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Research Article

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PUA, Sedentariety, Congestion, Infections, Microcalcification, Chronic Inflamation, Urethral Stricture, Prostatic Reflux, Capsule Role, Diets Irritants, Diabetes and Other Factor in Prostatic Reduced Uretral Flux: How to Reduce Infectious Episode

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ABSTRACT

Prostatic non neoplastic disease like BPH and LUTS show great reate of recurrent bacterial infectious with the need of repeated antibiotic cycle.

In order to reduce this phenomena it is necessary to consider all factor involved in order to verify if some of this are involved in the vicious circle typical of this pathology.

Aim of this work is to describe factors like chronic flogosis, PUA , and the effect played by Serenoa derivates.

The increase in the prostatic uretra flux also in moderate way can reduce the relapses. Not only antimicrobials but great relevance to the flogotic control and to the phisiology of the PUA can be The key factors.

Other relevant factor are analized related the pathogenic power to irritate bladder mucose or involved apparate structure prostate or prostatic uretra : dietary irritants , alchool, spicy, glucose (diabetic), prostate urinary reflux, abscesses, microcalcifications , uretral lesions and other.

The scope of the work start from the high rate of relapses in chronicized prostatitis and the standard used for therapy.

The novelty of this work is to take in consideration togheter various factor and noxa acting in the same apparatus and organ providing disconfort, pain , irritation and reduced quality of life.

This work is produced under a pharmaceutical pharmacological point of view throught the various aspect of the pathology and related conditions in order to better use the antimicrobials often greatly prescribed in this chronicized situation.

Keywords: BPH, LUTS, Prostatic Pathology, Inflamation, Alcool Etilic, Congestion, PUA, Sereona R, Vicious Circle Prostatic Uretral Flux, Bacteric And Non Bacteric Chronic Prostatitis, Antimicrobials, Local Steroids, Periodontal Disease, Biofilm, Relapses, Clinical Pharmacy.

Introduction

Between Urologist there is a common phrase related prostatitis: This are considered the "tomb of the urologist" that mean it is really difficut to treat in efficacy way avoiding relapses.

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Acute and chronic prostatitis are related to LUTS and other disorder. Many times there are chronicization with recurrent episode. The health and quality of life of the Patients are often heavily affected. And it is mandatory for the public health care systems to avoid misuse of antibiotics and relate MDR selections.

So patological movens, antimicrobial diffusion into the prostatic glande,pharmacokinetics, spectra of action, duration of therapy and association with other API are relevant aspect to be taken in consideration as well as the vicious cirgle aggravating the process.

Before to start this work is crucial to verify the Disorder of the prostata: Inflamations, infections, BPH, neoplams.

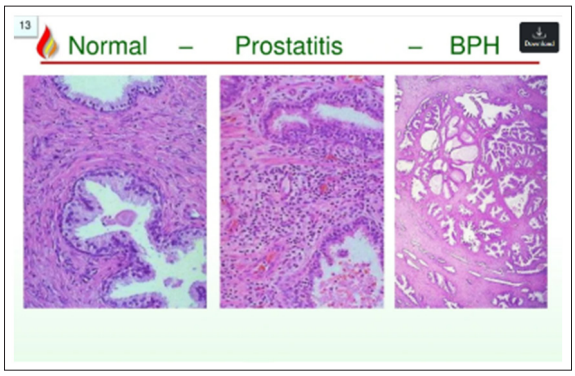

Figure 1: From VENKATESH MURTHY

"Prostatitis is inflammation of the prostate gland. It is the most common urological problem in men under 50 years old, with an overall prevalence of the 2.2-9.7%.

Prostatitis is comprised of acute bacterial prostatitis ABP, chronic bacterial prostatitis CBP, nonbacterial prostatitis, and prostatodynia.

Most cases of acute bacterial prostatitis are caused by ascending urethral infection AUI, although occasionally direct or lymphatic spread from the rectum or hematogenous spread via bacterial sepsis can be the cause.

Causative organisms include the E. Coli (most common), Enterobacter, Serratia, Pseudomonas, and the Proteus species. Sexually transmitted infections, such as Chlamydia or Gonorrhoea, are a rare cause.

Chronic bacterial prostatitis CBP is chronic bacterial infection of the prostate with or without prostatitis symptoms and is thought to be the sequelae of inadequately treated acute prostatitis cases.

Acute bacterial prostatitis ABP can present with lower urinary tract symptoms (LUTS), features of systemic infection (including also pyrexia), perineal or suprapubic pain, or urethral discharge.On the rectal examination, there is often a very tender and boggy prostate. Associated inguinal lymphadenopathy may also be present.

Chronic prostatitis CP should be suspected in men who complain of pelvic pain or discomfort for at least 3 months (Prostatodynia), alongside LUTS; the perineum is the most common site for the pain, however pain can occur in the suprapubic region, lower back, or rectum."

Urinary Tract Symptoms (LUTS) Secondary to Benign Prostatic Hyperplasia (BPH) and LUTS/BPH with Erectile Dysfunction in Asian Men: A Systematic Review Focusing on Tadalafil.

"Potential risk factors for LUTS/BPH include age, sedentary lifestyle and lack of exercise, smoking and excessive alcohol intake, depression, hypertension, cardiovascular disease, hyperlipidemia, TDM2 diabetes mellitus, obesity/waist circumference, hypogonadism, prostate disorder, inflammation, and genetic predisposition. other comorbidities that have been identified in men with LUTS/BPH. The BPH registry and patient survey reported the following comorbidities in the 6,909 men enrolled: hypertension, 53%; high cholesterol, 45%; erectile or other sexual dysfunction, 36%; digestive tract disorder, 21%; arthritis, 20%; heart disease/heart failure, 18%; diabetes, 17%; depression/anxiety/sleep disorder, 16%; allergies/cold/flu/congestion, 15%; and general pain/inflammation, 11%.".

Normal prostatic gland: glandular tissue ½, involuntary muscle ¼, fibrous tissue ¼

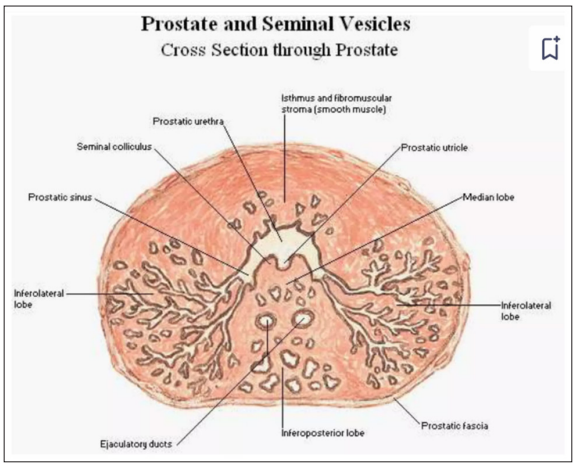

Figure 2: from Siddiqui

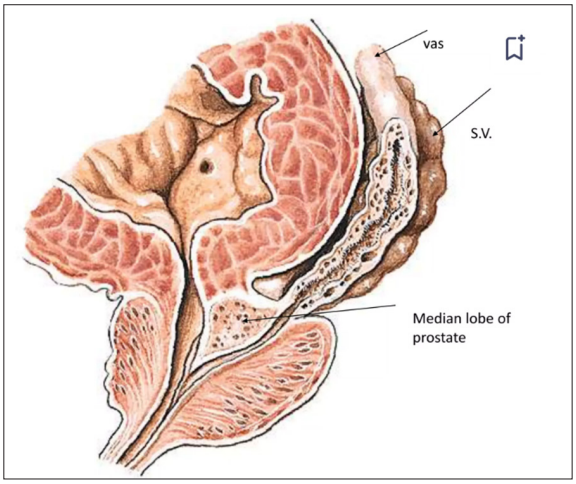

Figure 3: From Siddiqui

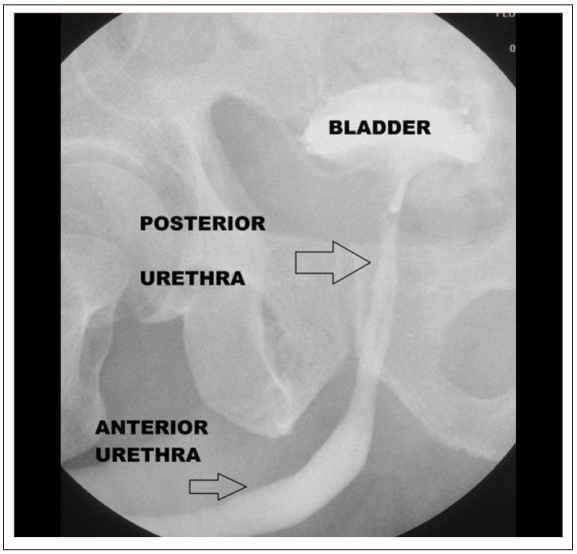

Figure 4: Male uretra from Radipaedia.org.

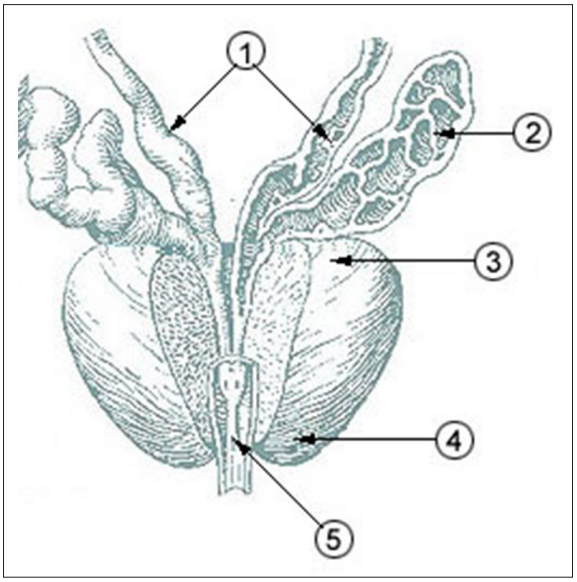

Figure 5: from Gray anatomy Dotti deferenti 2: Vescicole seminali 3: Base della prostata 4: Apice della prostata 5: uretra prostatica

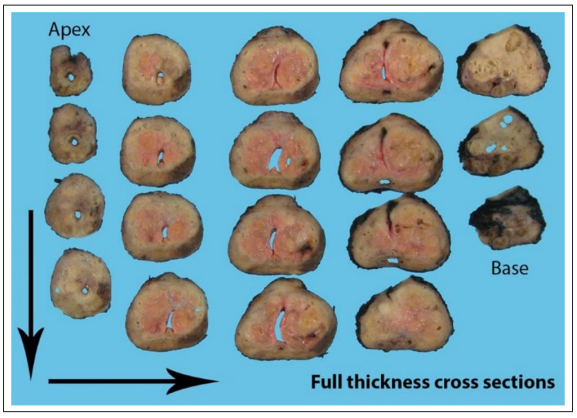

Figure 6: prostate From Gross pathology manual

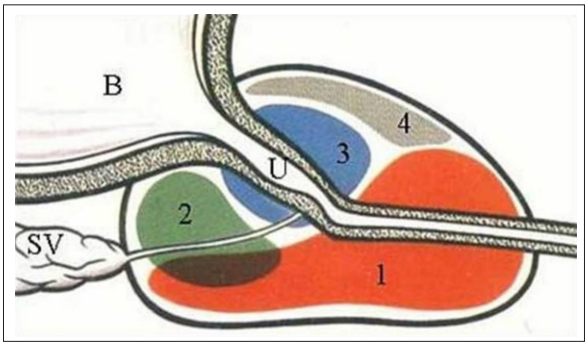

Figure 7: from1= Peripheral Zone, 2= Central Zone, 3= Transitional Zone, 4= Anterior Fibromuscular Zone. B= Bladder, U= Urethra, SV= Seminal Vesicle (adapted from Algaba)

Limphatic drainage of the prostata: trought internal iliac and sacral lymphonodes, the lymph vessel of the bladder to the external iliac lymph nodes.

Venous circle: the veins have thin wall, valveless, drained by several large trunks directly to the internal iliac vein.

Innervation of the prostate: parasympatic fibres and sympatic fibres prostate capsule role: in BPH the enlarged mass compress the tissue.

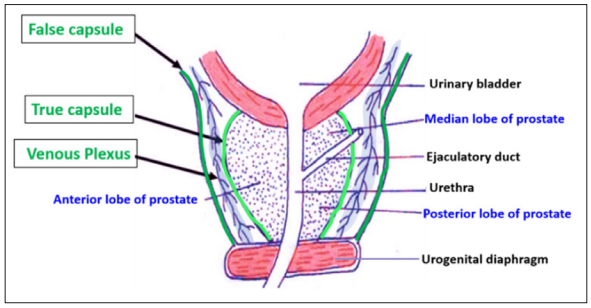

Figure 8: From Mayoclinic websiste

Recurrent prostate infection: What are the treatment options? by Garollo PC "Treating a prostate infection that keeps coming back might mean: Trying another antibiotic. One type of antibiotic might work better than another for the infection. Treatment also might involve taking more than 1 antibiotic.

Taking an antibiotic longer. This could mean taking an antibiotic for 6 weeks or longer. Using other medicines to help relieve symptoms. Medicines called alpha blockers can relieve urinary symptoms. Anti-inflammatory medicines such as ibuprofen or naproxen sodium can ease pain."

Table 1: National Institutes of Health Classification of Prostatitis

Classification	Description
I: Acute bacterial prostatitis	Acute bacterial infection of the prostate
II: Chronic bacterial prostatitis	Recurrent urinary tract infection caused by the same organism, secondary to chronic bacterial infection of the prostate
III: Chronic nonbacterial prostatitis/chronic pelvic pain syndrome	Chronic prostate pain without consistent cultures showing the same uropathogenic bacteria

IV: Asymptomatic inflammatory prostatitis	No history of prostate pain, but leukocytes or bacteria have been found incidentally on workup for other conditions
Information from reference 4.	

Risk Factors for Relapse in Acute Bacterial Prostatitis: the Impact of Antibiotic Regimens. Ester Marquez-Algaba, Carles Pigrau, Pau Bosch-Nicolau, Belen Viñado, J.Serra-Pladevall, Benito Almirante, and Joaquín Burgos.

"In our study, we observed a relapse rate of 6.3%, similar to the 5% to 10% published in previous studies. Diabetes mellitus, BPH, incontinence, and a history of prior UTI have been proposed as risk factors for relapse or progression to chronic prostatitis".

Material and methods

With an observational point of view some relavant literature are reported and analyzed. Figures and images (1-19) are used in order to better explain the general meaning of the work. An experimental project hypotesys is the submitted to the researcher to verify the hypotesys to be tested.

And related the multifactorial movens that are responsible of the recurrency and relapses in prostatitis chronicized even if trated with cycle of antibiotics. After this a global consulsion is provided.

Results

"LUTS and BPH are commonly associated. Only about 25% of men with BPH develop benign prostatic enlargement that causes obstruction and leads to LUTS. To confuse matters, sometimes small prostates are associated with LUTS and big prostates are not. LUTS is multifactorial in its etiology and cannot simply be equated with prostate pathology. In this work, I refer to "LUTS" as lower urinary tract symptoms in men that occur with or without documentation of BPH.Quantifying LUTS is most commonly done using the International Prostate Symptom Score (IPSS) or the American Urological Association Symptom Index (AUA-SI). Both scoring systems include questions relating to urinary symptoms: incomplete emptying; frequency; intermittency; urgency; weak stream; straining, and; nocturia. The IPSS has an additional question concerning the patient's quality of life, while the original AUA-SI did not. LUTS is a collective term used to describe subjective urinary symptoms that typically affect urine storage and flow, with these 2 categories considered as subsets of the IPSS. Storage symptoms: the acronym FUN, for frequency, urgency, and nocturia. Storage symptoms are also referred to in many publications as "irritative" or "filling" symptoms. Flow symptoms: the acronym WISE, for weak stream, intermittency, straining, and incomplete emptying. Flow symptoms have also been termed as "obstructive" or "voiding", but detailed urodynamic testing specifically designed for diagnosing outlet obstruction has failed to correlate obstructed from non-obstructed patients using the obstructive (also known as flow or voiding) subset score of the IPSS. The terminology is confusing, with "storage", "filling", and "irritative" being synonymous, as are the descriptors "flow", "voiding", and "obstructive". Of key importance is that the storage (also known as filling, irritative) subset of the IPSS is associated with a 2-fold or greater effect on what bothers patients, compared with the voiding (flow, obstructive) subset. This "bother" is what significantly diminishes the QoL score.

The acronym "FUN" is ironically the opposite case in men with LUTS. The use of Serenoa repens led to a Qmax improvement of +5.8 mL/s (51%). Kondas et al. only reported data on urinary flow (Qmax +4.08, 39%). For Redecker, multiple graphs within the publication were analyzed to objectify the clinical endpoints of nocturia and peak urinary flow, **with the finding of a 47.7% decrease in nocturia and an improvement in peak urinary flow by +3.4 mL/s (24% improvement)**" [1].

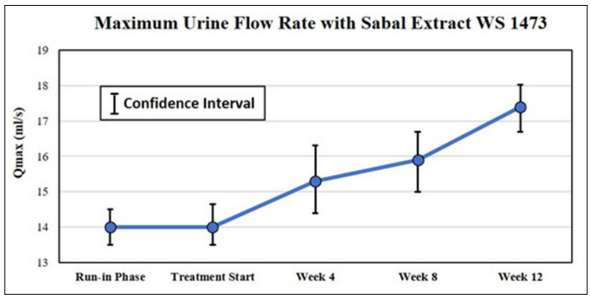

Figure 9: Data on maximum urine flow rate with the ethanolic extract of Serenoa repens (EESr) WS 1473 (Prostagutt Uno®) over a 12 wk study. Peak urinary flow rate (Qmax, mL/s) mean value curve with a 95% confidence interval reported. Modified based on Redecker et al. From Serenoa repens for Lower Urinary Tract Symptoms (LUTS): The Evidence for Efficacy and Safety of Lipidosterolic Extracts. Part I by Stephen B. Strum Community Practice of Hematology, Oncology and Int. Medicine, Focus on Prostate Cancer and Prostate Diseases, Nevada City, CA 95959, USA [1].

"Many proposed MOA mechanisms of action have been postulated to explain the effects of LSESr vs. LUTS. These include anti-androgenic, anti-proliferative, anti-α1-adrenergic, and anti-inflammatory activity. Each of these influences urinary tract symptoms through a different pathway.

5α-Reductase Inhibition

LSESr has been shown to inhibit the reduction of testosterone to dihydrotestosterone by inhibiting the activity of the 5α-reductase enzyme, of which there are 3 major isoforms (Types 1,2,3). In epithelial and fibroblast cell cultures, the hexane-sterolic extract of Serenoa repens (HSESr), commercially available as Permixon, has demonstrated the highest inhibitory activity and lowest variability in effect among 7 commercial LSESr products available in Europe. 2 of the long-chain fatty acids, linoleic and oleic acids account for one-third of the lipidosterolic profile and are active inhibitors of 5α-reductase Type 1 and to a lesser extent, 5α-reductase Type 2. LSESr has been shown to decrease DHT predominantly in the tissue of the periurethral zone of the prostate, an area primarily responsible for urinary obstruction caused by BPH. LSESr does not reduce serum levels of DHT, PSA, testosterone, or intra-prostatic testosterone levels. Instead finasteride and dutasteride significantly lower serum DHT levels. It does not appear that a decrease in tissue DHT in the periurethral zone accounts for the major impact of LSESr, especially when compared to the reliable effects of Avodart and Proscar in serum DHT reduction and associated decreases in PSA and prostate gland volume.

Anti-Inflammatory Effect

An important etiologic factor in the development of BPH, which typically clinically manifests as LUTS, is the finding of chronic histologic inflammation detected with prostate biopsies. Other factors such as age, hormone levels, lifestyle choices such as diet, smoking, alcohol consumption, and stress are also important. Adverse lifestyle factors appear to contribute to an increase in inflammatory cells infiltrating the prostate. **The inflammatory cells cause damage to both epithelial and stromal cells, stimulating cytokine release CK and increasing the concentration of growth factors, such as FGF. These inflammatory processes within the prostate lead to a progressive increase in prostate volume.** The presence of chronic prostatic inflammation is correlated with urinary tract symptoms, and for this reason, inflammation is an area of intense research in the treatment of BPH.

The effect of the hexanic extract of Serenoa repens (HESr) on measures of inflammation was evaluated in 2 controlled studies. In the Giulianelli 2012 open-label multicenter study, men with prostate diseases with associated inflammation showed significant improvement after 6 months in urinary flow rate, IPSS, and chronic prostatitis symptoms. In Latil 2015, men with moderate-to-severe LUTS were evaluated with biomarkers of chronic prostatic inflammation in an international, randomized, double-blind study comparing HESr at 320 mg/day vs. tamsulosin at 0.4 mg/day. Gene and protein expression biomarkers of inflammation were quantitated after 3 months of treatment. This revealed that 2 proteins involved in the recruitment and trafficking of inflammatory cells, monocyte chemoattractant protein-1(MCP-1), and IF- γ inducible protein 10 were decreased with HESr but slightly raised after tamsulosin. After a comprehensive gene expression analysis, a favorable anti-inflammatory effect on gene expression was observed in 73.3% of HESr patients vs. only 26.6% in patients receiving tamsulosin. In this work, a subset of patients with overexpression of macrophage migration inhibitory factor (MIF) had an average IPSS decline of 6.4 points for HESr vs. 6.5 for tamsulosin. MIF is a T-cell inflammatory cytokine, and its expression appears to be activated by a higher inflammatory micro-environment.

Other studies using histologic and immunohistochemical criteria have demonstrated that LSESr reduces prostatic inflammation. LSESr decreases B-cell infiltrates and serum levels of key cytokines such as IL-1β and TNF-α. **LSESr has been found to differentially affect proliferation and apoptosis in BPH by upregulating anti-inflammatory genes and downregulating pro-inflammatory genes.** In the process of inflammation, IL will upregulate androgen receptor (AR) activity and lessen the efficacy of 5α-reductase inhibitors like finasteride or dutasteride. 5α-reductase inhibitors decrease DHT, which is a ligand for the AR. The result is a decrease in DHT-AR binding and amelioration of BPH. Therefore, LSESr may prove to be a valuable adjunct to 5α-reductase inhibitors in the context of inflammation by inhibiting IL -interleukin-stimulated up-regulation of the AR.

Our study criteria excluded publications involving LSESr vs. LUTS in the context of non-bacterial prostatitis. Upon reflection, this may have been in error given the extremely high presence of histologically documented chronic inflammation in prostate biopsies of men with LUTS. A brief search of the literature reveals several articles on the effectiveness of LSESr vs. chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Given that LSESr lowers IL-1β, TNF-α, MCP-1, and other pro-inflammatory cytokines, the use of LSESr may be of paramount importance vs. other inflammatory conditions, age-related degenerative diseases, and neoplasia.

In such contexts, biomarkers of inflammation are routinely abnormal and signal transduction pathway aberrancies are commonly found. Peer-reviewed studies indicate cancer cell death resulting from the downregulation of tumor-associated growth factors such as IL-6, COX-2, akt, LTB4, STAT 3, urokinase-type plasminogen activator, basic fibroblast growth factor (bFGF, FGF-β, FGF2), and proinflammatory cytokines occurring with the use of Serenoa repens SR, and specifically LSESr. This warrants clinical investigation in light of the high therapeutic index evidenced in patients receiving LSESr in the treatment of LUTS" [2].

"The results of this study demonstrate how treatment for 6 months with an extract of Serenoa repens SR in routine clinical practice gives rise to a statistically significant improvement in Qmax values and in the IPSS, NHI-CPSI and IIEF-5 questionnaire scores, resulting not only in an improvement in the urinary symptoms but also in an overall improvement in patients' quality of life"[3].

"Another mechanism of action MOA attributed to Serenoa repens extract is the modulation of apoptosis via growth factors: it reverses the apoptosis/proliferation ratio seen in BPH tissue. Some studies have described a significant improvement in the International Index of Erectile Function score EFS following treatment with Serenoa repens extracts. If we take into consideration that retrograde ejaculation and reduced ejaculate volume related to α-blockers, and erectile dysfunction and decreased libido related to 5α-reductase inhibitors are frequently associated with dissatisfaction in medically treated BPH patients, Serenoa repens extract SRE may become a viable alternative in selected cases" [4].

"Statistically significant improvements in the International Prostate Symptom Score IPSS (5.5 points), quality of life (QoL; 1.8 points), Q(max) (5.6 ml/s), International Index of Erectile Function (IIEF; 6.4 points) and reduction in residual urinary volume were observed during the study period. **The mean prostate volume at 24 months was 36 ml, compared to 39.8 ml at baseline**" [5].

"Overall 97 patients were eligible for analysis. In the HESr group the mean inflammation grading and aggressiveness grading score significantly decreased from 1.55 and 1.55 at baseline to 0.79 ($p=0.001$) and 0.87 ($p=0.001$) at the 2nd biopsy, respectively. In the control group the mean inflammation grading score was 1.44 at first biopsy and 1.23 at the 2nd biopsy. The mean aggressiveness gradings core was 1.09 and 0.89, respectively. No statistical significance was found ($p=0.09$ and $p=0.74$).The mean decrease in all inflammation scores was statistically higher in the HESr patients compared to controls" [6].

"Effects of Permixon® on contractions of human prostate tissues

The α1-adrenergic agonists noradrenaline, methoxamine and phenylephrine, and the non-adrenergic agonists U46619 and

endothelin-1 induced concentration-dependent contractions of human prostate tissues, which were examined after addition of Permixon® in various concentrations (4.8 µg/ml, 16 µg/ml, 48 µg/ml) and of equivalent amounts of hexane in controls. Neurogenic contractions were induced frequence-dependently by EFS. Contractions induced by noradr., methoxamine and phenylephrine were inhibited partly by Permixon® in each of the 3 examined dilutions. **The degree of inhibition was similar with all 3 α1-adrenergic agonists, with inhibitions ranging mostly around one-third or higher.**

Effects of Permixon® on contractions of human detrusor tissues

The **cholinergic agonists** carbachol,methacholine, and the non-cholinergic agonists U46619 and endothelin-1 induced concentration-dependent contractions of human detrusor tissues, which were examined after addition of Permixon® extract (16 µg/ml) and of equivalent amounts of hexane in controls. Neurogenic contractions were induced frequence-dependently by EFS. Contractions induced by methacholine were inhibited by Permixon® around 50 %, while carbachol-induced contractions remained unchanged.

Effects of the Permixon® on **proliferation of WPMY-1 cells WPMY-1immortalized human prostate stromal cell line (benign).**

WPMY-1 cells were exposed to different amounts of Permixon® extract PE (1.6-48 µg/ml) and to equivalent amounts of hexane in controls. Permixon® reduced the proliferation rate in WPMY-1 cells in a concentration-dependent and time-dependent manner.

Effects of Permixon® **on colony formation of WPMY-1 cells**

Colony formation of WPMY-1 cells was reduced by Permixon®.

Effects of Permixon® on viability of WPMY-1 cells

Permixon® (1.6-48 µg/ml) reduced the viability of WPMY-1 cells in CCK-8 assays.

Effects of Permixon® **on actin organization of WPMY-1 cells**

Phalloidin-stained actin filaments in hexane-treated control cells were arranged to bundles of long and thin protrusions, and elongations from adjacent cells were overlapping each other. Permixon® (1.6-48 µl) caused concentration-dependent degradation of the actin filaments after incubation for 24, 48, 72 h, resulting in a rounded cell shape without any protrusions".

Effects of Permixon® on apoptosis and cell death of WPMY-1 cells Even at the highest concentration of 48 µg/ml, Permixon® did not increase the relative n. of cells in apoptosis or of dead cells compared to hexane-treated controls" [7].

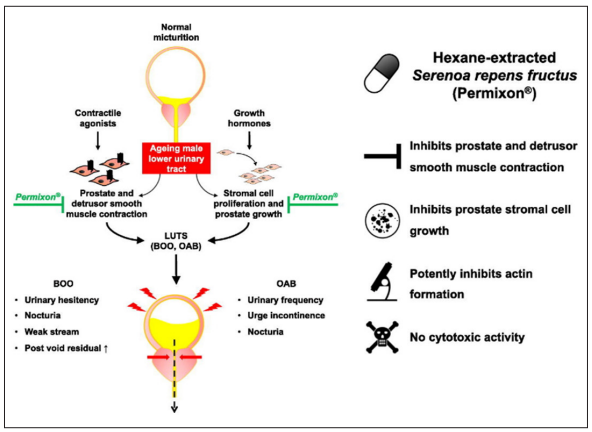

Figure 10: From Life Sciences

"To evaluate the association of prostatic urethral angle (PUA) with bladder outlet obstruction (BOO) index in men with LUTS suggestive of BPH. The Patients with higher PUA (PUA>or=35 degrees) had higher prostate-specific antigen levels (P=.043), larger prostate volume (P<.001), higher maximal urethral closure pressure (P=.004), higher detrusor pressure at maximum flow rate (P=.008), and higher BOO index (P=.032), in comparison with who had lower PUA (PUA<35 degrees)" [8].

"Using the fluid dynamic model FDM, the urinary flow rate increased in proportion to the urethral diameter and was inversely associated with the PUA. **The mathematical simulations showed that the urinary flow rate decreased by more than 27% as the PUA increased from 35° to 90°**. In the clinical setting, the peak flow rate was significantly associated with the PUA by linear regression analysis ($R = 0.34$, $\beta = -0.342$, $P = 0.005$), but it was not associated with the total prostate volume ($R = 0.18$, $\beta = -0.181$, $P = 0.150$).The prostatic urethra PU is a bent tube, and the clinical significance of the prostatic urethral angle (PUA) is poorly understood.The PUA was inversely associated with the urinary flow rate in this theoretical model and preliminary clinical study" [9].

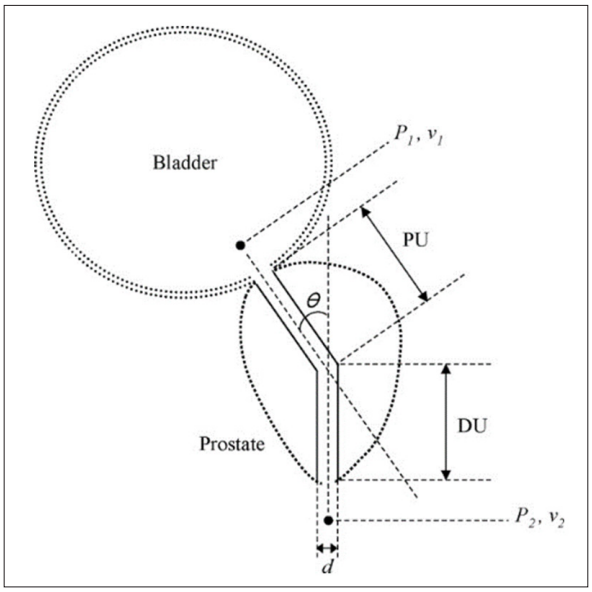

Figure 11

"The results of our study can explain the clinical findings that the severity of LUTS and the urinary flow rate are not relative

to prostate size. On the contrary, PUA prostatic urethral angle plays a very important role A study by Bang et al demonstrated that PUA has strong relationship with Qmax and IPSS in men with LUTS. Ku et al found that PUA correlates with the bladder outlet obstruction (BOO) index. As PUA increases, the severity of BOO also increases. We can see that the mean PUA of the patients whose IPSS scores are ≤ 20 is 40.83°, whereas that of patients whose IPSS scores are > 20 is 55.95°. There are significant differences between the 2 groups ($p < 0.001$).The mean IPP of patients whose IPSS scores are ≤ 20 is 3.99 mm, whereas that of patients whose IPSS scores are ≥ 20 is 7.05 mm. There are significant differences between the 2 groups as well ($p < 0.001$). Table reported shows a comparison of PUA and IPP according to Qmax. We can see that the mean PUA of the patients whose Qmax are < 10 mL/second is 45.28°, whereas that of patients whose Qmax ≥ 10 is 41.18° ($p = 0.016$). There are significant differences between the 2 groups" [9].

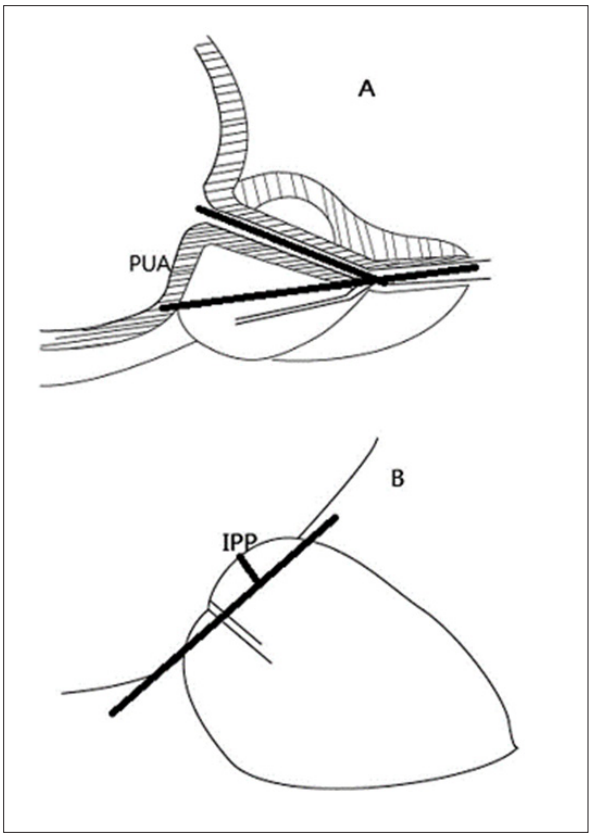

Figure 12: The relationship between the prostatic urethral angle (PUA) and the length of intravesical prostatic protrusion (IPP). (A) PUA is defined as the angle formed by the proximal prostate urethra and distal prostate urethral. (B) IPP is measured from the tip of the protruding prostate into the bladder to the bladder circumference at the prostate base in the sagittal plane.

Nonbacterial prostatitis NP, together with chronic pelvic pain syndrome, accounts for 90-95 % of prostatitis cases. Anti-inflammatory medications are commonly used to reduce storage/inflammatory symptoms that can deteriorate quality of life. The purpose of this study work was to observe the efficacy and safety of beclomethasone dipropionate rectal suppositories in inflammations of the lower urinary tract in men.

Efficacy Assessments: voiding parameters, perineal pain, International Prostate Symptom Score (IPSS), digital rectal examination. Adverse events AE and patient compliance were recorded throughout the study.

One hundred eighty patients were enrolled, mean age 52 ± 14.97. Diagnosis: nonbacterial prostatitis (85 %). All patients completed visits 1 and 2. All patients were treated with beclomethasone dipropionate (BDP) suppositories, 136/180 also with Serenoa repens (SR) extract. Antibiotics were rarely required. 62/180 patients presented clinically significant improvements and terminated treatment.

Mean change vs. baseline in voiding frequency: −3.55 ± 2.70 n/day in patients taking only BDP and −3.68 ± 2.81 n/day in those taking both BDP and SR (P<.0001 in both groups). Uroflowmetry improved significantly; change from baseline 3.26 ± 5.35 ml/s in BDP only group and 5.61 ± 7.32 ml/s in BDP + SR group (P = 0.0002 for BDP, P<.0001 for BDP + SR). Urine stream normal in 35 % of patients at visit 1 and 57.22 % of patients at visit 2. Mean change in perineal pain, on 0-10 VAS, −0.66 ± 2.24 for BDP only group (P = 0.0699) and −1.37 ± 2.40 for BDP + SR group (P<.0001). IPSS increased at visit 2. No adverse events AE were reported" [10].

"This work indicated that alcohol could aggravate the severity of prostatic inflammation in EAP model though activating the NLRP3 inflammasome. The role of MCC950 in inhibiting NLRP3 inflammasome and decreasing IL-1β secretion to alleviate EAP severity may show that it is a promising therapeutic molecule for CP/CPPS. The Histological analyses showed diffuse inflammation in the stromal tissues that were characterized by severe infiltration of neutrophils and mononuclear cells in mice in the EAP-alcohol group compared with EAP-vehicle group" [11].

"Caffeine is probably the most significant dietary prostatic irritant for most patients, but each individual will likely have specific and unique sensitivities. Other nutritional prostatic irritants include alcohol, high potassium foods like dried fruit and bananas, cranberry juice, colas and other carbonated beverages, dairy, red meat, spicy foods like "hot sauce," salt, coffee, highly acidic foods (citrus, vinegar), chocolate, and lemon juice.

A higher fluid intake is recommended as dehydration makes the urine more concentrated and irritating.

Quercetin, lycopene, selenium, curcumin, Cernilton (a pollen extract), Serenoa repens (saw palmetto), rapeseed bee pollen, various other flower pollen and plant extracts, and many other nutraceuticals, bioflavonoids, and phytotherapeutics, have shown at least some limited benefit in treating the symptoms of CP/CPPS.

Exercise and increased physical activity have been shown to improve symptoms of CP/CPPS in at least 1 randomized study. This underutilized treatment modality is easily implemented, has no side effects, and provides substantial additional health benefits beyond reducing bothersome symptoms of CP/CPPS. Hot sitz baths offer significant relief, but the effects are temporary, and the water must be hot. This thermal treatment must be a bath rather than a heating pad or hot shower to facilitate deeper heat penetration minutes is sufficient. Most patients find multiple sitz baths helpful daily, particularly during symptom

exacerbation. As symptoms improve, the frequency of the sitz baths can be reduced. An initial frequency of 3 or 4 times daily is recommended for patients with significant symptoms.

Soft but supportive cushions when sitting, including inflatable "donuts," are recommended as they often help, have no side effects, and are quite inexpensive. Inflatable cushions and donuts should be inflated just sufficiently to minimize perineal pressure.

Patients should avoid sitting on cold, hard surfaces like as a stone bench, and bicycle riding should be avoided as the narrow seat puts undue pressure directly on the sore and inflamed perineum" [12].

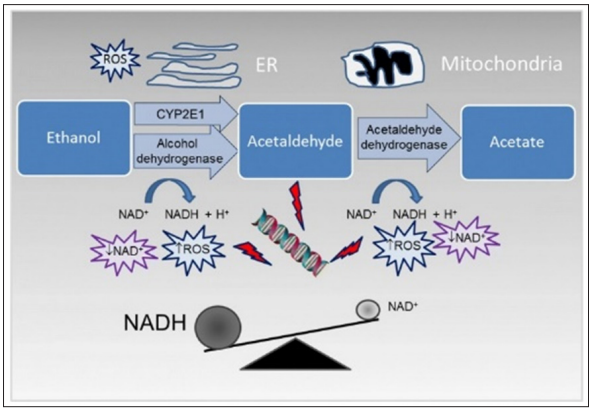

Figure 13: Main pathways of alcohol oxidative metabolism. Etoh is converted into acetaldehyde by the cytosolic enzyme alcohol dehydrogenase and by the microsomal cytochrome P450 2E1 (CYP2E1); acetaldehyde is then oxidized into acetate by the mitochondrial enzyme aldehyde dehydrogenase 2. Etoh metabolism increases the ratio of the reduced nicotinamide adenine dinucleotide (NADH) to the oxidized nicotinamide adenine dinucleotide (NAD+) and promotes reactive oxygen species (ROS).

"The urinary bladder is 1 of the many organs affected by DM. Urine production is increased as hyperglycemia results in elevated glucose filtered load, which when exceeding the reabsorption capacity (renal threshold) of the kidney, leads to osmotic diuresis. It is proposed that initially the bladder adapts to polyuria by compensatory, increased activity but subsequently decompensates due to the direct effects of chronic systemic hyperglycemia on bladder tissues A number of studies in animal models of DM have shown that morphological and functional manifestations of DBD are time dependent. Bladder hypertrophy BH and remodeling, increased contractility, and associated neurogenic changes occur soon after the onset of DM, while decreased peak voiding pressure, evidenced in urodynamic measurements, develops only at a later stage of DM. Alterations in bladder smooth muscle (detrusor) and innervation have also been reported in the DM patients. Quantitative polymerase chain reaction PCR analysis and electron microscopy were used to evaluate UT gene expression and cell morphology 3, 9, and 20 wk following streptozotocin induction of DM in female Sprague-Dawley rats compared with age-matched control tissue. Desquamation of superficial (umbrella) cells was noted at 9 wk DM, indicating a possible breach in barrier function.

One other causative factor may be metabolic burden due to a chronic hyperglycemia, suggested by upregulation of the polyol pathway and glucose transport genes in DM UT. While superficial UT repopulation occurred by 20 wk DM, the phenotype was different, with significant upregulation of receptors associated with UT mechano-sensation (transient receptor potential vanilloid subfamily member 1; TRPV1) and UT autocrine/paracrine signaling (ACH receptors AChR-M2 and -M3, purinergic receptors P2X2 and P2X3). Compromised barrier function and alterations in the UT mechanosensitivity and cell signaling could contribute to bladder instability, hyperactivity, and altered bladder sensation by modulating activity of afferent nerve endings, which appose the urothelium. Our results show that DM impacts urothelial homeostasis and may contribute to the underlying mechanisms of the DBD" [13].

"Calcifications in the prostate can be seen in the form of a calculus or microcalcifications and this may have clinical significance: they may be misinterpreted as carcinoma; they may cause prostatitis and pain; they may cause injuries in the prostatic parenchyma when manipulation is performed; they may cause bladder neck obstruction; and they may pose other difficult diagnostic and therapeutic problems" [14].

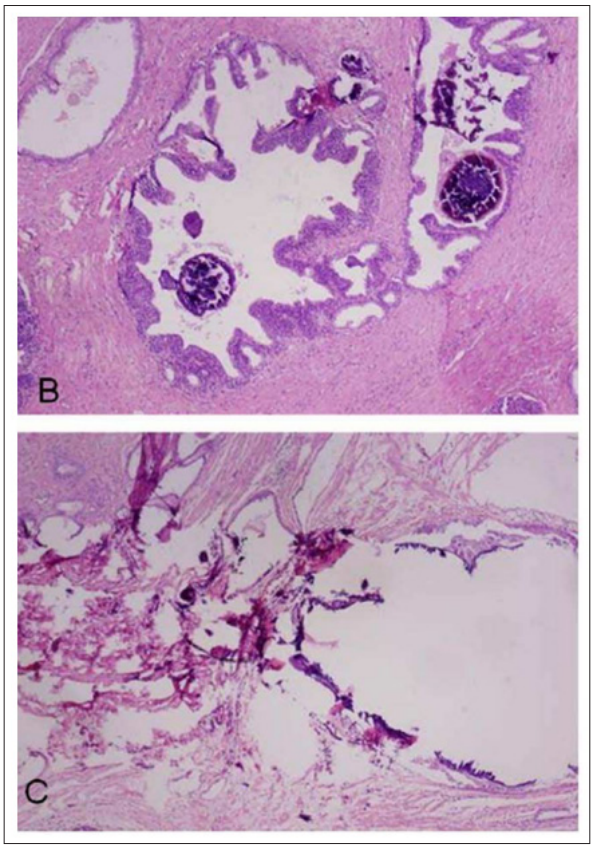

Figure 14: (B) moderate calcification in prostatic glands; (C) severe calcification with section Damage.

"Urine reflux into the prostatic duct induces abacterial prostatitis AP. Silodosin relieved prostatic inflammation PI and bladder overactivity by increasing microcirculation in the prostate" [15]. "The most common causes of a urethral stricture US are chronic (long-term) inflammation or an injury that causes scar tissue. Scar tissue causes the urethra to become narrow, which makes it more difficult for pee to flow.

Scar tissue can gradually form from:

- An injury to penis or scrotum (the pouch of skin behind penis that holds testicles).

- An infection, usually a sexually transmitted infection, such as chlamydia.
- Placement of urinary catheters or surgical instruments in your urethra during surgery or other medical procedures.
- Urethral or prostate cancer.
- Radiation therapy."

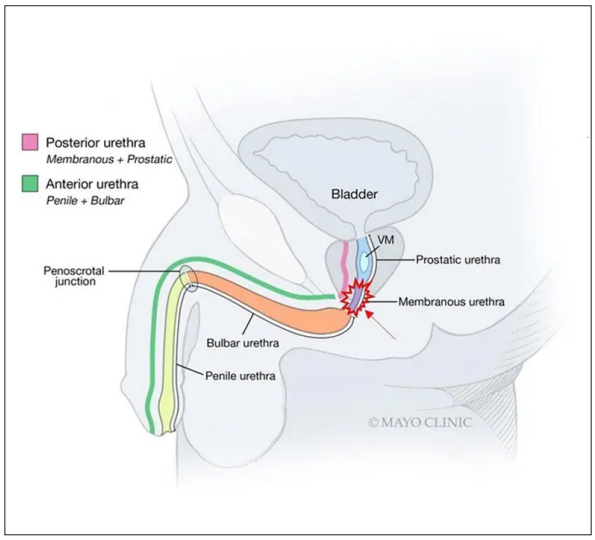

Figure 15: from Mayoclinic

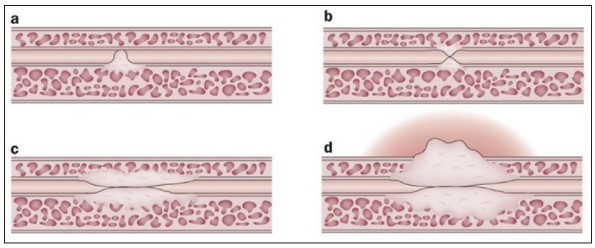

Figure 16: from Male urethral strictures and their management

"A prostatic abscess is a localised collection of purulent fluid within the prostate, frequently arising as a complication of acute bacterial prostatitis" [16].

"Several kinds of beverages and foods, including coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners and hot peppers can exacerbate the symptoms in patients with bladder pain syndrome/interstitial cystitis BPS/IC" [17].

"LUTD is a progressive disease that can lead to bladder dysfunction if left untreated or treated ineffectively. Sequelae include urinary retention, recurrent UTI, bladder calculi, and, eventually, renal impairment. LUTD involving the prostate is associated with both ageing and inflammation. Tissue inflammation resulting from ageing, infection, or other inflammatory disease (in ex TDM 2 diabetes) is epidemiologically associated with the subsequent development of tissue fibrosis in multiple organ systems, including the prostate. Recent works show that tissue fibrosis in the lower urinary tract is associated with LUTD, and suggest that fibrosis might be a previously unrecognized pathobiology that contributes to LUTD" [18].

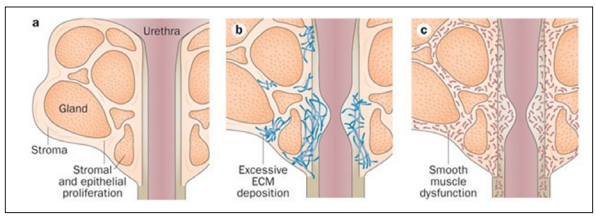

Figure 17: from Rodriguez

American Urological Association

"Common known causes of the urethral injury UI include trauma to the perineum or urethra, as seen in straddle injuries and pelvic fractures; iatrogenic causes, such as pelvic radiation, surgery for hypospadias, urethral catheterization, and endoscopic procedures; infections, primarily recurring chlamydial or gonococcal sexually transmitted infections; and inflammatory pathologies, like as lichen sclerosus LS. The leading causes of penile urethral strictures US are iatrogenic and inflammatory pathologies, followed by idiopathic and traumatic etiologies. The leading causes of bulbar urethral strictures US, in order of prevalence, are idiopathic, iatrogenic, traumatic, and inflammatory conditions."

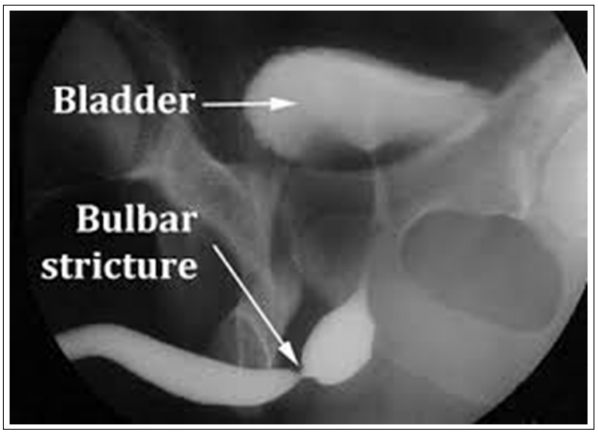

Figure 18: from British assoc

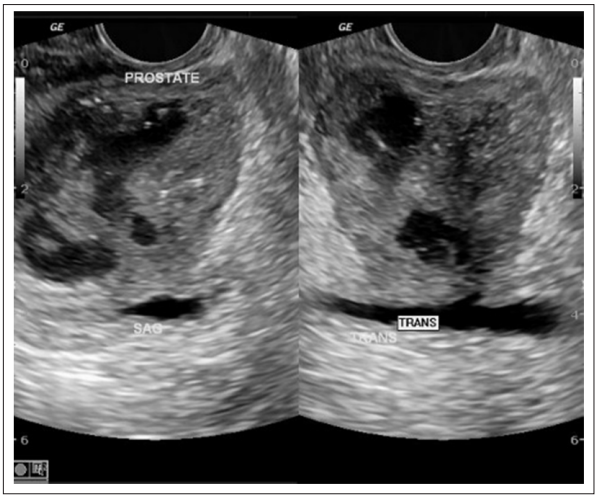

Figure 19: form Transrectal ultrasound shows an enlarged prostate with a volume of approximately 34 cc. It shows irregular cavities / cystic spaces of turbid fluid, suggestive of an intraprostatic abscess IA. Extra-prostatic spread is noted on the right side. Form Radiopaiedia 2024.

"We found high rates of resistance to the most frequently used antibiotics and a high relapse rate in patients whose treatment was not adjusted according to their microbiological susceptibility. We did not observe differences, though, in mortality or relapse according to appropriate or inappropriate empirical treatment. What is new in this work is the different relapse rates observed depending upon the definitive adequate antibiotic used. Quinolones and intravenous (i.v.) beta-lactam have lower rates of relapse (1.8% and 3.6%, respectively) compared to co-trimoxazole and oral beta-lactam (3.3% and 9.8%, respectively) [19].

"137 patients with a diagnosis of chronic bacterial prostatitis (CBP) were subjected to combination pharmacological therapy with antibacterial agents (ciprofloxacin/azithromycin), alpha-blockers (alfuzosin) and Serenoa repens extracts. 88 patients (64.2%) showed microbiological eradication at the completion of a 6-week cycle of therapy. 49 patients showing persistence of the causative organism(s) or reinfection at the end of treatment, 36 completed a 2nd cycle of combination therapy for 6 weeks: 27 patients (75%) showed eradication of the causative organism, whereas in 9 cases persistence or reinfection was observed. The cumulative eradication rate- calculated on a total of 137 enrolled patients - is 83.9%.Our results indicate that about 20% of patients enrolled in this study, who were refractory to a protocol of 6-week combination therapy, could be 'rescued' by a 2nd cycle of treatment. Clinical follow-up data show that combination therapy could ensure extended relief from CBP symptoms, and a general improvement in quality of life"[20].

"Fluoroquinolones remain 1 st -line therapy, followed by trimethoprim-sulfamethoxazole or doxycycline if the pathogen is susceptible. Fosfomycin has emerged as a repurposed and useful agent because of the increasing incidence of MDR pathogens" [21].

"According to the epidemiological survey of ABP, E. coli (accounting for 65%-80%) comprises the overwhelming majority of the bacteria that cause this infection. Other agents include Enterococcus, Pseudomonas aeruginosa, Proteus, Klebsiella, Enterobacter, and Serratia. Neisseria gonorrhoeae, Chlamydia trachomatis, some fungi (Cryptococcus, Salmonella, and Candida), and Mycobacterium tuberculosis also reportedly cause ABP, especially among sexually active and immunocompromised IC patients the increasing difficulty of antibacterial treatment (emergence of MDR bacteria and ESBL-producing Escherichia coli, bacterial biofilms production, and shift in bacterial etiology) and the transformation of therapeutic strategy have attracted worldwide attention" [22].

"Young men who are single and suffering from NBP must be informed about their illness in detail and, if they are not doing so, they should be encouraged to ejaculate in regularly way" [23].

"172 CNBP patients and 151 healthy males were recruited as CNBP and control group, respectively. The prostatic fluid was collected and tested by pre- and post-massage test. WBC number was counted, and the contents of COX-2 and PGE2 were determined. The pain and discomfort of each patient were scored according to the NHI chronic prostatitis symptom index. Compared with the control group, CNBP group displayed significantly higher WBC count, COX-2 level, and PGE2 level. Contents of COX-2 and PGE2 in prostatic secretion PS of CNBP group were positively correlated with pain scores ($r = 0.855$ and 0.675, respectively, $P < 0.01$), total symptom scores ($r = 0.674$ and 0.566, respectively, $P < 0.01$). A significantly positive correlation between COX-2 and PGE2 levels was also discovered ($r = 0.493$, $P < 0.05$). The WBC number was not obviously correlated with the accumulations of COX-2 and PGE2 or the clinic symptoms of CNBP" [24].

"In the multivariate analysis MVA of all patients, after adjustment for different factors, the only independent risk factor for relapse was inadequate definitive antibiotic treatment (OR, 12.3; 95% confidence interval [95% CI], 3.5 to 43.1; $P<0.001$). Even if not statistically significant, BPH showed a trend as a risk factor for relapse (OR, 2.9; 95% CI, 0.9 to 9.5; $P=0.07$)" [25].

From Prostatitis (Infection of the Prostate) - Urology Care Foundation

"Bacterial prostatitis BP is caused by a bacterial infection in the prostate. Bacteria can get into the prostate when infected urine flows backwards from the urethra".

"3 major factors determining the diffusion and concentration of antimicrobial agents in prostatic fluid and tissue are the lipid solubility, dissociation constant (pKa) and protein binding. The normal pH of human prostatic fluid is 6.5-6.7, and it increases in chronic prostatitis CP, ranging from 7.0 to 8.3. A greater concentration of antimicrobial agents in the prostatic fluid occurs in the presence of a pH gradient across the membrane separating plasma from prostatic fluid. Good to excellent penetration into prostatic fluid PF and tissue has been demonstrated with many antimicrobial agents, including tobramycin, netilmicin, tetracyclines, macrolides, quinolones, sulfonamides and nitrofurantoin" [26].

"180 patients were enrolled, mean age 52 ± 14.97. Most frequent diagnosis: nonbacterial prostatitis (85%). All patients completed visits 1 and 2. All patients were treated with beclomethasone dipropionate (BDP) suppositories, 136/180 also with Serenoa repens extract. Antibiotics were rarely required.

162/180 patients presented clinically significant improvements and terminated the treatment. We also observed an improvement in the main storage symptoms and clinical findings associated with lower urinary tract inflammation in patients treated with beclomethasone diprop. suppositories" [27].

"Quinolones and i.v. beta-lactam have lower rates of relapse (1.8% and 3.6%, respectively) compared to co-trimoxazole and oral beta-lactam (3.3% and 9.8%, respectively). Clinicians should carefully choose an adequate antibiotic for definitive ABP treatment depending on the results of microbiological isolation, using quinolones as the first option. Whenever quinolones cannot be administered, i.v. beta-lactams seem to be the 2nd -best option"[28].

"N-Acetylcysteine NAC is a thiol-based antioxidant with antibacterial as well as antibiofilm, proteolytic and anti-

adherence effects in vitro against several pathogens. NAC plays a key role in enhancing the effect of co-administered antibiotics showing an antibiofilm activity with ciprofloxacin against P. aeruginosa. According to a previously published study, NAC showed an intrinsic antimicrobial activity due to perturbation of the intracellular IC redox equilibrium and antibiofilm activity. In the last case, NAC disrupts the structure of bacterial biofilm and improves the penetration of antibiotics.It is known that several bacteria involved in the development of acute and chronic prostatitis form biofilms. This environment increases resistance to antibiotics, and the extracellular matrix protects the interior of the community. Bartoletti et al. showed that biofilm-producing bacteria were commonly involved in BP with a negative impact on the response to antibiotic therapy. Many studies reported polyphenols, tocopherols, phenolic acids, ascorbic acid and flavonoids. Polyphenols have been associated in vitro with strong antibacterial, antiviral, antimutagenic, anticancer, anti-inflammatory and antioxidant properties, including scavenging of free radicals, inhibition of lipid oxidation and a reduction of hydroperoxide formation. Ribes nigrum RN is a well-recognized source of polyphenols, as well as anthocyanins, phenolic acid derivatives and proanthocyanidins. Ikuta et al. reported the antimicrobial and anti-inflammation activities of the Ribes nigrum, in particular, due to its capacity to prevent the adsorption and growth of the bacteria" [30].

"Spermatozoa may induce seminal vesiculitis through the activation of innate immune responses in seminal vesicular epithelial cells, which provide novel insights into the mechanisms underlying non-infectious NI seminal vesiculitis" [31].

"Seminal vesiculitis SV is usually found in association with inflammation of the prostate. Imaging findings are nonspecific, including thickened seminal vesicle walls, increased internal echogenicity, cystic dilatation and irregularity of the vesicle lumen, Transrectal US can easily differentiate low ejaculatory volume secondary to impaired seminal vesicle secretion from that of enlarged seminal vesicles SV due to ejaculatory duct obstruction" [32].

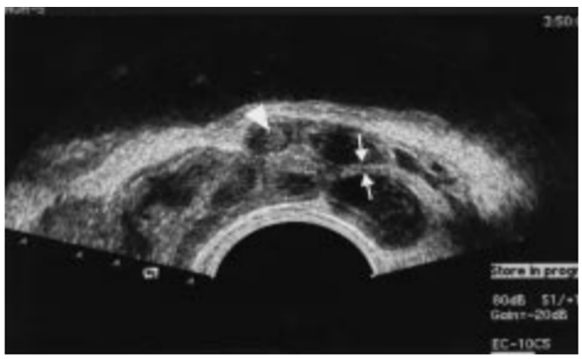

Figure 10: *Diffuse inflammation of the seminal vesicles in a 32-year-old man. Transrectal US along the left seminal vesicle (oblique sagittal scan) shows diffuse enlargement and a thickened wall (arrows), with internal hypoechoic debris (arrowhead).*

Figure 20: From Seung-Hyup Kim

"The immune system plays a crucial role in the development and progression of BPH. Indeed, chronic inflammation is a hallmark of BPH, with increased infiltration of T cells, macrophages, and mast cells in the prostate tissue. In line with a chronic inflammation, BPH tissue exhibits a fundamental re-landscaping of immune infiltrates similar to PCa, showing a higher density of immune cells (mostly T cells) than healthy prostates. The pro-inflammatory cytokines, like as TNFα, IL-6, and IL-8, are elevated in the serum and prostate tissue of BPH patients" [33].

"The mathematical simulations showed that the urinary flow rate UFR decreased by more than 27% as the PUA increased from 35 degrees to 90 degrees" [34].

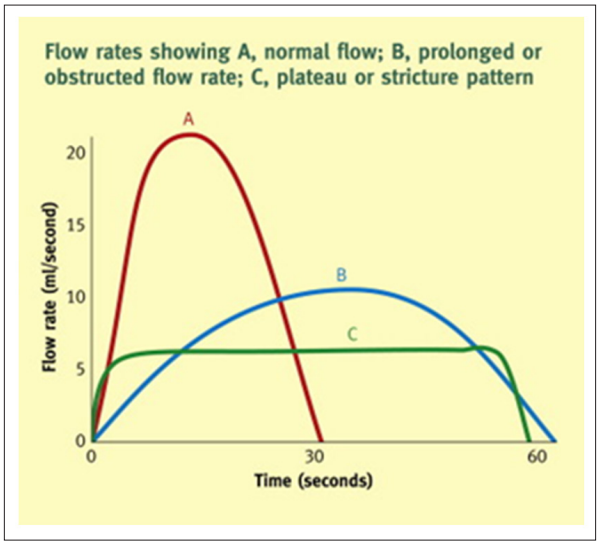

Figure 21: from Kate D. Linton

"voiding time was significantly higher in the sitting position than in the standing position" [35].

"The development of prostatitis in patients with periodontitis is up to 4.6 times more likely than in patients without periodontitis" [36].

Experimental Project Hypotesys

In order to test the hypotesys that for cronic prostatitis or cronicized the best therapy imply a variety of factors to be take in consideration it is neeted to follow 100 patient:

group A with Antimicrobial therapy only and **group B** 100 other patient treated not only with antimicrobials but associated local steroids, FANS, serenoa, dietary measure diabete control, lifestyle habits change and since PUA factors.

Tor this study it must to be followe an specific written therapeutic plan for antimicrobial prescription: kind of prostatitis: Abacterical/ bacterical

Acute- chronicized

Microorganism bacteria involved: gram+ /-, micetes, clamidia, mycoplasma, virus (HPV)

Presence absence of specific conditions: absesses, microcalcification, uretral restrictions, seminal vesciculitis.

Cultural tests, sensibility tests, other diagnostic tests, imaging, clinical sign, quality of life Imaging

Antimicrobial therapy: monotherapy, associations, duration, number of cycle, relapses

BPH therapy: alfa blokers or 5-ARI, or phytotherapy (Serenoa R.) Cumulative amount of mg of antimicrobial used Prostatic tissue penetration of antimicrobials used- analysis

Antinflamatory measure adopted: local and duration, FANS os steroids

Behaviors habits change: increase movement to reduce congestion and other, avoid irritants (yes/no)

Sexual activity: regular or not

Prevenction of trauma: anatomic saddle for cyclistys or other

In this studies it must to be registered if: antimicrobial monotherapy or association or in sequence duration of cycle and number of cycle.ADR-and toxicity

Costs: of the pharmacological therapy

Time of observation: 1 year

Measure: relapses, quality of life, amount of antimicrobial used

Discussion

Related PROSTATITIS (chronic or acute) and its relapses and BPH or other specific conditions like Microcalcifications, uretral restrictions, diabete un controlled, unhealthy habits like sedentarieriety or Diet intake of dangerous irritants like spicy, etoh or other factor it is possible to say that all this factors or various of this can be responsible in recurrency or relapses of cronicized prostatitis in a visious circle.

Fundamental so it is not only to to control the glucose level in urine, fight the infectious disease with the right antibiotics for the right time and in an efficacy posology, but also treat the flogosys with local steroids (suppository) to limits the systemic toxicity and to interrups the cronicization: see the lynphocite role in this situations.

It is necessary to Increase the movement reducing sedentariety to avoid congestion, reducing use of spicy or etoh but aslo verify other factors: Absces presence or absence, microcalcification presence or prostatic uretral restriction.

Uretral restriction can cause urine reflux into prostatic tissue with a chemical tissue irritation. Related the antimicrobial molecule it is necessary to verify the pharmacokinetiks in order to reach the prostatic tissue in a right way considering also associations or sequence of antimicrobials. It is necessary to verify not only the bacterial infections but also micotic or other microorganism (calamidia, micoplasma, HPV and other). Relevant in this way the cultural microbiogical and other test usefull.

Obiously the neoplasy presence/ absence must to be consider. It is clear by literature the effect played by some irritants like alchool or spicy on bladder epitelium and other related structure (uretra, prostate) as well as the role of diabetes not adequately controlled (direct irritation of the epietlium, bacterial infectious increased).

Today polithearpy in example in DM2 make possible to set the glicemia in order to avoid glucosuria.

The same are reported the effect played by sedentariety in the prostate congestion related the lymphatic and venous drainage systems

Related phytotherapy: the serenoa R.

"The finding of a 47.7% decrease in nocturia and an improvement in peak urinary flow by +3.4 mL/s (24% improvement)" [1].

And related inflamation

"The inflammatory cells cause damage to both epithelial and stromal cells, stimulating cytokine release and increasing the concentration of growth factors, such as fibroblast growth factor (FGF). These inflammatory processes within the prostate lead to a progressive increase in prostate volume" [2].

Related the sexual activity

"Some physicians recommend reducing congestion in the prostate by ejaculating more frequently."

Treatment of Bacterial Prostatitis

"Poor drainage of secretions from peripheral ducts or reflux of urine into prostatic tissue may lead to inflammation, fibrosis, or stones."

"N-Acetylcysteine is a thiol-based antioxidant with antibacterial as well as antibiofilm, proteolytic and anti-adherence effects in vitro against several pathogens. NAC plays a key role in enhancing the effect of co-administered antibiotics showing an antibiofilm activity with ciprofloxacin against P. aeruginosa.

Several studies reported polyphenols, tocopherols, phenolic acids, ascorbic acid and flavonoids. Polyphenols have been associated in vitro with strong antibacterial, antiviral, antimutagenic, anticancer, anti-inflammatory and antioxidant properties, including scavenging of free radicals, inhibition of lipid oxidation and a reduction of hydroperoxide formation " [30].

BPH therapy: improve the urinary flux (The α1A-adrenergic receptor has been shown to mediate the contraction of human prostatic smooth muscle), Finasteride, Dutasteride involved in reduced progression of BPH (effect on prostate volume).

Conclusion

Related a clinical pharmacy point of view is revelant to verify the righ use of drugs and antimicrobial also.

In order to reduce MDR phenomena it is necessary that the antimicrobial therapy are adopted considering all cofactor acting in some pathological condition.

The significative rate of recurrency - relapses in some chronic prostatitis and the partial in some cases inefficacy of the therapy prescribed need a deeply uderstanting in the complex patological movens that can influence or aggravate the vicious circle.

The Antibiotic therapy prescribed to this kind of patients without consider aggravating conditions

Can produce inefficacy: a right therapy of the flogosis for the right time can be useful also in some abatterical flogosys.

Not all the antibiotic used show the same prostatic penetration and efficacy in preventing relapses.

The same a right glicemia in DM2 make possible to reduce infections, and avoiding spicy or bladder irritant can have great impact.

The behaviour aspects are crucial. no sedentariety, right water intake, no spicy in diet are real useful.

It is opinion of the authors that all this fact must to be taken in right consideration in this kind of pathology.

And the introduction of a specific written therapeutic plan by the specialist or the general phisicians practitioner can be an useful instrument to reduce the antimicrobial use, or to aviod unsuseful antimicrobial resistence.

The specific Therapeutic plan oblige the physician to consider all the factor involved and it is useful in the right monitoring of the relapses.

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