (a) a screening visit for evaluation of inclusion and exclusion criteria, presentation of the



**FIGURE 1** Inflammatory hypothesis underlying BPH pathogenesis and biophysical mechanism of PEMF efficacy: during inflammation mitogen substances such as cytokines (IL-2, IL-4, IL-8, IL-15, IL-17, IFN- $\gamma$ ) and growth factors (VEGF, TGF- $\beta$ , FGF-2, FGF-7) are released, resulting in an abnormal proliferation of prostatic cells and stroma. FGFs primarily stimulate fibroblasts to produce fibromuscular tissue and also stimulate angiogenesis, proliferation, and differentiation of stromal and epithelial prostatic cells. The TGF- $\beta$  stimulates the differentiation of smooth muscle cells and the development of abundant extracellular matrix. The overproduction of stroma strongly increases oxygen consumption, and it is therefore responsible for hypoxia in the transition zone of the prostate. Hypoxia itself activates several signaling pathways that regulate angiogenesis and tissue proliferation. Furthermore, local hypoxia promotes the release of reactive oxygen species (ROS) that, in turn, stimulate the release of growth factors (IL-8, FGF-7, TGF- $\beta$ , FGF-2) and consequent glandular hyperplasia. The biophysical mechanism of PEMF efficacy is likely to involve an electrochemical model of the cell membrane: PEMF seems to increase intracellular calcium ( $\text{Ca}^{2+}$ ) binding to calmoduline. This bond activates the calmoduline pathway which catalyzed endothelial nitric oxide synthase isoform (eNOS), an enzyme responsible for the synthesis of nitric oxide (NO) and citrulline from L-arginine and  $\text{O}_2$ . NO activates an anti-inflammatory response by recalling lymphocytes from the blood, and it also causes vasodilation with a consequent increase in local blood flow and reduction of hypoxia. Furthermore, NO regulates cGMP signaling cascades that promote angiogenesis and tissue remodeling. The overall effect is a reduction in tissue hypoxia and therefore a reduction in prostatic growth.<sup>6,12,16,17</sup>

**FIGURE 2** Magcell® Microcirc, Physiomed Elektromedizin AG, Scaittach, Germany set on frequency of 4–12 Hz and on an intensity of 1000 Gauss. A, (1) effective area; (2) start button; (3) status LED. B, Correct position with the marked active surface placed on the perineal region



protocol, and signature for informed consent; (b) a baseline visit ( $V_0$ ) with complete medical history, full physical exam, clinical questionnaires administration, blood tests, transrectal ultrasound (TRUS), handover to patient of PEMF device, and use instructions; (c) a visit after 28 days of PEMF therapy ( $V_1$ ) with same procedures of  $V_0$ .

The primary outcome measure was the PV change at  $V_1$ .

After the  $V_1$ , three patients withdrew from the study for personal reasons, 9 patients were randomized to continue the PEMF up to 3 months (PT group), and 15 stopped the treatment (FU group). In order to evaluate possible time-dependent effects, a further visit ( $V_2$ ) was then performed for both groups three months after  $V_1$ , with same procedures.

## 2.4 | Procedures

The device (Magcell® Microcirc, Physiomed Elektromedizin AG, Schnaittach, Germany, Figure 2), with a frequency of 4-12 Hz and an intensity of 1000 Gauss, was provided to patients at  $V_0$ . Precise use instructions were given to patients: the effective area was to be placed onto the perineal region without pressure. The device was to be kept in place for 5 minutes, twice daily (morning and evening) for 28 consecutive days. Patients were asked to complete a diary of performed administration of the PEMF. A reminder for each administration was completed by an automatic message sent to each patient's cell phone.

Medical history and physical examination (general physical examination, digital rectal exploration, anthropometric measures, blood pressure, and heart rate) were taken at  $V_0$ .

Self-administered questionnaires were provided to patients at each visit: (a) the International Prostate Symptom Score (IPSS),<sup>28</sup> consisting of seven questions with scores from 0 to 35 (indicating mild, moderate, or severe symptoms with scores ranging, respectively, from 0 to 7, 8 to 19, or 20 to 35), (b) the International Index of Erectile Function-15 (IIEF-15) for sexual function (with scores  $\leq 25$  indicating the presence of erectile dysfunction). Regarding IPSS, question number 8 was also considered separately as an indicator of quality of life (IPSS-QoL).<sup>29</sup>

Blood samples for full blood count, kidney function, inflammatory markers, lipid and glucose metabolism, and sexual hormones (gonadotropins, total testosterone, estradiol) were performed at each visit at 8.00 AM, in fasting state. PSA was measured at  $V_0$  and  $V_2$ , but not at  $V_1$  for the short time frame occurring from the baseline procedures (DRE and TRUS) which could have been responsible for a high risk of false positives.<sup>30,31</sup>

TRUS was performed by two expert operators (GF, VO) using a Philips IU22 units (Philips, Bothell, WA, USA) through a pre-set transrectal 9.5 Mz end-fire probe with patient in left and prone decubitus position. The same patient was examined by the same operator at each visit. PV was calculated using the ellipsoid formula.<sup>32</sup>

## 2.5 | Statistical analysis

Outcome measurements were assessed for normality using the Shapiro-Wilk test, and non-parametric tests were used when violations of parametric test assumptions were evident. Values are then expressed as median and interquartile range (IQR). A Wilcoxon signed-rank test was performed to compare the effects of treatment at different timepoint evaluations ( $V_0$  vs  $V_1$  and  $V_2$ ). The Mann-Whitney U test was used to determine whether there were differences between the change over time (delta,  $\Delta$ ) in the two treatment groups. An ANCOVA model was used to determine the effects of the treatment on changes in PV and IPSS among the different timepoints ( $V_0$ - $V_1$ - $V_2$ ), after controlling for baseline values of any dependent variable. A Spearman's rank order correlation was run for baseline univariate correlations.

A first stratification of the cohort was performed based on the severity of LUTS defined as absence or mild symptoms (IPSS < 8, Group 1) or moderate-severe symptoms (IPSS  $\geq$  8, Group 2).

A second stratification was carried out based on the presence or absence of MetS.

A one-way ANOVA was conducted to determine whether there were differences in the  $\Delta$ IPSS between Group 1 and Group 2 and differences in PV between patients with or without MetS. A two-way ANOVA was conducted to examine the mixed effects of treatment duration (PT/FU) and severity of LUTS (Group 1/Group 2) on IPSS changes.

A relative risk was finally calculated considering the presence or absence of MetS and the treatment response, where responders were defined as patients having a reduction in PV higher than the median of the respective visit ( $\Delta$ PV <sub>$V_1$</sub>  = PV <sub>$V_1$</sub> -PV <sub>$V_0$</sub> ,  $\Delta$ PV <sub>$V_2$</sub>  = PV <sub>$V_2$</sub> -PV <sub>$V_0$</sub> ). A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS Statistics version 25.0 (IBM SPSS Statistics Inc, Chicago, IL, USA).

The protocol has been conducted in accordance with the Declaration of Helsinki and was approved by the internal Ethics Committee of Policlinico Umberto I in Rome (approval number 4906, 31st January 2018).

## 3 | RESULTS

### 3.1 | Study population

A total of 30 patients with diagnosis of BPH and/or complaining of LUTS underwent the screening visit from April to December 2018. Three patients were excluded due to suspicious prostatic lesions ( $n = 2$ ) and intravesical polyp ( $n = 1$ ) at  $V_0$ . Histology confirmed diagnosis of prostatic adenocarcinomas and bladder urothelial carcinoma.

Therefore, 27 patients were enrolled. Median age was 67 years (59;70). Full blood count, kidney function, and lipid and glucose metabolism were within normal limits. PSA median value was 1.9 ng/dL (0.7;3.6), PV was 44.5 mL (38.0;61.6), and IPSS was 11 (6;23) (Table 1).

Excellent compliance was observed: all patients used the device properly and attended  $V_1$ . No patient showed signs of discomfort, local, or systemic adverse effects through the trial.

### 3.2 | Primary outcome measure

A significant reduction in PV was observed from  $V_0$  to  $V_1$ : PV <sub>$V_0$</sub>  44.5 mL (38.0;61.6) vs PV <sub>$V_1$</sub>  42.1 mL (33.7;61.5), median difference ( $\Delta$ PV <sub>$V_1$</sub> ) -1.0 mL (-6.0;0.9), *P* = .039 (Table 1).

### 3.3 | Secondary outcome measures

Similarly, IPSS was significantly reduced at  $V_1$ : IPSS <sub>$V_0$</sub>  11 (5.7;23.2) vs IPSS <sub>$V_1$</sub>  10 (6;16), *P* = .045. IPSS-QoL also significantly improved at  $V_1$ : IPSS-QoL <sub>$V_0$</sub>  3 (1;3.25) vs IPSS-QoL <sub>$V_1$</sub>  1 (1;3), *P* = .018 (Table 1).

**TABLE 1** Characteristic of study population. Comparison between patients (n = 27) before ( $V_0$ ) and after 28 days of therapy ( $V_1$ ). Values are expressed in median (IQR). Wilcoxon test *P*-value reported (\**P* < .05). IPSS-QoL corresponds to IPSS question number 8. IIEF-15 domains

	$V_0$ (n = 27)	$V_1$ (n = 27)	<i>P</i>
Age (years)	67 (59;70)	-	-
BMI (kg/m <sup>2</sup> )	25.4 (24.7;28.9)	-	-
Ultrasound			
PV (mL)	44.5 (38.0;61.6)	42.1 (33.8;61.5)	0.039*
Adenome volume (mL)	16.7 (12.0;27.3)	14.3 (10.1;24.0)	0.089
LUTS questionnaire			
IPSS	11.0 (5.8;23.2)	10.0 (6.0;16.0)	0.045*
IPSS-QoL	3.0 (1.0;3.2)	2.0 (1.0;3.0)	0.018*
Sexual function questionnaire (IIEF-15)			
EF	27.0 (15.0;28.0)	27.0 (12.0;28.0)	0.417
IS	9.0 (7.0;12.0)	10.0 (5.0;12.0)	0.554
SD	7.0 (6.0;9.0)	8.0 (6.0;8.0)	0.551
OF	10.0 (6.0;10.0)	10.0 (9.0;10.0)	0.152
OS	8.0 (4.0;8.0)	8.0 (6.0;8.0)	0.542
Hormones			
FSH (mUI/mL)	7.1 (4.2;12.2)	6.5 (4.4;11.0)	0.583
LH (mUI/mL)	3.4 (2.3;5.9)	3.0 (2.1;7.1)	0.075
Testosterone (nmol/L)	16.0 (13.0;20.3)	15.6 (12.6;21.1)	0.738
Estradiol (pg/mL)	23.8 (18.9;34.1)	21.5 (17.6;25.7)	0.073
Lipid and glucose metabolism			
Glycemia (mg/dL)	97.0 (90.0;108.0)	102.0 (94.0;113.0)	0.989
HbA1c (%)	5.5 (5.2;6.1)	5.7 (5.2;6.0)	0.092
Total cholesterol (mg/dL)	183.0 (149.0;196.0)	179.0 (155.2;208.0)	0.109
HDL (mg/dL)	48.0 (42.0;64.0)	49.0 (41.9;63.7)	0.909
LDL (mg/dL)	98.0 (78.0;112.0)	99.0 (82.7;124.2)	0.106
Triglycerides (mg/dL)	110.0 (81.0;135.0)	108.0 (72.0;165.5)	0.611
Kidney function			
Creatinine (mg/dL)	1.0 (0.8;1.2)	0.9 (0.9;1.1)	0.274
Urea (mg/dL)	36.0 (32;41.4)	38.9 (31.9;46.7)	0.679
Inflammation markers			
WBCs ( $\times 10^9/L$ )	6.7 (5.2;8.2)	6.3 (5.4;8.1)	0.755
Neutrophils ( $\times 10^9/L$ )	3.7 (2.9;4.7)	3.8 (2.9;4.5)	0.719
Lymphocytes ( $\times 10^9/L$ )	1.9 (1.4;2.3)	1.9 (1.4;2.2)	0.943
ESR (mm/h)	9.0 (3.5;15.0)	6.0 (4.0;10.0)	0.088
CRP ( $\mu g/L$ )	1600 (600;2500)	1400 (500;2025)	0.078
Fibrinogen (g/L)	3.1 (2.6;3.3)	2.9 (2.6;3.3)	0.548
PSA (ng/mL)	1.9 (0.7;3.6)	-	-

Abbreviations: EF, erectile function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; SD, sexual desire.

A reduction in total PV was also observed in  $V_2$  compared to  $V_0$ :  $PV_{V_0}$  44.5 mL (38.0;61.6) vs  $PV_{V_2}$  41.7 mL (32.7;62.8), median difference ( $\Delta PV_{V_2}$ ) -0.4 mL (-3.4;3.4), *P* = .045. A parallel reduction of symptoms was also observed: IPSS $_{V_0}$  11 (6;23) vs IPSS $_{V_2}$  9 (6;14), *P* = .015; IPSS-QoL $_{V_0}$  3 (1;3.25) vs IPSS $_{V_2}$  1 (1;2.75), *P* = .018 (Table 2).

Interestingly, when comparing FU group and PT group at  $V_2$  no differences were found between the groups in terms of PV, IPSS, IPSS-QoL, or other outcome measures (Table 3).

When compared to the baseline assessments, no changes were found in PSA values at  $V_2$  and in all the other variables (adenoma volume, inflammation markers, glucometabolic test, kidney function, hormonal profile, or sexual function index) both at  $V_1$  (Table 1) and at  $V_2$  (Table 2).

An ANCOVA test was performed in order to evaluate whether the treatment duration (FU vs PT) could have different impact on PV or IPSS variations ( $\Delta PV$ ,  $\Delta IPSS$ ): no differences were found both in PV (*P* = .339) and IPSS (*P* = .295) (Table 4).

In order to identify any correlation between  $\Delta PV$  and  $\Delta IPSS$  both at  $V_1$  and at  $V_2$ , a univariate analysis was performed: no correlations were found for  $\Delta PV$ , whereas a moderate and strong correlation was found between baseline IPSS and  $\Delta IPSS_{V_1}$  ( $r_s$  = 0.540; *P* = .004) or  $\Delta IPSS_{V_2}$  ( $r_s$  = 0.800; *P* < .001), respectively.

Stratification by severity of symptoms resulted in 10 patients in Group 1 (IPSS < 8) and 17 patients in Group 2 (IPSS  $\geq$  8). Consistent with previous results, patients with higher scores (and therefore worse symptoms) had a higher reduction of IPSS both at  $V_1$  ( $\Delta IPSS_{Group1}$  1.3, 95% CI -1.9;4.5 vs  $\Delta IPSS_{Group2}$  -4.1, 95% CI -6.5; -1.8; *P* = .009) and at  $V_2$  ( $\Delta IPSS_{Group1}$  2.0, 95% CI -2.9;6.9 vs  $\Delta IPSS_{Group2}$  -6.7, 95% CI -9.9; -3.5; *P* = .006). No differences in  $\Delta IPSS$  were found when comparing the two treatment timings (FU vs PT) between Group 1 and Group 2 (*P* = .886).

To evaluate possible effects of MetS on treatment success, the same analysis was performed on affected (MetS, n = 7) vs non-affected (nMetS, n = 19) patients. A reduction was found in  $PV_{V_1}$  only for nMetS patients ( $\Delta PV_{V_1}$ MetS 1.7 mL, 95% CI -2.69;6.1 vs  $\Delta PV_{V_1}$ nMetS -4.7 mL, 95% CI -7.3;-2.0; *P* = .017) (Figure 3), giving MetS patients a relative risk of non-response to therapy of 6.0 (95% CI 0.8;43.1, *P* = .07) (Table 5).

No correlations with response to treatment were found regarding age, smoking habit, obesity, diabetes, or hypertension.

## 4 | DISCUSSION

Our study confirms that a handheld PEMF device is able to reduce PV and IPSS in patients affected by BPH. The effects were already significant after one month of therapy and were sustained even after discontinuation, particularly in patients with moderate-severe disease and without metabolic derangement.

According to EAU guidelines,<sup>1</sup> the current standard therapy for moderate-to-severe LUTS/BPH is represented by  $\alpha$ -blockers (AB) and 5 $\alpha$ -reductase inhibitors (5ARI), as monotherapy or in combination.

**TABLE 2** Characteristic of study population. Comparison of patient measurements at baseline ( $V_0$ ,  $n = 27$ ) and after 4 months ( $V_2$ ,  $n = 24$ ). Values are expressed in median (IQR). Wilcoxon test  $P$ -value reported ( $*P < .05$ ). IPSS-QoL corresponds to IPSS question number 8. IIEF-15 domains

	$V_0$ ( $n = 27$ )	$V_2$ ( $n = 24$ )	$P$
<b>Ultrasound</b>			
PV (mL)	44.5 (38.0;61.6)	41.7 (32.7;62.8)	0.045*
Adenome volume (mL)	16.7 (12.0;27.3)	13.3 (10.6;24.5)	0.224
<b>LUTS questionnaire</b>			
IPSS	11.0 (5.7;3.2)	9.0 (6.0;14.0)	0.015*
IPSS-QoL	3.0 (1.0;3.25)	1.0 (1.0;2.75)	0.018*
<b>Sexual function questionnaire (IIEF-15)</b>			
EF	27.0 (15.0;28.0)	26.0 (17.7;29.0)	0.694
IS	9.0 (7.0;12.0)	10.0 (9.0;12.0)	0.561
SD	7.0 (6.0;9.0)	8.0 (7.0;8.0)	0.235
OF	10.0 (6.0;10.0)	10.0 (7.2;10.0)	0.362
OS	8.0 (4.0;8.0)	8.0 (6.0;10.0)	0.179
<b>Hormones</b>			
FSH (mUI/mL)	7.1 (4.2;12.2)	6.9 (4.72;11.75)	0.148
LH (mUI/mL)	3.4 (2.3;5.9)	4.2 (2.9;6.1)	0.498
Testosterone (nmol/L)	16.0 (13.0;20.3)	15.2 (13.3;18.7)	0.205
Estradiol (pg/mL)	25.0 (20.0;35.0)	20.0 (16.7;22.5)	0.172
<b>Lipid and glucose metabolism</b>			
Glycemia (mg/dL)	97.0 (90.0;108.0)	95.4 (90;106)	0.126
HbA1c (%)	5.5 (5.2;6.1)	5.5 (5.3;5.9)	0.189
Total cholesterol (mg/dL)	183.0 (149.0;196.0)	180.4 (159.7;209.6)	0.137
HDL (mg/dL)	48.0 (42.0;64.0)	50.3 (43.8;59.0)	0.568
LDL (mg/dL)	98.0 (78.0;112.0)	100.5 (85.4;129.9)	0.137
Triglycerides (mg/dL)	110.0 (81.0;135.0)	92.08 (71.7;156.0)	0.909
<b>Kidney function</b>			
Creatinine (mg/dL)	1.0 (0.8;1.2)	1.0 (0.9;1.2)	0.123
Urea (mg/dL)	36.0 (32;41.4)	36.6 (30.3;42.6)	0.068
<b>Inflammation markers</b>			
WBCs ( $\times 10^9/L$ )	6.7 (5.2;8.2)	7.0 (5.4;7.9)	0.784
Neutrophils ( $\times 10^9/L$ )	3.7 (2.9;4.7)	3.8 (3;4.9)	0.403
Lymphocytes ( $\times 10^9/L$ )	1.9 (1.4;2.2)	1.8 (1.1;2.3)	0.553
ESR (mm/h)	9.0 (3.5;15)	5.0 (3;9.7)	0.132
CRP ( $\mu g/L$ )	1600 (600;2500)	1300 (600;1875)	0.721
Fibrinogen (g/L)	3.1 (2.6;3.3)	3.0 (2.5;3.5)	0.247
PSA (ng/mL)	1.9 (0.7;3.6)	2.3 (0.9;4.7)	0.366

Abbreviations: EF, erectile function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; SD, sexual desire.

**TABLE 3** Characteristic of study population at  $V_2$  ( $n = 24$ ). Comparison between patients who suspended therapy after 1 month (FU group,  $n = 15$ ) and patients who continued therapy for other 3 months (PT group). Values are expressed in median (IQR). Mann-Whitney test  $P$ -value reported ( $*P < .05$ ). IPSS-QoL corresponds to IPSS question number 8. IIEF-15 domains

	FU group ( $n = 15$ )	PT group ( $n = 9$ )	$P$
<b>Ultrasound</b>			
PV (mL)	41.3 (31.6;62.8)	42.0 (34.3;70.1)	0.640
Adenome volume (mL)	11.6 (8.9;23.6)	13.3 (12.5;38.0)	0.108
<b>LUTS questionnaire</b>			
IPSS	9.0 (6.0;14.0)	8.0 (6.0;14.5)	0.770
IPSS-QoL	2.0 (1.0;3.0)	1.0 (1.0;2.0)	0.446
<b>Sexual function questionnaire (IIEF-15)</b>			
EF	28.0 (23.0;30.0)	23.0 (15.0;27.0)	0.073
IS	10.0 (9.0;12.0)	10.0 (4.5;12.5)	0.815
SD	8.0 (7.0;9.0)	7.0 (6.0;8.0)	0.123
OF	9.0 (6.0;10.0)	10.0 (9.0;11.0)	0.084
OS	8.0 (4.0;10.0)	8.0 (6.0;9.0)	0.861
<b>Hormones</b>			
FSH (mUI/mL)	8.7 (5.2;14.0)	5.0 (4.4;9.0)	0.174
LH (mUI/mL)	5.3 (3.5;7.2)	3.3 (2.7;5.0)	0.104
Testosterone (nmol/L)	16.1 (13.4;21.7)	14.2 (10.9;16.4)	0.121
Estradiol (pg/mL)	20.6 (16.6;23.9)	20.5 (16.4;28.6)	0.097
<b>Lipid and glucose metabolism</b>			
Glycemia (mg/dL)	102.6 (90.0;113.4)	95.4 (90.4;103.5)	0.392
HbA1c (%)	5.6 (5.3;6.3)	5.5 (5.3;5.7)	0.558
Total cholesterol (mg/dL)	174.4 (158.5; 224.3)	182.5 (146.4;204.2)	0.682
HDL (mg/dL)	49.1 (43.3;57.2)	52.2 (44.3; 63.8)	0.411
LDL (mg/dL)	110.5 (85.1;132.6)	96.7 (78.3;127.2)	0.599
Triglycerides (mg/dL)	95.6 (83.2; 157.6)	81.4 (66.4;152.7)	0.318
<b>Kidney function</b>			
Creatinine (mg/dL)	0.9 (0.9;1.2)	1.0 (0.9;1.2)	0.861
Urea (mg/dL)	33.0 (30.0;46.8)	39.0 (30.6;41.7)	0.815
<b>Inflammation markers</b>			
WBCs ( $\times 10^9/L$ )	7.0 (5.4;8.5)	7.0 (4.6;7.7)	0.548
Neutrophils ( $\times 10^9/L$ )	4.0 (3.0;4.9)	3.7 (2.9;5.0)	0.925
Lymphocytes ( $\times 10^9/L$ )	1.8 (1.5;2.3)	1.8 (1.2;2.6)	0.875
ESR (mm/h)	7.0 (4.0-10.0)	3.0 (2.5;7.5)	0.155
CRP ( $\mu g/L$ )	1500 (600-2300)	800 (600-1700)	0.446
Fibrinogen (g/L)	3.1 (2.9-3.6)	2.6 (2.5;3.3)	0.155
PSA (ng/mL)	2.1 (0.9;3.2)	4.9 (0.9;7.2)	0.165

Abbreviations: EF, erectile function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; SD, sexual desire.

Two large randomized trials<sup>33,34</sup> and a recent meta-analysis<sup>35</sup> demonstrated that, when compared to placebo, the use of these drugs, alone and even more in combination, is able to reduce clinical BPH progression. The exponential efficacy of combined treatment depends on the different mechanism of action of these drugs. ABs improve LUTS providing prostate and bladder neck muscles relaxation, resulting in increased urine flow. 5ARIs, instead, reduce prostate (but not stromal) volume through prostate epithelium cell apoptosis by the inhibition of peripheral testosterone conversion in DHT.

However, despite their proved clinical efficacy, ABs and 5ARIs do not target one of the main triggers for BPH: the prostatic inflammatory infiltrate and consequent fibrosis.<sup>5</sup> This has been recently shown to be an independent risk factor for BPH progression, even in patients under combined therapy.<sup>36</sup>

In this regard, PEMFs therapy could play an important role adding an anti-inflammatory effect on top of the mentioned pharmacological outcomes. In particular, a pre-clinical study demonstrated the effectiveness of PEMF therapy in reducing PV in dogs affected by BPH.<sup>37</sup> To the best of our knowledge, only two human studies have used PEMF in the treatment of BPH.<sup>23,24</sup> So far, different devices have been used for PEMFs therapy, tailoring treatment duration according to tissue-specific conductivity and field strengths produced by the device used. In this context, our device was selected taking into account its specific technical features.<sup>38</sup>

Giannakopoulos et al<sup>24</sup> evaluated PEMFs against  $\alpha$ -blockers (AB), demonstrating a reduction of IPSS together with PV in patients treated with electromagnetic waves. However, one of the limitations

of this study was the difference in basal PV among the treatment groups: the PEMF group's PV was lower than the minimum threshold (40 mL) needed to justify a first-line medical treatment prescription, according to EAU Guidelines.<sup>1</sup> In our cohort, the baseline median PV was 44.5 mL. Elgohary and Tantawy<sup>23</sup> also evaluated PEMF treatment, alone or in combination with pelvic floor exercises, compared to placebo. PEMF effects resulted in a reduction of IPSS and post-urination residue together with increased urinary flow. No evaluation of PV was performed in this study.

Confirming these results, our analysis demonstrated a median PV reduction of 5.4% after one month of PEMF treatment, accompanied by IPSS and QoL improvement both at  $V_1$  and at  $V_2$ .

We need to acknowledge that  $V_2$  data include both patients who continued therapy (PT group) and those who stopped after one month (FU group). However, no differences were found between the two groups in terms of PV and IPSS reduction. We therefore could speculate that those PEMFs effects, achieved shortly after one month, are independent from treatment duration, being maintained also over time. This finding can be affected by the small sample size and should be confirmed in larger cohorts.

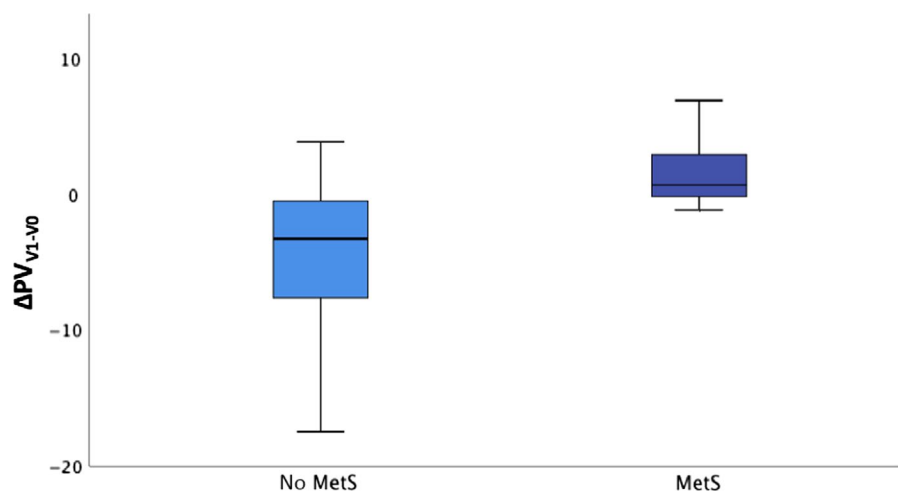
PSA values did not change throughout the study. However, the values showed a tendency toward increase in PT group, even if not statistically significant. If in the one hand this could simply be due to the small sample size, on the other hand this finding could be judged as an increase secondary to tissue remodeling during PEMFs' therapy. Larger cohort and longer follow-up evaluation are needed to confirm these data.

Notably, IPSS improvement is not associated with adenoma volume reduction, which is likely to be responsible for BPH symptoms. However, as previously mentioned, there is recent evidence supporting the finding that symptoms improvement is strongly related to the reduction of chronic low-grade inflammation in glandular parenchyma besides adenoma volume itself.<sup>5,6,8,39-41</sup> This is confirmed also by *Serenoa repens* efficacy studies<sup>42</sup> where the direct anti-inflammatory effect represented a further potential advantage to improve storage and voiding LUTS, regardless of PV reduction.

**TABLE 4** ANCOVA models for comparisons of group with different time of therapies (FU group = 1 month vs PT group = 4 months) as fixed factor and basal PV and basal IPSS as covariates, respectively. Values represent the estimated marginal medians (lower-upper limit of 95% CI)

	FU group (n = 9)	PT group (n = 15)	P
$\Delta PV_{V_2-V_0}$ (mL)	0.9 (-2.8;5.0)	-2.4 (-6.8;1.7)	0.339
$\Delta IPSS_{V_2-V_0}$	-1 (-7.2;2.5)	-3 (-11; -1.5)	0.295

**FIGURE 3** PV reduction ( $\Delta$ ) at  $V_1$  in patients without (no MetS) and with metabolic syndrome (MetS) ( $P = .017$ ). Colored boxes indicate interquartile range (IQR), and center vertical lines indicate median



**TABLE 5** Relation between MetS and PV response to therapy. Values in the table represent the number of patients and percentages in parentheses. Responders were defined as patients having a reduction in PV higher than the median delta at the respective visit ( $\Delta PV_{V1} = PV_1 - PV_0$ ,  $\Delta PV_{V2} = PV_2 - PV_0$ ). Relative risk 6.0 (95% CI 0.8;43.1) is higher in MetS patients

	MetS (n = 7)	nMetS (n = 19)
PV responders	1 (14.3)	12 (63.2)
PV non-responders	6 (85.7)	7 (36.8)

Note: Relative risk 6.0 (95% CI 0.8;43.1,  $P = .07$ ).

Bearing all these evidences in mind, it is necessary to identify those patients who are more inclined to benefit from this treatment, in order to plan a tailored therapy. Confirming the hypothesis that more severe symptoms would be more prone to improve after PEMFs therapy, our results showed that patients with moderate-severe grade LUTS are more likely to respond, as the greater improvement measured in our cohort was in patients with IPSS  $\geq 8$  compared to those with mild symptoms at baseline.

In addition, the metabolic profile should also be evaluated in the treatment choice. In fact, MetS was a negative prognostic factor regarding the response to treatment in our patients: being affected by MetS gave 6-times greater risk of not responding to therapy. In line with this result, a greater reduction in PV was measured in nMetS patients. This result has already been reported in literature in the evaluation of BPH response to traditional medical treatment.<sup>43</sup> A possible explanation involves MetS as a chronic systemic inflammatory state, which represents continuous stimulation of glandular proliferation, and therefore reduces the efficacy of a localized and temporary anti-inflammatory treatment. Therefore, in these patients, a preliminary treatment aimed to improve metabolic control could ensure higher therapeutic efficacy.

Electromagnetic waves have been widely demonstrated to be safe and side effect-free. No local or systemic adverse effects were reported through the trial, and both sexual function and gonadal hormonal profile remained unchanged throughout the study. In this context, AB and 5ARI have been reported to be safe and effective but not free from side effects (such as dizziness, orthostatic hypotension, increased fall risk, erectile dysfunction, ejaculation disorders, reduction of sexual desire) that may reduce quality of life and, consequently, patient adherence to therapies. Furthermore, 5ARI has been very recently associated with a modest increase in development of type 2 diabetes,<sup>44</sup> worsening the metabolic condition and therefore, probably, prostatic inflammation.

Our study also showed a good compliance without patients' discomfort. The device used was small, portable, and easy to apply at home by the patient himself. In the previously mentioned studies,<sup>23,24</sup> both of the devices required hospital admission and administration by healthcare professionals with longer daily treatment duration (30 minutes in-office application 5 days/week).

In summary, if confirmed in larger trials, PEMF may represent a safe and relatively inexpensive add-on procedure to medical treatment, which can be very useful mainly in elderly men with

multimorbidity and consequent polypharmacy.<sup>45</sup> However, the improvement we obtained using PEMF was still relatively small when compared to medical treatment or surgery. In this context, further trials aiming to compare the long-term effect of PEMF vs medical therapy in larger cohorts are warranted to better understand the utility of PEMF in clinical management of BPH.

Our study did have limitations: this was a pilot study on a very small sample size and without a control group. This may limit the interpretation of results. Randomized controlled studies with a larger cohort are certainly needed to confirm our results. Finally, it is critical to confirm PEMF action on the prostate, identifying molecular pathways and specific prostatic inflammation markers involved in the damage that can be modulated with PEMF therapy.

## 5 | CONCLUSIONS

The present trial represented the first attempt to use a portable 4-12Hz PEMF device for BPH therapy. PEMF was able to reduce PV after 28 consecutive days of therapy.

Our study reported that PEMF provided a highly compliant, safe, side effect-free therapy which resulted in the reduction of PV and improvement of symptoms in a short time with no side effects in hormonal and sexual function. Patients with moderate-to-severe LUTS and without MetS appear to be the most likely to benefit from this treatment.

Although results should be confirmed, PEMF could represent an effective, short-term, non-pharmacological add-on therapy for BPH and LUTS in order to improve therapeutic outcomes. Larger randomized clinical trials are needed to confirm these findings and to identify more accurate predictive factors of treatment response.

## ACKNOWLEDGMENTS

The authors are deeply grateful to Parsemus Foundation for financial assistance, and interest in this study. Particularly, the authors want to sincerely acknowledge Linda Brent for study continuous support, and language revision. The authors are also grateful to Physiomed Elektromedizin AG, Germany for supplying Magcell® Microcirc and for technical support. Finally, authors wish to express their sincere thanks to all patients participating in the study.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

## AUTHORS' CONTRIBUTIONS

MT and MGT involved in conception, design, and coordination of the study, acquisition, analysis and interpretation of data, draft of the article and critical revision for important intellectual content. PM, LL, and FS involved in acquisition of data, patient's enrollment and follow-up. CP involved in acquisition of data, analysis,



interpretation, and critical revision of data. GF and VO involved in acquisition of data and US performance. FN involved in patient's enrollment, critical revision of the article for important intellectual content, and final approval of the version to be published. DG involved in conception and design, acquisition of data, and interpretation and critical revision of data, and final approval of the version to be published. AL involved in critical revision of the article for important intellectual content and final approval of the version to be published. AMI involved in conception and design, acquisition, analysis, and interpretation of data, draft of the article, critical revision for important intellectual content, and final approval of the version to be published. RP involved in acquisition, analysis and interpretation of data draft of the article and critical revision for important intellectual content, and final approval of the version to be published.

#### ORCID

Marta Tenuta  <https://orcid.org/0000-0002-7476-0737>

Daniele Gianfrilli  <https://orcid.org/0000-0002-2682-8266>

Andrea M. Isidori  <https://orcid.org/0000-0002-9037-5417>

Riccardo Pofi  <https://orcid.org/0000-0001-7808-5735>

#### REFERENCES

1. Gratzke C, Bachmann A, Descazeaud A, et al. EAU Guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2015;67:1099-1109.
2. Gravas S. Prostate volume as a risk factor for lower urinary tract symptoms: the quest continues. *Eur Urol*. 2016;69:892-893.
3. Ngai HY, Yuen KS, Ng CM, Cheng CH, Chu SP. Metabolic syndrome and benign prostatic hyperplasia: an update. *Asian J Urol*. 2017;4:164-173.
4. Gianfrilli D, Pierotti S, Pofi R, Leonardo C, Ciccariello M, Barbagallo F. Sex steroid metabolism in benign and malignant intact prostate biopsies: individual profiling of prostate intracrinology. *Biomed Res Int*. 2014;2014:464869.
5. Ficarra V, Rossanese M, Zazzara M, et al. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. *Curr Urol Rep*. 2014;15:463.
6. Gandaglia G, Briganti A, Gontero P, et al. The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH). *BJU Int*. 2013;112:432-441.
7. Gacci M, Sebastianelli A, Salvi M, et al. Benign prostatic enlargement can be influenced by metabolic profile: results of a multi-center prospective study. *BMC Urol*. 2017;17:22.
8. Mishra VC, Allen DJ, Nicolaou C, et al. Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? *BJU Int*. 2007;100:327-331.
9. Kohnen PW, Drach GW. Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. *J Urol*. 1979;121:755-760.
10. Di Silverio F, Gentile V, De Matteis A, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur Urol*. 2003;43:164-175.
11. Berger AP, Kofler K, Bektic J, et al. Increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia. *Prostate*. 2003;57:57-65.
12. Ropiquet F, Giri D, Lamb DJ, Ittmann M. FGF7 and FGF2 are increased in benign prostatic hyperplasia and are associated with increased proliferation. *J Urol*. 1999;162:595-599.
13. Frey AH. Differential biologic effects of pulsed and continuous electromagnetic fields and mechanisms of effect. *Ann N Y Acad Sci*. 1974;238:273-279.
14. Markov MS. Expanding use of pulsed electromagnetic field therapies. *Electromagn Biol Med*. 2007;26:257-274.
15. Hug K, Roosli M. Therapeutic effects of whole-body devices applying pulsed electromagnetic fields (PEMF): a systematic literature review. *Bioelectromagnetics*. 2012;33:95-105.
16. Pilla AA, Muehsam DJ, Markov MS, Siskin BF. EMF signals and ion/ligand binding kinetics: prediction of bioeffective waveform parameters. *Bioelectrochem Bioenerg*. 1999;48:27-34.
17. Strauch B, Herman C, Dabb R, Ignarro LJ, Pilla AA. Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery. *Aesthet Surg J*. 2009;29:135-143.
18. Yap TL, Brown C, Cromwell DA, van der Meulen J, Emberton M. The impact of self-management of lower urinary tract symptoms on frequency-volume chart measures. *BJU Int*. 2009;104:1104-1108.
19. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol*. 2010;57:123-131.
20. Sterling J, Farber N, Gupta NK. Comparing outcomes of medical management and minimally invasive surgical techniques for lower urinary tract symptoms due to BPH. *Curr Urol Rep*. 2019;20:29.
21. DeWitt-Foy ME, Gill BC, Ulchaker JC. Cost comparison of benign prostatic hyperplasia treatment options. *Curr Urol Rep*. 2019;20:45.
22. Borchert A, Leavitt DA. A review of male sexual health and dysfunction following surgical treatment for benign prostatic hyperplasia and lower urinary tract symptoms. *Curr Urol Rep*. 2018;19:66.
23. Elgohary HM, Tantawy SA. Pulsed electromagnetic field with or without exercise therapy in the treatment of benign prostatic hyperplasia. *J Phys Ther Sci*. 2017;29:1305-1310.
24. Giannakopoulos XK, Giotis C, Karkabounas S, et al. Effects of pulsed electromagnetic fields on benign prostate hyperplasia. *Int Urol Nephrol*. 2011;43:955-960.
25. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2017;71:618-629.
26. Gwechenberger M, Rauscha F, Stix G, Schmid G, Strametz-Juraneck J. Interference of programmed electromagnetic stimulation with pacemakers and automatic implantable cardioverter defibrillators. *Bioelectromagnetics*. 2006;27:365-377.
27. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10:1-10.
28. Barry MJ, Fowler FJ, O'Leary MP, et al. The American urological association symptom index for benign prostatic hyperplasia. *J Urol*. 1992;148(5 Part 1):1549-1557; discussion 1564.
29. Johnson TV, Abbasi A, Ehrlich SS, et al. IPSS quality of life question: a possible indicator of depression among patients with lower urinary tract symptoms. *Can J Urol*. 2012;19:6100-6104.
30. Lechevallier E, Eghazarian C, Ortega JC, Roux F, Coulanges C. Effect of digital rectal examination on serum complexed and free prostate-specific antigen and percentage of free prostate-specific antigen. *Urology*. 1999;54:857-861.
31. Rodriguez-Rubio FI, Robles JE, Gonzalez A, et al. Effect of digital rectal examination and flexible cystoscopy on free and total prostate-specific antigen, and the percentage of free prostate-specific antigen. Differences between two PSA assays. *Eur Urol*. 1998;33:255-260.
32. Lee JS, Chung BH. Transrectal ultrasound versus magnetic resonance imaging in the estimation of prostate volume as compared with radical prostatectomy specimens. *Urol Int*. 2007;78:323-327.

33. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2387-2398.
34. Roehrborn CG, Siami P, Barkin J, et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol*. 2008;179(2):616-621; discussion 621.
35. Zhou Z, Cui Y, Wu J, Ding R, Cai T, Gao Z. Meta-analysis of the efficacy and safety of combination of tamsulosin plus dutasteride compared with tamsulosin monotherapy in treating benign prostatic hyperplasia. *BMC Urol*. 2019;19:17.
36. Macoska JA, Uchtmann KS, Levenson GE, McVary KT, Ricke WA. Prostate transition zone fibrosis is associated with clinical progression in the MTOPS study. *J Urol*. 2019;202:1240-1247.
37. Leoci R, Aiudi G, Silvestre F, Lissner E, Lacalandra GM. Effect of pulsed electromagnetic field therapy on prostate volume and vascularity in the treatment of benign prostatic hyperplasia: a pilot study in a canine model. *Prostate*. 2014;74:1132-1141.
38. Funk RH, Knels L, Augstein A, Marquetant R, Dertinger HF. Potent stimulation of blood flow in fingers of volunteers after local short-term treatment with low-frequency magnetic fields from a novel device. *Evid Based Complement Alternat Med*. 2014;2014:543564.
39. Chughtai B, Lee R, Te A, Kaplan S. Role of inflammation in benign prostatic hyperplasia. *Rev Urol*. 2011;13:147-150.
40. Inamura S, Ito H, Shinagawa T, et al. Prostatic stromal inflammation is associated with bladder outlet obstruction in patients with benign prostatic hyperplasia. *Prostate*. 2018;78:743-752.
41. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. *BJU Int*. 2013;111:304-311.
42. Novara G, Giannarini G, Alcaraz A, et al. Efficacy and safety of hexanic lipidosterolic extract of *Serenoa repens* (permixon) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. *Eur Urol Focus*. 2016;2:553-561.
43. Cyrus A, Kabir A, Goodarzi D, et al. Impact of metabolic syndrome on response to medical treatment of benign prostatic hyperplasia. *Korean J Urol*. 2014;55:814-820.
44. Wei L, Lai EC, Kao-Yang YH, Walker BR, MacDonald TM, Andrew R. Incidence of type 2 diabetes mellitus in men receiving steroid 5alpha-reductase inhibitors: population based cohort study. *BMJ*. 2019;365:l1204.
45. Oelke M, Becher K, Castro-Diaz D, et al. Appropriateness of oral drugs for long-term treatment of lower urinary tract symptoms in older persons: results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014). *Age Ageing*. 2015;44:745-755.

**How to cite this article:** Tenuta M, Tarsitano MG, Mazzotta P, et al. Therapeutic use of pulsed electromagnetic field therapy reduces prostate volume and lower urinary tract symptoms in benign prostatic hyperplasia. *Andrology*. 2020;00:1-10. <https://doi.org/10.1111/andr.12775>