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ORIGINAL PAPER

Variation of inflammatory indexes in patients with chronic abacterial prostatitis treated with an herbal compound/extract

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Summary ***Introduction: Inflammation is a highly prevalent finding in the prostate. Men with inflammation have higher IPSS score and increased prostate size. For men with prostatic inflammation, there is a significantly increased risk of developing acute urinary retention and the need of a surgical approach to the disease. Some laboratory tests (i.e. fibrinogen, C-reactive protein), can play a role in identifying patients at greatest risk of complications and adverse outcomes after surgery. There have been several experiences exploring the role of nutraceutical approach to the prostate inflammation. Aim of our study were to describe the variation in symptoms and inflammatory indexes in men affected by chronic abacterial prostatitis, treated with an herbal extract containing Curcuma Longa 500 mg, Boswellia 300 mg, Urtica dioica 240 mg, Pinus pinaster 200 mg and glycine max 70 mg.***
Materials and methods: A prospective multicenter study was conducted from February 2021 and March 2022. One hundred patients, with a diagnosis of Chronic Prostatitis were enrolled in a multicentric phase III observational study. They were treated with the herbal extract, one capsule per day, for 60 days.
No placebo arm was included. In each patient, inflammatory indexes, PSA, prostate volume, IIEF-5, PUF, uroflowmetry (Q_{max}), IPSS-QoL, NIH-CPPS were registered and statistically compared at baseline and at the follow up visit.
Results: The variation obtained on the inflammation indexes showed a global improvement after treatment, including the PSA reduction. We also recorded a significant improvement on IPSS-QoL, NIH-CPPS, PUF and Q_{max} scores.
Conclusions: The herbal extract considered in our study may represent a promising and safe therapeutic agent leading to a reduction of inflammation markers, and could be used in the treatment of prostatitis and benign prostatic hyperplasia.

KEY WORDS: *Nutraceuticals; Inflammation; Inflammatory indexes; PSA.*

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INTRODUCTION

In recent years many authors highlighted the central role of inflammation in the pathogenesis of urological diseases. In particular, in patients with some neoplastic diseases, it has been shown that the presence of locoregional chronic inflammation is involved in carcinogenesis (1, 2). In the field of prostate diseases, recent studies have shown that patients with chronic inflammation of the prostate are at greater risk of more severe voiding symptoms, acute urinary retention and prostate surgery (3, 4). The gold standard for the diagnosis of tissue inflammation is represented by histological examination of tissue specimen. A biopsy cannot always be performed for both ethical and procedural issues (5). For this reason, in recent years, several studies attempted to identify a serological marker of inflammation for the various neoplastic and benign urological pathologies (6). However, most of the markers used at preclinical and *in vitro* levels have poor diagnostic specificity, significant variability over time or high costs. In recent years, several authors have shown how some laboratory tests (*Complete Blood Count/CBC, albumin, fibrinogen, C-protein reactive/PCR and procalcitonin/PCT*), that are routinely performed in preparation for various urological surgeries, can play a role in identifying patients at greatest risk of complications and adverse outcomes after surgery (7). In particular, these markers can be considered as proxies of inflammation of the organism and are related to an increased risk of mortality in numerous diseases. The role of these inflammation markers in urology is still unclear today and the scientific evidence comes mainly from retrospective studies (8). There is currently no consensus on the pharmacological management of inflammatory prostatic diseases in a unique way.
Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically prescribed together with antibiotics without clear evidence. The use of herbal remedies is very common, but the clinical evidence remains scarce (9). Above all, it remains unclear whether the use of such preparations can affect the reduction of the inflammatory state inferred on blood chemistry tests. The primary purpose of this multicenter study is to describe the variation in subjective, objective and biochemical inflammatory indexes in men affected by chronic abacterial prostatitis, treated with herbal extracts, containing *Curcuma Longa* 500 mg, *Boswellia* 300 mg, *Urtica dioica* 240 mg, *Pinus pinaster* 200 mg and *glycine max* 70 mg, for each administration, as described in the manufacturer's instructions (*Naturneed, Macerata, Italy*).

Materials and methods

From February 2021 and March 2022, all 100 consecutive patients, with prostatitis-like symptoms (10) attending each one of participating urologic centers, were enrolled in a multicentric phase III observational study. The patients were treated with an herbal extract, containing *Curcuma Longa* 500 mg, *Boswellia* 300 mg, *Urtica dioica* 240 mg, *Pinus pinaster* 200 mg and *glycine max* 70 mg (*PROSTAFLOG®*), taking one capsule at bedtime every 24h for 60 days. No placebo arm was included. The demographic characteristics were studied using descriptive analysis tables and the calculation on the sample size has not been determined because the sample will be a "*convenience sample*". Inclusion criteria were: age more than 18 years, diagnosis of diagnosis of chronic abacterial prostatitis, any prostatic volume, Q_{max} between 11 and 25, post voiding volume < 50 ml. Exclusion criteria were patient under 18 years old, history of neurological or psychiatric disorders which may impair evaluation of urinary symptoms, patients with urethral stricture or history of bladder or prostatic cancer or concomitant bladder stones, previous pelvic radiation therapy, inability to assess urinary symptoms, chronic opioid or opioid derivatives (for any reason) or cortisone therapy, alpha blockers or 5-alpha-reductase therapies, *phosphodiesterase-5 inhibitors* (PDE5i) or NSAIDs assumption during the study period, intolerance/allergies to the ingredients of the herbal extracts. After the diagnosis of chronic prostatitis, all patients who met the inclusion criteria signed a written informed consent and underwent baseline questionnaires: International Prostatic *Symptoms Score-Quality of Life* (IPSS-QoL), *National Institutes of Health Chronic Prostatitis Symptom Index* (NIH-CPSI), *Pelvic Pain and Urgency/Frequency* (PUF) Patient Symptom Scale, *International Index of Erectile Function-5* (IIEF-5) (11, 14). A urological examination using the *expressed prostatic secrete* (EPS) culture or seminal fluid culture and a prostatic *transrectal ultrasound* (TRUS) were performed. Uroflowmetry, CBC, inflammation indices (*erythrocyte sedimentation rate/ESR; PCR; prothrombin time/PT; partial thromboplastin time/PTT; fibrinogen; PSA*) were tested. The first follow-up visit was scheduled at 2 months from starting therapy, with a urological and microbiological examination, questionnaire collection, *transrectal ultrasound* (TRUS), *Treatment Benefit Scale* (TBS) questionnaire compilation (15).

The softwares used for statistical analyses were Excel 2019, StatPlus Pro 7.6.5 (*Med Calc to confirm*). Mean, standard deviation, median, differences were calculated for the quantitative variables interquartile.

The scores obtained in the responses to the IPSS, NIH CPSI, PUF and IIEF 5 questionnaires were assimilated to variables quantitative, but IPSS and IIEF 5 were also evaluated based on the frequency distribution for expected score ranges, which is perhaps a more correct way of considering them, since there is a division into interpretation classes.

For the QOL questionnaire, the frequency distributions recorded in the baseline versus follow up visit were evaluated, for the 5 scheduled answers. For TBS, the distribution of frequencies recorded in each of the 4 responses was equally evaluated as provided in the questionnaire. For each quantitative variable examined, the normality of the distribution of data was preliminarily evaluated, using Shapiro Wilk's test. In case of confirmed H0 and of normal distribution, parametric tests were used in the evaluation of the statistical significance of the differences between the different variables at baseline and after follow up (*ANOVA within subjects*). In case of data non-normally distributed, the evaluation of the differences between the variables (*baseline vs follow-up*) was performed using non-parametric tests (*Wilcoxon Signed Rank Test*). The differences between the frequency distributions were evaluated by Pearson's Chi-square test.

Results

One hundred patients were included in the study. The main characteristics were: mean age 52.1 ± 12.0 yeras, mean Body Mass Index 25.5 ± 2.8. Essential systemic arterial hypertension, dyslipidemia and diabetes mellitus occurred in 37%, 37% and 13%, respectively.

The changes in baseline vs follow up clinical and biochemical variables were reported in Table 1 and 2. These changes between visit 1 and visit 2 were significant for prostate volume, Q_{max} and for all the questionnaires but the IIEF score variation which showed was not significant (Table 1). The TBS score revealed an interesting improve-

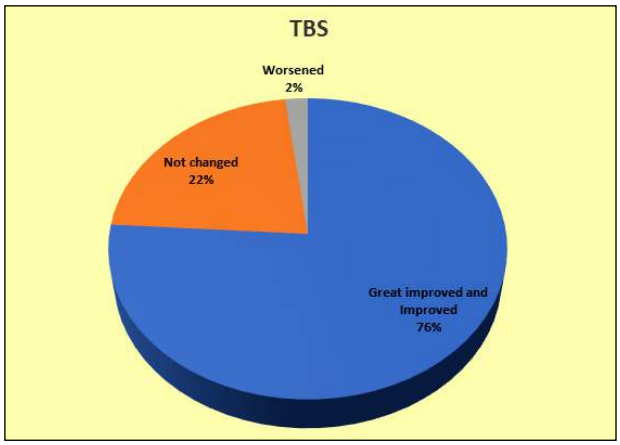
Table 1.
The clinical variables at baseline visit and follow-up.

	Baseline		Follow-up		
Variable	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**Baseline vs follow-up (p)**
Prostate Volume (ml)	35.58 ± 15.98	33.50	33.82 ± 15.64	30.00	< 0.001
Uroflowmetry Q_{max} (ml/s)	17.74 ± 5.40	17.00	19.00 ± 5.41	18.00	< 0.001
IPSS	15.94 ± 5.01	17.5	13.78 ± 4.89	14.00	< 0.001
QOL	2.60 ± 0.89	3.00	2.16 ± 0.94	2.00	0.003
NIH CPSI	17.34 ± 5.43	18.00	14.56 ± 5.83	14.00	< 0.001
PUF	12.77 ± 4.36	15.00	10.74 ± 4.8	10.00	< 0.001
IIEF 5	18 ± 4	19	18 ± 4	19	0.909

Table 2.
Variation of inflammation indices.

	Baseline		Follow-up		
Variable	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**Baseline vs follow-up (p)**
WBC (10^3/mL)	6.36 ± 1.76	6.17	6.02 ± 1.30	5.80	0.0039
Lymphocyte count (10^3/mL)	2.08 ± 0.55	2.05	1.96 ± 0.53	1.95	< 0.001
Neutrophil count (10^3/mL)	3.97 ± 1.25	3.86	3.64 ± 0.90	3.60	< 0.001
ESR (mm/h)	7.76 ± 7.99	6.00	5.98 ± 5.40	5.00	< 0.001
CRP	2.40 ± 2.92	0.80	2.22 ± 2.90	0.50	< 0.001
Fibrinogen (mg/dL)	261.33 ± 57.28	246.00	250.56 ± 57.27	230.00	< 0.001
Total serum PSA (ng/ml)	3.57 ± 3.70	2.80	2.37 ± 1.73	2.20	< 0.001

Figure 1.
Treatment benefit scale (TBS) after therapy.



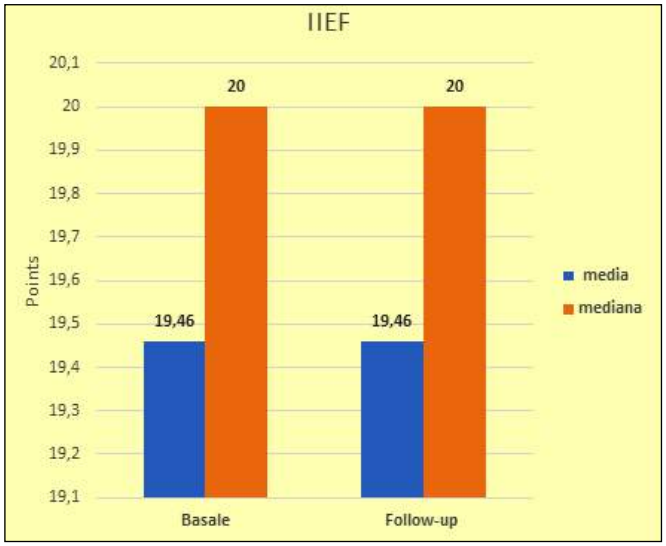
ment of perceived clinical status. At follow up visit, the patients declared an improvement (great also) in 76% of cases. No changes were declared in 22% and a worsened situation only in 2% (Figure 1). For the IIEF-5 questionnaire the differences are not significant both if we evaluate the scores or if we consider it a quantitative variable dividing the patients into categories based on the score intervals (Figure 2a, b). The variation obtained on the biochemical inflammation indexes was reported in Table 2, showing a global improvement of all parameters at follow-up visit, including a significant reduction in PSA as proxy of inflammatory status.

Discussion

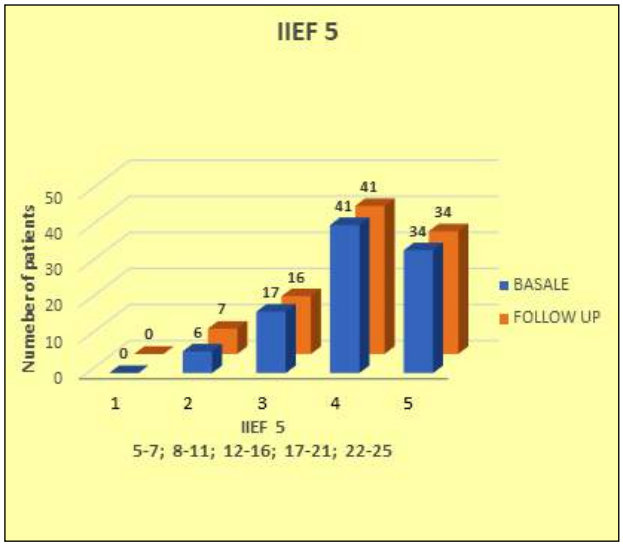
Inflammation is a highly prevalent finding in the prostate, both at histological and biochemical level. Men with inflammation have higher IPSS scores and increased prostate size, even if these differences appear to be imperceptibly small. For men with prostatic inflammation, there is a significantly increased risk of developing acute urinary retention and the need of a surgical approach to the disease (4). In recent years, several authors have shown how some laboratory tests (*CBC, albumin, ESR, fibrinogen, PCR*) that are routinely performed in preparation for various urological surgeries can play a role in identifying patients at greatest risk of complications and adverse outcomes after surgery (6). The effects of systemic inflammatory conditions, most notably metabolic syndrome, and their role in *lower urinary tract symptoms* (LUTS) have also been examined. When the data are examined at a clinically relevant level, we must take into high consideration that inflammation is a common process in the prostate and that the clinically significant impact of ingland inflammation is variable and difficult to define. For a long time, we know that the location of inflammation is important and that there are subsets of inflammation that are more frequently associated with the development of urinary symptoms or the prostate growth (16). In recent years, there was several experiences exploring the role of nutraceutical approach to the prostate inflammation. In particular, *Cai and co-workers* (17) evaluated the efficacy of a combination of soyabean extracts associated with *Curcuma Longa*, *Boswellia*, *Pinus pinaster* and *Urtica dioica* (*PROSTAFLOG®*) in patients affected by CP/CPPS, through the evaluation of *interleukin-8* (IL-8) plasma seminal levels. All patients diagnosed with CP/CPPS, attending the same urologic center, were enrolled in this randomized, controlled phase III study. Participants were randomized to receive oral capsules of *PROSTAFLOG®* (two capsules at bedtime every 24 h) or *Ibuprofen* 600 mg (1 tablet daily), lasting for a period of four weeks. NIH-CPSI and SF-36 questionnaires in association with urological evaluations with TRUS, Meares-Stamey test, and IL-8 dosage in seminal plasma were performed at baseline and at 3 months follow-up. A total of 77 patients were enrolled [*PROSTAFLOG®* (n = 39); ibuprofen (n = 38)] in the study and followed for 3 months. In the *PROSTAFLOG®* series, 69.2% of patients showed a significant reduction in the NIH-CPSI score, compared with 34.2% in the ibuprofen group ($p < 0.0001$). The mean IL-8 levels were significantly lower in the *PROSTAFLOG®*

Figure 2a, b.
No improvement of IIEF score after therapy.

a.



b.



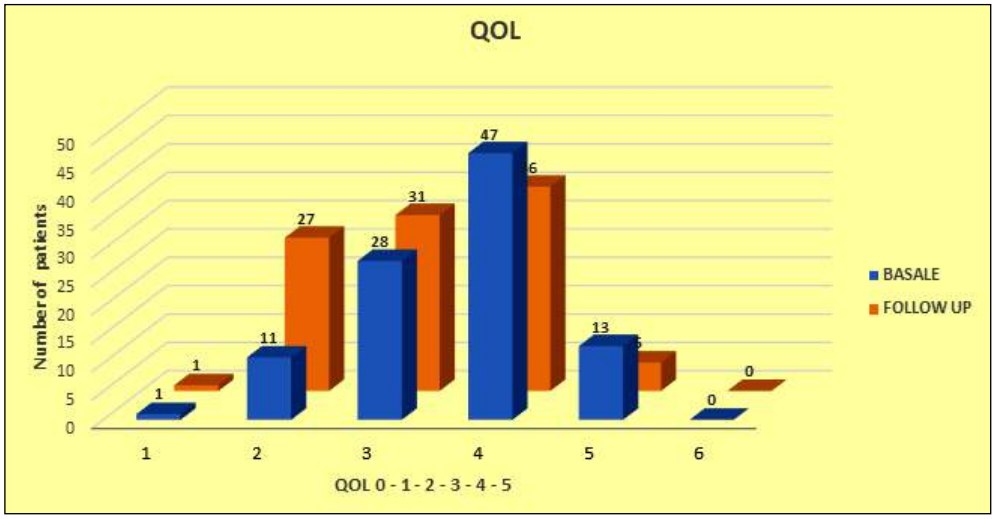
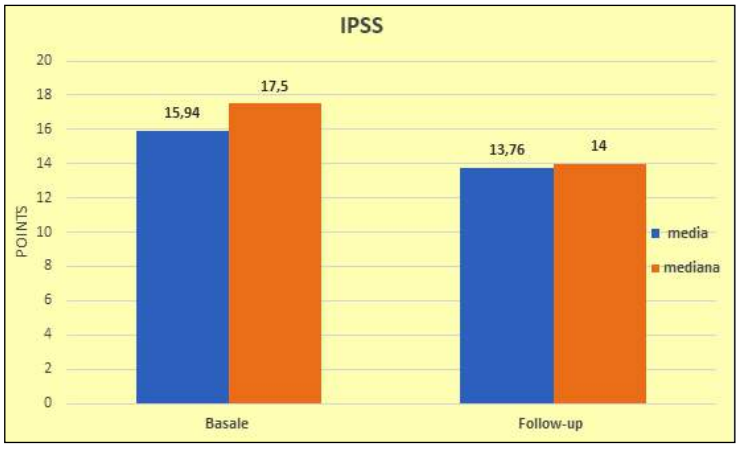


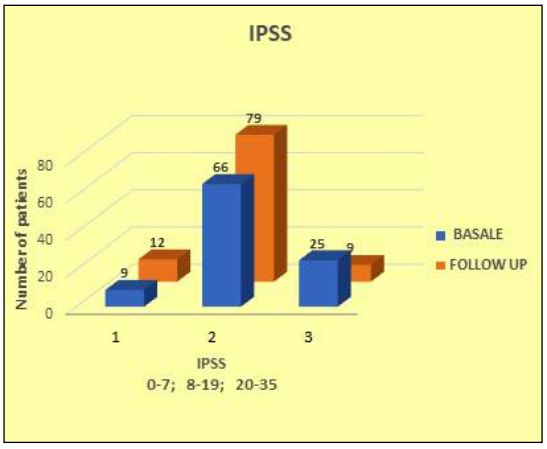
Figure 3.
QoL improvement after therapy.

Figure 4a, b.
IPSS global score improvement at follow up visit, but not in cases with severe basal symptoms.

a.

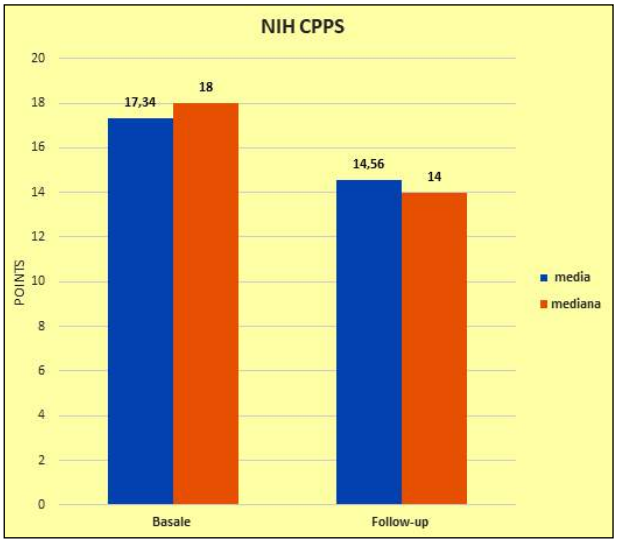


b.



cohort compared with the ibuprofen series ($p < 0.0001$), while a significant reduction in the IL-8 level between the enrollment and last follow-up evaluation was also observed in this group ($p < 0.0001$). Additionally, a significant reduction in the volume of the seminal vesicles assessed by TRUS was also found in the *PROSTAFLOG*® series during the observational timeframe. The Authors concluded that *PROSTAFLOG*® significantly improves the QoL in patients affected by CP/CPPS and provides a significant reduction in IL-8 seminal levels as the overall seminal vesicles volume. In our present study, the same observation in terms of QoL improvement was made (Figure 3). Especially in case of moderate QoL alteration, patients declared a positive impact from therapy on symptoms. These data are confirmed at the follow up evaluation with TBS questionnaire. The 20% of population studied reported a great improvement after treatment. The rate moves to 76% considering improvement to any extent.

Figure 5.
NIH-CPSI score improvement at follow up visit.



The statistically significant amelioration recorded at the follow-up visit after two months of therapy in IPSS, NIH CPPS and PUF scores (Figures 4a-b, 5, 6) confirms how the control of prostatic inflammation is correlated closely with a better perception of urinary symptoms characteristic of chronic prostatitis. The IIEF-5 scores registered before treatment did not improve. This finding could be related to the markedly multifactorial nature of the etiology of *erectile dysfunction* (ED). Given the age of the patients

Figure 6.
PUF score improvement after therapy.

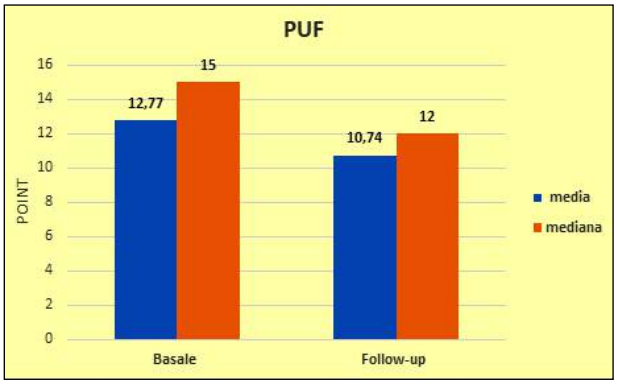


Figure 7.
Decreased PSA level from baseline after 2 months of treatment.

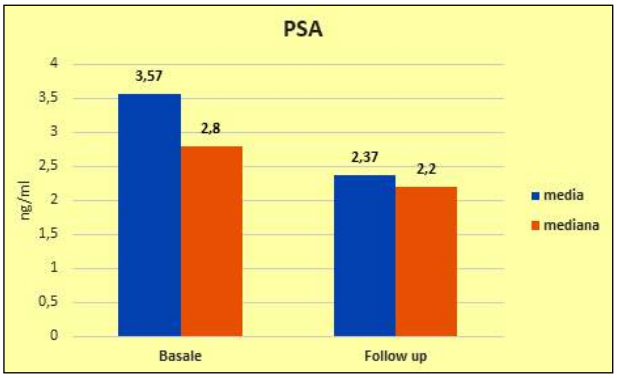


Figure 8.
Prostate volume decrease after therapy.

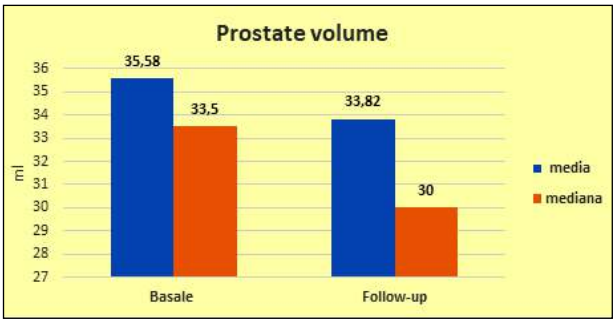
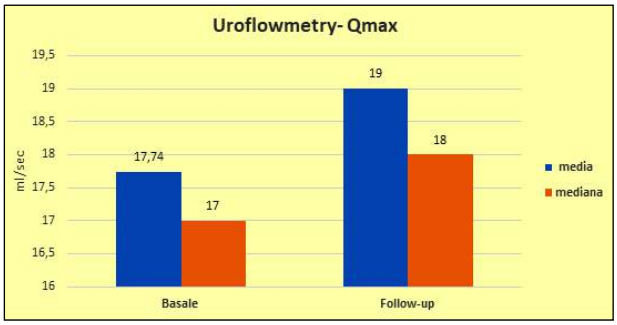


Figure 9.
Q_{max} improvement at follow up visit.



enrolled and the presence of known risk factors for ED, such as systemic hypertension and diabetes mellitus, the lack of improvement after treatment is not surprising as the therapy is aimed at the management of the prostatic inflammatory process which is only one of the possible causative factors of ED. Considering inflammation indicators, we preferred to investigate laboratory tests more accessible in daily clinical practice than seminal IL-8 levels. The routinely determined markers of inflammation showed a statistically significative improvement between the first visit and the visit performed at the follow-up. This clearly depends on prostatic inflammation etiology and confirm the anti-inflammatory role of the nutraceutical product. The first experience with *PROSTAFLOG*® was by *Fabiani et al.* (18). They described their real-life experience with this anti-inflammatory mixture on PSA levels and, in a prospective mono-institutional study of 50 patients, admitted for a first PSA raising, reported a lowered PSA value in 80% of cases, with a mean of reduction of 2.94 ng/ml (0.26-16.2 ng/ml) in one month therapy (two pill per day). No differences were reported in term of prostate volume variation. They concluded that *PROSTAFLOG*® use was able to lower the value of PSA, inviting to evaluate in appropriate studies the nutraceuticals products use in the treatment of prostatic pathology. In our present experience, we can confirm the lowering effect on PSA value by the *PROSTAFLOG*® administration. After 60 days of treatment, with one pill per day, we observed, at follow-up visit, a mean PSA levels of 2.74 ng/ml, starting from a 4.63 ng/ml mean value (Figure 7). Moreover, in our results, we reported a statistically significant reduction on prostate volume (38.01 ml *vs* 35.86 ml), presumably linked to the anti-inflammatory effect of prolonged administration (Figure 8). From a functional point of view, we found a significant improvement on flow parameters (Figure 9). The Q_{max} registered at the enrollment visit was significantly increased after *PROSTAFLOG*® treatment. This is evidently the effect induced by the reduction of the static and dynamic factors which underlie the typical symptoms of BPH (9).

Conclusions

PROSTAFLOG® treatment employed in case of chronic prostatitis may significantly increase QoL, providing a significant improvement of symptomatic scores. A critical reduction in PSA level may be eventually take into account in clinical decision making. *PROSTAFLOG*® may represent a promising and safe therapeutic agent leading to a reduction of inflammation markers, able to interrupt the pathophysiological mechanism of benign prostatic hyperplasia.

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Conflict of interest: The authors declare no potential conflict of interest.