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

Marta Tenuta1 | Maria G. Tarsitano1 | Paola Mazzotta1 | Livia Lucchini1 | Franz Sesti1 | Giorgio Fattorini1 | Carlotta Pozza1 | Valerio Olivieri1 | Fabio Naro2 | Daniele Gianfrilli1 | Andrea Lenzi1 | Andrea M. Isidori1 | Riccardo Pofi1

1Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
2Department 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

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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 (V0), all patients had blood tests, transrectal ultrasound, and questionnaires (IPSS, IIEF-15) and received a perineal PEMF device (Magcell Microcirc, Physiomed Elektromedizin). PEMF was delivered on perineal area 5 minutes twice daily for 28 days, then (V1) 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 (V2) was performed in both groups.

Results: A reduction was observed both at V1 and at V2 in PV: PVV0 44.5 mL (38.0;61.6) vs PVV1 42.1 mL (33.7;61.5, P = .039) vs PVV2 41.7mL (32.7;62.8, P = .045). IPSS was reduced both at V1 and at V2: IPSSV0 11 (5.7;23.2) vs IPSSV1 10 (6;16, P = .045) vs IPSSV2 9 (6;14, P = .015). Baseline IPSS was related to IPSS reduction both at V1 (rs = 0.313; P = .003) and at V2 (rs = 0.664; P < .001). PV reduction in patients without metabolic syndrome ($\Delta PV_{V1MetS}$ −4.7 mL, 95%CI −7.3;−2.0) was greater than in affected patients ($\Delta PV_{V1MetS}$ 1.7 mL, 95%CI −2.69;6.1)(P = .017, Relative RiskMetS = 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.
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.1,2

The underlying etiology is not completely understood. Risk factors include age, diabetes, cardiovascular disease, hypertension, and metabolic syndrome (MetS).3 Due to the wide expression of androgen receptors (AR), hormonal stimulation of prostate growth may play a role: 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 damage4–6 as the trigger for subsequent fibrosis and tissue hypoxia resulting in structural changes in the prostate.7,8 To confirm this, some histological studies have shown intraprostatic inflammatory infiltration in 43%-98% of BPH tissues.9–10 During inflammation, in fact, mitogen substances (cytokines, growth factors) are released, causing abnormal proliferation of prostatic cells and stroma11,12 (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 prostastic architecture, and adenoma's growth. This etiopathogenetic hypothesis represents the rationale of our study.

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

The biophysical mechanism of PEMF efficacy is likely to involve an electrochemical model of the cell membrane16 with intracellular pathways that promote angiogenesis, vasodilatation, and tissue remodeling. The overall effect is reduction in tissue hypoxia17 (Figure 1).

Traditional BPH treatment, together with lifestyle changes,18 includes medical and surgical therapy.19,20 However, they are both expensive21 and can have side effects22 (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.23,24

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.

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.1,2

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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/mL25 urogenital malformations, genetic syndromes, ongoing tumors, and autoimmune diseases; pacemakers and automatic implantable cardioverter defibrillators.26

2.2 | Sample size

Sample size was calculated with the optimal two-stage design27: 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
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 V₀. 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 V₀.

Self-administered questionnaires were provided to patients at each visit: (a) the International Prostate Symptom Score (IPSS), 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 ≤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).

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 V₀ and V₁, but not at V₂ 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.

TRUS was performed by two expert operators (GF, VO) using a Philips IU22 units (Philips, Bothell, WA, USA) through a pre-set transectorical 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.

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 (V₀ vs V₁ and V₂). The Mann-Whitney U test was used to determine whether there were differences between the change over time (delta, Δ) 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 (V₀-V₁-V₂), 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 ≥ 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 ΔIPSS 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 (ΔPV₀ = PV₁–PV₀, ΔPV₁ = PV₂–PV₁). 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 V₀. 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 V₁. 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 V₀ to V₁: PV₀ 44.5 mL (38.0;61.6) vs PV₁ 42.1 mL (33.7;61.5), median difference (ΔPV₁) = -2.4 mL (-6.0;0.9), P = .039 (Table 1).

3.3 | Secondary outcome measures

Similarly, IPSS was significantly reduced at V₁: IPSS₀ 11 (5.7;23.2) vs IPSS₁ 10 (6.16), P = .045. IPSS-QoL also significantly improved at V1: IPSS-QoL₀ 3 (1;3.25) vs IPSS₁ 1 (1;3), P = .018 (Table 1).
A reduction in total PV was also observed in V2 compared to V0: PV$_{V0}$ 44.5 mL (38.0;61.6) vs PV$_{V2}$ 41.7 mL (32.7;62.8), median difference (ΔPV$_{V2}$) = −0.4 mL (−3.4;3.4), P = .045. A parallel reduction of symptoms was also observed: IPSS$_{V0}$ 11 (6;23) vs IPSS$_{V2}$ 9 (6;14), P = .015; IPSS-QoL$_{V0}$ 3 (1;3.25) vs IPSS-QoL$_{V2}$ 1 (1;2.75), P = .018 (Table 2).

Interestingly, when comparing FU group and PT group at V2 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 V2 and in all the other variables (adenoma volume, inflammation markers, glucometabolic test, kidney function, hormonal profile, or sexual function index) both at V1 (Table 1) and at V2 (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 (ΔPV, ΔIPSS): no differences were found both in PV (P = .339) and IPSS (P = .295) (Table 4).

In order to identify any correlation between ΔPV and ΔIPSS both at V1 and at V2, a univariate analysis was performed: no correlations were found for ΔPV, whereas a moderate and strong correlation was found between baseline IPSS and ΔIPSS$_{V1}$ ($r_s = 0.540; P = .004$) or ΔIPSS$_{V2}$ ($r_s = 0.800; P < .001$), respectively.

Stratification by severity of symptoms resulted in 10 patients in Group 1 (IPSS < 8) and 17 patients in Group 2 (IPSS ≥ 8). Consistent with previous results, patients with higher scores (and therefore worse symptoms) had a higher reduction of IPSS both at V1 (ΔIPSS$_{Group1}$ = 1.3, 95% CI = −1.9;4.5 vs ΔIPSS$_{Group2}$ = −4.1, 95% CI = −6.5; −1.8; P = .009) and at V2 (ΔIPSS$_{Group1}$ = 2.0, 95% CI = −2.9;6.9 vs ΔIPSS$_{Group2}$ = −6.7, 95% CI = −9.9; −3.5; P = .006). No differences in ΔIPSS 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$_{V1}$ only for nMetS patients (ΔPV$_{V1}$MetS 1.7 mL, 95% CI = −2.6;9.6 vs ΔPV$_{V1}$nMetS = −4.7 mL, 95% CI = −7.3;−2.0; P = .007) (Figure 3), giving MetS patients a relative risk of non-response to therapy of 6.0 (95% CI 0.8;43.1, P = .14).

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, the current standard therapy for moderate-to-severe LUTS/BPH is represented by α-blockers (AB) and 5α-reductase inhibitors (SARI), as monotherapy or in combination.
**TABLE 2** Characteristic of study population. Comparison of patient measurements at baseline (V₀, n = 27) and after 4 months (V₂, 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

| Characteristic | V₀ (n = 27) | V₂ (n = 24) | P     |
|---------------|-------------|-------------|-------|
| Ultrasound    |             |             |       |
| 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 |
| LUTS questionnaire |             |             |       |
| 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* |
| Sexual function questionnaire (IIEF-15) |             |             |       |
| 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 |
| Hormones      |             |             |       |
| FSH (mIU/mL)  | 7.1 (4.2;12.2) | 6.9 (4.72;11.75) | 0.148 |
| LH (mIU/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 |
| Lipid and glucose metabolism |             |             |       |
| Glycemia (mg/dL) | 97.0 (90.0;108.0) | 95.4 (90.0;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 |
| Kidney function |             |             |       |
| 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) | 36.0 (30;42.6) | 0.068 |
| Inflammation markers |             |             |       |
| WBCs (×10⁹/L) | 6.7 (5.2;8.2) | 7.0 (5.4;7.9) | 0.784 |
| Neutrophils (×10⁹/L) | 3.7 (2.9;4.7) | 3.8 (3.4;9) | 0.403 |
| Lymphocytes (×10⁹/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;7.7) | 0.132 |
| CRP (µg/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 V₂ (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

| Characteristic | FU group (n = 15) | PT group (n = 9) | P     |
|---------------|------------------|-----------------|-------|
| Ultrasound    |                  |                 |       |
| 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 |
| LUTS questionnaire |              |                 |       |
| 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 |
| Sexual function questionnaire (IIEF-15) |             |             |       |
| 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 |
| Hormones      |             |             |       |
| FSH (mIU/mL)  | 8.7 (5.2;14.0) | 5.0 (4.4;9.0) | 0.174 |
| LH (mIU/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 |
| Kidney function |             |             |       |
| 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 |
| Inflammation markers |         |             |       |
| WBCs (×10⁹/L) | 7.0 (5.4;8.5) | 7.0 (4.6;7.7) | 0.548 |
| Neutrophils (×10⁹/L) | 4.0 (3.0;4.9) | 3.7 (2.9;5.9) | 0.925 |
| Lymphocytes (×10⁹/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 (µg/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\textsuperscript{33,34} and a recent meta-analysis\textsuperscript{35} 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.\textsuperscript{5} This has been recently shown to be an independent risk factor for BPH progression, even in patients under combined therapy.\textsuperscript{36}

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.\textsuperscript{37} To the best of our knowledge, only two human studies have used PEMF in the treatment of BPH.\textsuperscript{23,24} 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.\textsuperscript{38}

Giannakopoulos et al\textsuperscript{24} 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.\textsuperscript{1} In our cohort, the baseline median PV was 44.5 mL. Elghohary and Tantawy\textsuperscript{23} 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.\textsuperscript{5,6,8,39-41} This is confirmed also by \textit{Serenoa repens} efficacy studies\textsuperscript{42} 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) | $P$  |
|--------------------|-----------------|-------------------|------|
| $\Delta PV_{V2-V0}$ (mL) | 0.9 (−2.8;5.0)   | −2.4 (−6.8;1.7)   | 0.339|
| $\Delta IPSS_{V2-V0}$     | −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.
has been very recently associated with a modest increase in development, consequently, patient adherence to therapies. Furthermore, 5ARI (e.g., reduction of sexual desire) that may reduce quality of life and, 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. 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.

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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. AM 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. 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. AL involved in critical revision of the article for important intellectual content and final approval of the version to be published. AM involved in conception and design, critical revision for important intellectual content, and final approval of the version to be published. AM involved in conception and design, critical revision for important intellectual content, and final approval of the version to be published. AM involved in conception and design, 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

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