Clinical Trial

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Gender medicine: the impact of probiotics on male patients

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Abstract

Purpose. Numerous studies in the literature confirm the importance of the use of probiotics in inflammatory states of the prostate in humans. Our pilot study aimed to test probiotics strains ability to improve urinary bacterial load in male subjects.

Methods. Twenty healthy men aged 55–65 years, with recurrent urinatory infections were enrolled and randomized into 2 groups. Urine culturing to detect Enterobacteriaceae (*Escherichia Coli* and *Enterococcus faecalis*) was performed at baseline and at 12 weeks after the starting of the study.

Results. We found that taking the probiotic reduces the bacterial load of *E. coli* and *E. faecalis* in urine cultures. The use of the probiotic in these inflammatory states does not affect the change in weight in the tested subjects.

Conclusions. Our data confirm and improve the main results reported in the scientific literature on the importance of taking probiotics in prostatitis. ***Clin Ter 2021; 172 (1):e8-15. doi: 10.7417/CT.2021.2274***

Key words: *probiotics, wellbeing, gender medicine*

Introduction

Prostatitis is a prostate condition characterized by prostate inflammation, pain and a variety of urinary symptoms such as urinary frequency, urgency, dribbling and the need to urinate often at night. This can have a bacterial origin and from the etiological point of view it appears very aggressive. Men who previously had prostatitis have a very high risk of recurrence of 20% -50% (1). Oxidative stress plays a key role in inflammation of the prostate, in men, while in women the points related to these processes are other, as in the case of the mouth and gastrointestinal system (2-3). In fact, the presence of ROS activates the NF-κB factor and consequently triggers the production of pro-inflammatory cytokines, FGF and TGF-β growth factors and other inflammatory mediators such as COX-2 and lipoxygenase (4). As inflammation progresses, fibrotic, calcified, and necrotic areas are inevitably formed which certainly increase the damage causing dysuria and reinfections (5). The cause of prostate infection, in most cases, is of bacterial origin and the most common germs are Gram-negative bacteria including Escherichia coli (*E.coli*), Enterococcus faecalis (*E. faecalis*), *Klebsiella, Pseudomonas and Proteus* species, but also the presence of Gram- bacteria positive, especially Enterococcus, these may be responsible for prostate infection (6-7). Research has also found that men with chronic prostatitis have lower seminal lactobacilli levels than healthy men, due to frequent antibiotic treatments (8).

Most of the data reported in the literature show that the antibiotic treatment of prostatitis alone is not adequate for the treatment and consequently the integration with probiotics can restore the loss of healthy bacteria in the intestinal microflora. This would reduce the risk of recurrence of bacterial and viral infection (9).

The benefits of probiotics for the treatment of bacterial prostatitis have been demonstrated in human clinical research. One study looked at the effects of probiotic supplementation alongside antibiotics for the treatment of chronic bacterial prostatitis (10). A growing number of research supports the theory that probiotics can help prevent recurrent infections in men, especially *Lactobacillus* strains.212 men with chronic bacterial prostatitis were randomly assigned to two groups: one group with the only antibiotic as cure, the other group with more probiotic antibiotic treatment. The cure was followed for 30 days. At the end of the study, 27.6% of the group that received only antibiotics had a recurrence of urinary tract infections while only 7.8% of the combination group had a recurrence (10). Recent evidence has shown that the urinary microbiome is implicated in inflammation of the prostate and in the possible tumor onset mainly due to its anatomical proximity and the potential of the urinary tract to act as a transport vehicle for contamination by external microorganisms. The urinary microbiome has also been shown to have peculiar compositional characteristics that

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distinguish it from the skin of the adjacent genital areas and to be substantially different between males and females. In detail, the male urinary microbiota was mainly formed by *Corynebacterium, Staphylococcus, Streptococcus, Anaerococcous, Finegoldia, Lactobacillus, Peptoniphilus, Enterobacteriaceae, Pseudomonas, Actinobaculum, Gammaproteobacteria*, and *Actinomyces.* It is interesting to note how it partially changes with age (11). Probiotics can protect against harmful bacteria and restore the loss of bacteria that support health lost during treatment with antibiotics. This makes probiotics one of the best treatments for bacterial prostatitis. Probiotics have been found to have interesting activity in several gender-related diseases. Preclinical studies indicate that an optimal diet and the use of probiotics after pelvic cancer and during radiotherapy may be able to prevent radiation-induced survivorship diseases. *Lactobacillus acidophilus, Lactobacillus fermentum*, and *Lactobacillus plantarum* seem to be useful in chronic or relapsing infections, often able to trigger neoplastic onset. *Lactobacillus strains* induce TRAIL production and facilitate natural killer activity against cancer cells: tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is an endogenous cytokine that induces apoptosis in malignant tumor cells including gastrointestinal tumors. Moreover, Curcumin is a botanical with anti-tumor and immunomodulatory properties (12-14). The aim of this study was to evaluate the efficacy of specific probiotics strains to improve prostrate health.

Materials and Methods

Study Design

This study is a clinical trial carried out on volunteers. It was conducted in collaboration with the Elbasan University (School of Technical Medical Sciences, "A. Xhuvani"), Albania, and the University of Bari Aldo Moro as a randomized, double-blinded placebo-controlled study. The Institutional Ethics Committee of the Faculty of Technical Medical Sciences of Elbasan "ALEKSANDËR XHUVANI" has approved the application to conduct the clinical trial in the Faculty. Title of the Protocol: Probiotics efficacy and safety in humans. Protocol Identification: INTL_ALITCOOP/Probiotics/INRES2019_w/a/c.

The study was carried out according to the Helsinki declaration and informed written consent was obtained from all the subjects. Twenty healthy men aged 55–65 years, with recurrent infections due to enterobacteriaceae *E. coli* and *E. faecalis* were enrolled and randomized into 2 groups each to receive *PRO-Men Hyperbiotics*, USA (Group A- 10 men) or Placebo containing maltodextrin (Group B- 10 men), 1 tablet daily for 12 weeks (after receiving a proper antibiotic treatment with subsequent culture negativization). The main endpoint was the reduction of prostatitis episodes (graphical abstract).

Participants agreed not to take any other probiotics in addition to the allocated intervention during the course of the study. Exclusion criteria were complex bladder disturbances requiring surgical intervention, current uncomplicated pyelonephritis, known urinary tract calculi, pre-existing infection on intervention commencement, known long-standing osteomyelitis, long-term antibiotic therapy, adverse reaction to probiotic products, severe renal or hepatic failure, sexually transmitted infection (STI), risk factors for STIm diabetes, drug or alcohol abuse and immunosuppression.

All participants consumed a normal and various diet (about 55% carbohydrate, 30% fat (8% saturated fat), 15% protein, ≤8 g/1000 kcal total dietary fiber, ≤2 g/1000 kcal soluble fiber) isocaloric for 12 weeks. Prebiotics/probiotics foods (e.g., yogurt) were not included in the menu. Participants were allowed to consume 450 g/day (~16 fl. oz./day) caffeinated black coffee or unsweetened black tea if used to consuming them regularly. Measurements of key outcome variables (body weight) were performed at baseline and following the intervention period.

Urine culturing and probiotic formulation

Urine culturing to detect Enterobacteriaceae (*Escherichia Coli* and *Enterococcus faecalis*) was performed at baseline and at 12 weeks after the starting of the study. A specific probiotics formulation (*PRO-Men Hyperbiotics*, USA), containing 6 Targeted Probiotic Strains *Probi Lactobacillus plantarum 6595, Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus casei, Lactobacillus acidopilus, Bifidobacterium longum*), also contains Meriva Curcumin Phytosome has been investigated to improve men's prostrate health.

Statistical Analyses

Outcome measures of the exploratory study were analyzed with a t-test for paired samples for pre–post differences with time as the factor using Statistical Package for Social Sciences (SPSS for Windows, Version 11.5, Chicago, Ill) software, to detect significant differences between pre-test and post-test scores.

Results

The data of the evaluation of the main variable that is body weight both in the Placebo group and in the Test Group were evaluated and taken into consideration both at the baseline (T0) and after the study period (T1) (Table 1).

Table 1. Weight in Test and Placebo Group at T0 and T1

WEIGHT (Kg) GROUP A (TEST)			**WEIGHT (Kg) GROUP B (PLACEBO)**		
ID	T0	T1	ID	T0	T1
GF	80	79	MDR	79	79
CR	76	75,1	BR	81,4	81
FT	73,5	71,5	DC	85	86
PP	89	88	PB	76	76
MCP	80,5	79	FM	74,7	74
PL	78,2	77	RS	88	88,2
RD	75,5	75	OV	90,2	90
LA	71	70	GC	96,3	96,2
GM	69,6	68,7	DD	85,5	85,5
IO	70,8	70	SK	89	89

The bacterial load is measured in Colony Forming Units - CFU / ml,: we indicate with "-" a low bacterial load, then a negative test with values <10,000 CFU / ml, with "+" a high bacterial load, then a positive test with values> of 100,000 CFU / ml while we indicate with values> 10,000 <100,000 CFU / ml doubtful urine cultures (Table 2-3).

Table 2. Urine Culturing – E. coli in Test and Placebo Group at T0 and T1

Urine Culturing - E. coli (CFU/ml) GROUP A (TEST)			Urine Culturing - E. coli (CFU/ml) GROUP B (PLACEBO)		
ID	T0	T1	ID	T0	T1
GF	-	+	MDR	-	>10.000 <100.000
CR	-	-	BR	-	-
FT	-	-	DC	-	+
PP	-	+	PB	-	+
MCP	-	>10.000 <100.000	FM	-	>10.000 <100.000
PL	-	-	RS	-	>10.000 <100.000
RD	-	-	OV	-	>10.000 <100.000
LA	-	>10.000 <100.000	GC	-	>10.000 <100.000
GM	-	-	DD	-	+
IO	-	-	SK	-	-

Table 3. Urine Culturing – E. faecalis in Test Group at T0 and T1

Urine Culturing - E. faecalis (CFU/ml) GROUP A (TEST)			Urine Culturing - E. faecalis (CFU/ml) GROUP B (PLACEBO)		
ID	T0	T1	ID	T0	T1
GF	-	+	MDR	-	>10.000 <100.000
CR	-	-	BR	-	-
FT	-	-	DC	-	+
PP	-	+	PB	-	+
MCP	-	>10.000 <100.000	FM	-	>10.000 <100.000
PL	-	-	RS	-	>10.000 <100.000
RD	-	-	OV	-	>10.000 <100.000
LA	-	>10.000 <100.000	GC	-	>10.000 <100.000
GM	-	-	DD	-	+
IO	-	-	SK	-	-

By evaluating the weight trend of the subjects enrolled in the Test group, from baseline to T1 (12 weeks) (Fig. 1), there is a minimum reduction of the parameter after taking the probiotic *Pro-Men Hyperbiotics*, USA in association with a specific diet. Instead, it is clear that the trend of the weight in Group B (Placebo) in the two periods (T0-T1) (Fig. 2), has no change, in fact the weight of the subjects has remained unchanged. Comparing the two graphs we can say that the integration of the probiotic, associated with a specific and controlled diet, has allowed a minimal reduction in the weight of the subjects, who with an age between 55 and 65 years are more prone to weight gain therefore the probiotic could be used as an aid or as a modulating element.

From the bacterial count of *E. coli* in group A, at T0 and T1 (Fig. 3), it is noted that at the time 0 all subjects had negative urinary cultures, therefore UFC / ml <10,000, this because all the subjects had been subjected to antibiotic treatment before starting treatment, resulting in negative culture. Group A carried out the *Pro-Men Hyperbiotics*, USA probiotic treatment for 12 weeks (T1) and it can be seen from the graph how the urine cultures changed over the weeks. We have about 60% of the group which despite having increased CFU / ml values appears to have negative exams, about 20% of the subjects are in the range> 10,000 <100,000, therefore with a doubtful result of the exam while the remaining 20% has passed from negative urine culture to positive urine culture.

Instead, the results of urinary cultures changed in group B, Placebo from T0 to T1 (Fig. 4). Also, in the Placebo group at T0 we have all negative urinary cultures, due to the antibiotic treatment carried out before baseline. After 12 weeks, we can see that only 20% of the enrolled subjects maintain the negativity of the exam, while 30% are positive for *E. coli*, while in the remaining 50% we found values between 10,000 and 100,000 (doubtful result). From the comparison, we can say that the intake of *Pro-Men Hyperbiotics, USA* probiotic associated with a controlled diet allowed more subjects in the Test group than the Placebo to have no recurrence, most of the subjects maintained negativity and only 2 out of 10 positive cases. These data allow to evaluate the intake of the probiotic as a possible additional element in the lowering of bacterial infections, liked to the re-stabilization of the good bacterial flora, reduction of the inflammatory process and reduction of episodes of connected prostatitis.

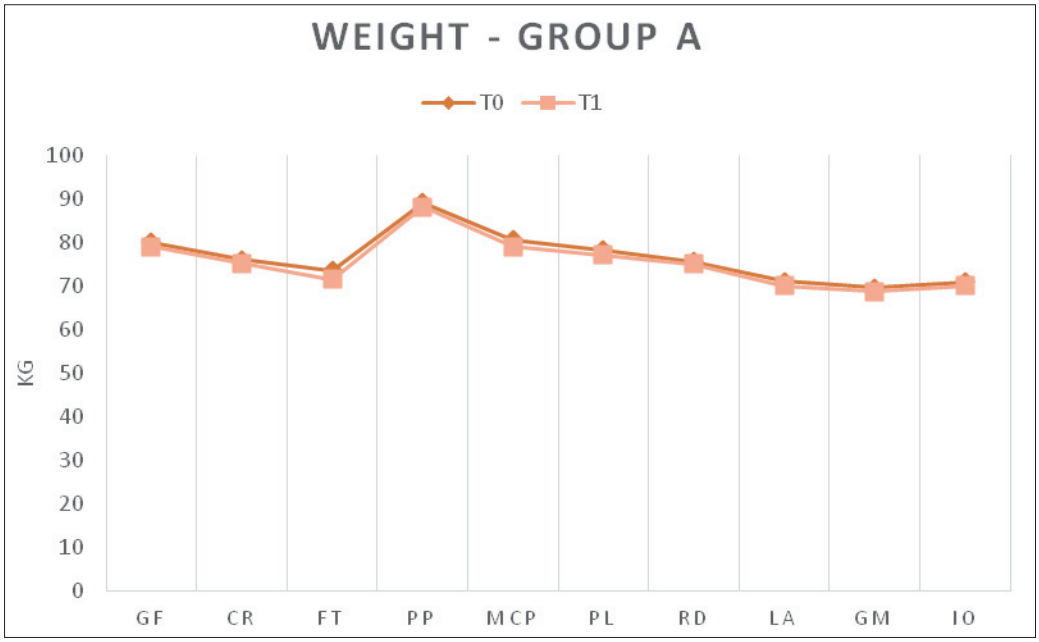


Fig. 1. The weight trend of the subjects enrolled in the Test group, from baseline to T1 (12 weeks).

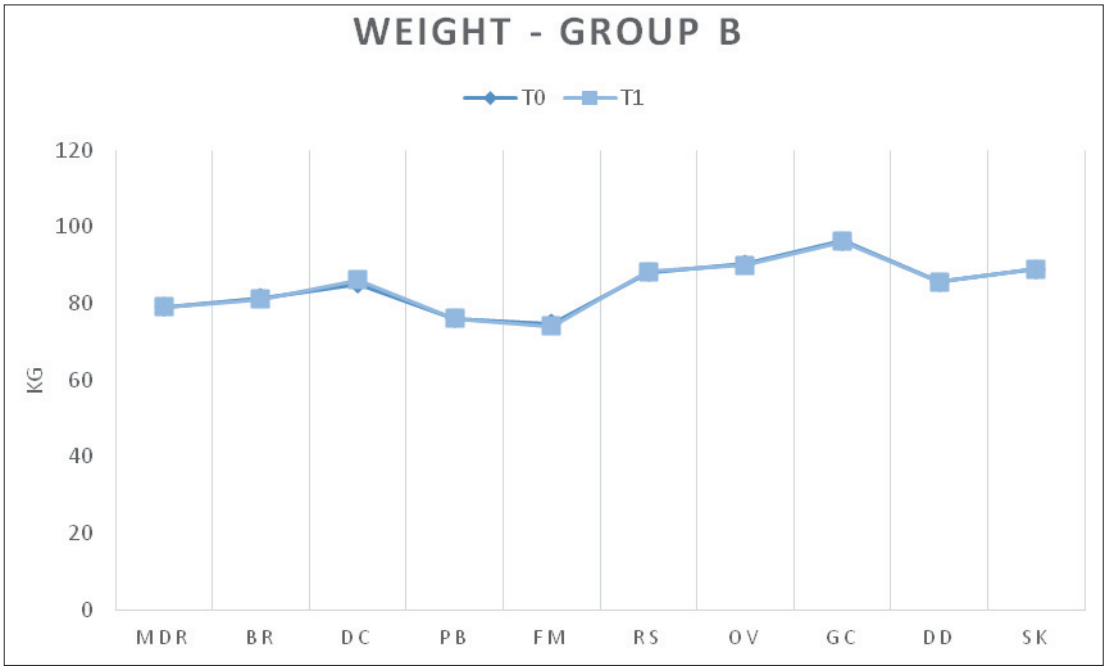


Fig. 2. The weight trend of the subjects enrolled in the Control group, from baseline to T1 (12 weeks).

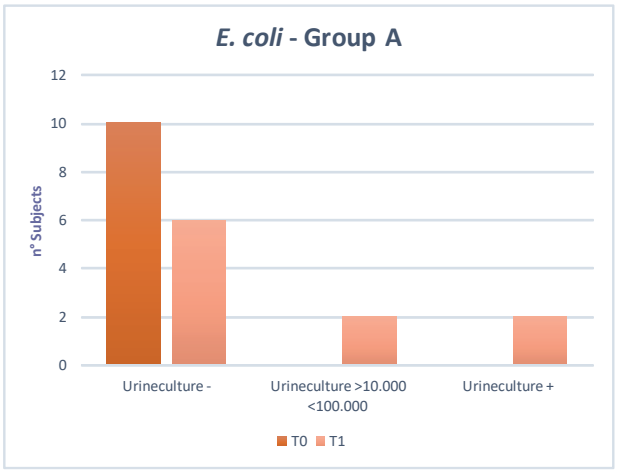


Fig. 3. The bacterial count of E. coli in group A, at T0 and T1.

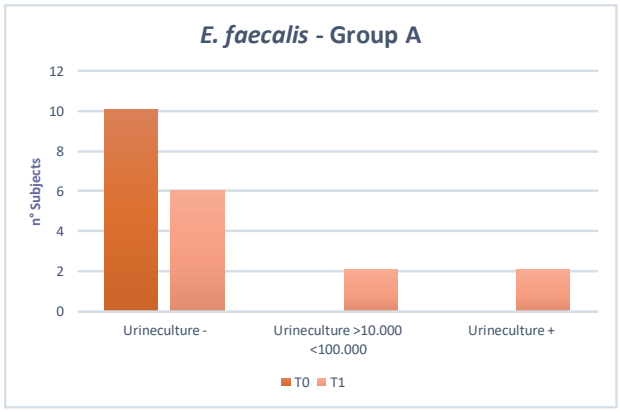


Fig. 5. The urine cultures bacterial load of E. faecalis in subjects belonging to group A (Test)

Urine cultures clearly changed for *E. faecalis* in group A from baseline to T1 (Fig. 5). Also, in this case the urine cultures are all T0 negative, because the subjects carried out antibiotic treatment before starting the treatment. At T1, however, we can see from the graph how the situation has changed, most of the subjects (6/10) continue to have negative urine culture, only 2 subjects instead have positive urine culture therefore with an excessive increase in the values of CFU / ml, while the remaining 2 subjects have values between 10,000 and 100,000. Also, in the urine cultures and in particular the bacterial load of *E. faecalis* in subjects belonging to group B (Placebo) there was an evident change between the two times (Fig. 6). Here also at T0 urine culture is negative for all 10 subjects in the group while at T1 the situation has changed, in fact, only 20% of the subjects maintain a negative result, therefore absence of infection and possible prostatitis, while 30% have high values and positivity of the exam, therefore relapse. The other half of the group instead remains in the range> 10,000 <100,000. Also in the case of *E. faecalis* we can note that in the Test group the subjects who present infection or doubtful values are less in number than in the Placebo Group, data that demonstrate how the intake of probiotic for 12 weeks in men with recurrent prostatitis can help in the control of the inflammatory process and avoid the possibility of relapse.

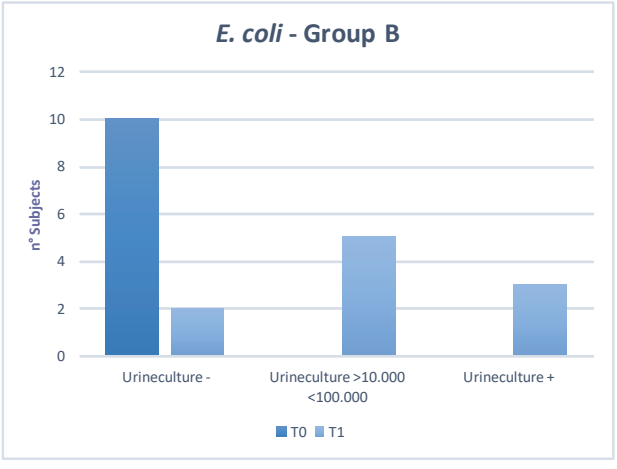


Fig. 4. The bacterial count of E. coli in group B, at T0 and T1.

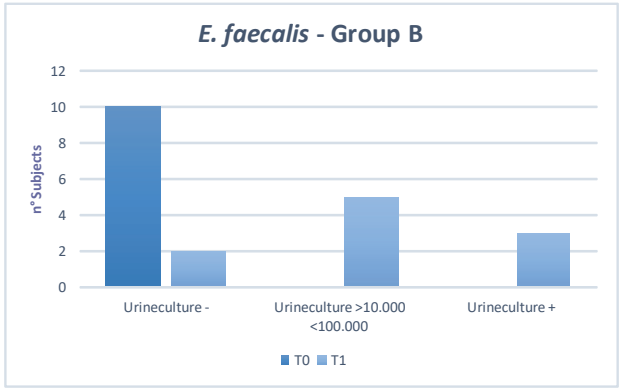
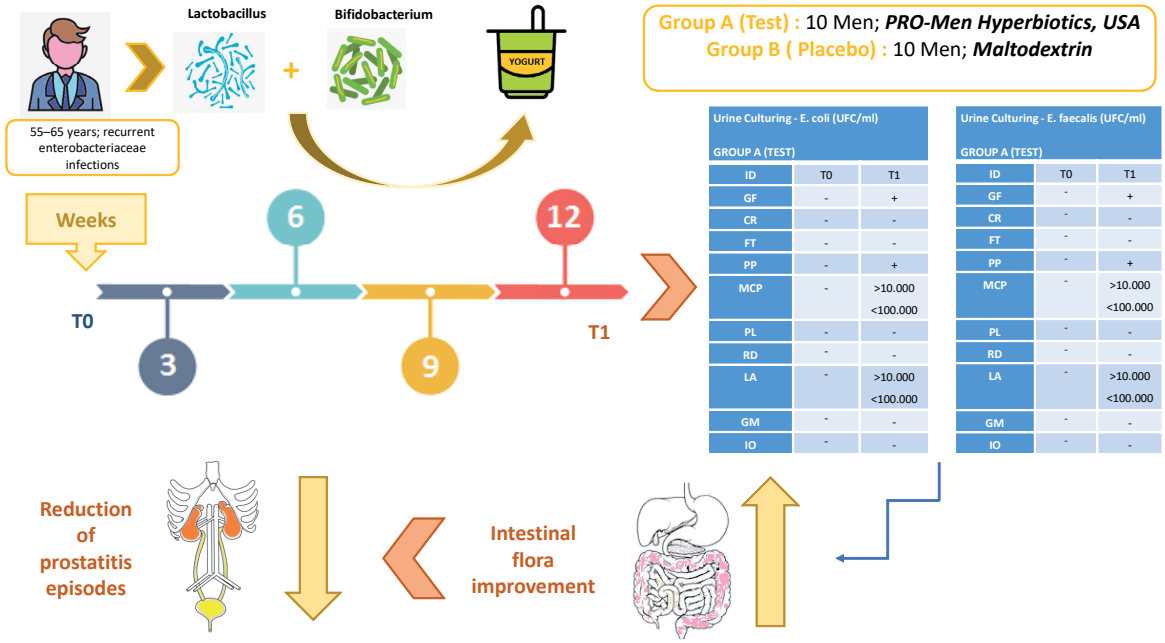


Fig. 6 The bacterial count of E. faecalis in group B.

Graphical Abstract: Study design



ID	T0	T1
GF	-	+
CR	-	-
FT	-	-
PP	-	+
MCP	-	>10.000 <100.000
PL	-	-
RD	-	-
LA	-	>10.000 <100.000
GM	-	-
IO	-	-

ID	T0	T1
GF	-	+
CR	-	-
FT	-	-
PP	-	+
MCP	-	>10.000 <100.000
PL	-	-
RD	-	-
LA	-	>10.000 <100.000
GM	-	-
IO	-	-

Discussion

Inflammation of the prostate or prostatitis is a very common phenomenon in adult men but also at a young age. In most cases it is not easily diagnosed considering the variable symptomatology with which it occurs, especially in cases of chronic or recurrent prostatitis (15). The triggers are often linked to lifestyle habits such as frequent travel, diets, prolonged antibiotic therapies, unbalanced nutrition, chronic constipation, psycho-physical stress, irritable bowel. Prostatitis is a disease linked to a specific cause, which must be discovered to treat the subjects in an optimal way and not to have relapses. Recognizing the cause and symptoms is very important to reduce the intensity and duration of the disease but also to avoid frequent relapses by reflecting on the patients' lifestyle habits (16).

Food intolerances are extremely widespread and cause altered permeability of the intestine and consequently favor the passage of bacterial species towards the urinary tract and in particular the prostate, triggering prostatitis. Awareness of the relationship between intestinal balance and prostate well-being allows for more effective prevention and more timely treatment of prostatitis (12). Probiotics have an important role in the prevention and management of prostates but also in benign prostatic hyperplasia. This is because the "good" bacteria present in probiotics are essential for the functioning of the immune system and for the control of inflammation, key elements of both pathologies. In fact, one of the best ways to prevent prostatitis is to keep the immune system in optimal conditions. The bacteria that cause prostatitis can be controlled or eliminated by helping to improve the intestinal bacterial flora. Therefore, regular ingestion of probiotics can help prevent the development of acute and chronic prostatitis by fighting both inflammation and the possibility of infection (17).

Emerging studies indicate that the microbiome can affect prostate inflammation, prostatitis / chronic pelvic pain syndrome and benign prostatic hyperplasia, as well as prostate cancer. The human microbiome present in multiple anatomical sites (urinary tract, gastrointestinal tract, oral cavity, etc.) can play essential roles such as regulation of homeostasis and the immune system and also affect systemic hormone levels (18). Recent studies seem to confirm that, in inflammatory and bone loss conditions, the use of probiotics with stem therapies could positively influence regenerative clinical practice (19-20).

The oral microbiome is also implicated in prostate health not only for the potential to give systemic inflammation but also for the ability of some oral pathogens to specifically colonize the prostate. In fact, bacteria characteristic of dental plaque has been found in prostatic secretions of patients with chronic prostatitis or benign prostatic hyperplasia and, simultaneously, periodontitis (21- 22).

In a study published in 2017, 162 patients with chronic infections were recruited at various sites including 56 (35.8%) who had uro-genital inflammations to evaluate the quantitative and qualitative composition of intestinal microflora before and after treatment with probiotics. In most subjects, quantitative and qualitative changes in intestinal microflora were found, in fact, in all study groups after using probiotics, the number of pathogenic microorganisms (*S. aureus, S. saprophyticus, S. epidermidis,* and *C. albicans*) was reduced and tended to restore the normal range of the microbial landscape, inducing a reduction and improvement of the inflammatory state (23-24).

In a study by Sherman et al., it was possible to evaluate how probiotics provide a barrier that allows the intestinal epithelium to respond to pathogenic infections (25).

Resta-Lenert and Barrett have shown that probiotic bacteria are essential to protect intestinal epithelial cells

in tissue culture from the adverse effects induced by the entero invasive *E. coli* (26-27). Boudeau et al. reported that a probiotic reduces both the binding and internalization of adherent and invasive *E. coli* strains (28). In summary, probiotic strains play an important role in attenuating host epithelial responses to pathogenic infections (29-39).

The major limitation of our study was the small number of participants and not comparable with other probiotics and just with placebo. Another limitation of our study is not following up participants after trial completion (e.g. 3 or 6 months) to see whether their incidence of clinical and microbiological parameters changed. Further research into dosages as well as task selectivity of probiotics should be conducted in the future.

Conclusions

In conclusion from the comparison between our data and the studies found in the literature we can affirm that the intake of probiotics containing bacterial strains such as *Corynebacterium, Staphylococcus, Streptococcus, Anaerococcous, Finegoldia, Lactobacillus*, *Peptoniphilus, Enterobacteriaceae, Pseudomonas, Actinobaculum,* in association with a controlled and specific diet, allows to reduce the cases of prostatitis in subjects men aged 55-65 years with recurrent infections and inflammations. The probiotics strains *PRO-Men Hyperbiotics*, taken for 12 weeks by the subjects in the Test group allowed to restore a good bacterial flora, creating an epithelial barrier that allows to protect against attacks by *E. coli* and *E. faecalis* and reduce the permeability of the tissue. In addition, probiotics allow to regulate and help the homeostasis of the immune system thus helping the subjects to respond better to possible attacks, also controlling the onset of extraintestinal infections. However more longitudinal studies are needed in different experimental settings for in-depth understanding with broader data analysis.

Prostate infection caused by certain pathogens, most likely present in combination, involves the onset of chronic inflammation, a common condition in adulthood and positively related to an increased tumor risk, this also allows us to say that the use of probiotics specific that allows to restore a healthy microbiota and to reduce inflammatory processes indirectly also reduces the risk of developing cancer. Considering potential health benefits-probiotics as an aid but also as a modulating factor for various pathological conditions related to the urogenital system.

Author Contributions

Conceptualization, R.S., L.P, K.H., S.T., L.S. and S.S. validation S.C. and A.P. data curation, F.P., F.I. , G.C., and S.T.; writing—original draft preparation, A.B., S.C., V.A., D.D.V.; writing—review and editing, all the authors. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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