Journal: Salient Journal of Urology

Salient Visionary Publications

There is a Relationship Between in Efficiency of External Uretral Sfincther and BPH? The Growth Factor and Pharmacological–Phytotherapic Role: The Inversion of The Classic Paradigmas Hypotesys of work

Luisetto M[1*], Mashori Gulam Rasool[2], Gamal A[3], Cabianca L[4] and **Latyshev O[5]**

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[5]IMA academy president

ABSTRACT

AAim of this work is to observe the indirect role played by external uretral sfinchter in the developement of BPH. There is any correlation between the reduced efficiency of this sfinctere and prostate benign ipertrofia? The inefficiency of the external uretral sfinthere need an additional work by the upper prostatic uretra . This process can increase the autocrine and paracrine effetc of the growth factor that can contribute to BPH.

Can this movens to be added to the ormonal effect played by androgen ? and If confirmed this patholoical proceess can have therapeutic implication?

All this phenomena are analized to veryfy the hypotesys.

Keywords: BPH, hyperplasia , external uretral sfinctere inefficiency, uretral pressure , growth factor, autocrine, oncology

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Introduction: This work start observing the efficacy of the KEGEL exercise for pelvic floor rehabilitation in BHP (and overactive bladder) and the effect played by 5 alfa reduttase inibitors and by Urtica dioica in this condition . The increase of the efficiency of the external uretral sfincthere help in controlling urge minction.

So is is inteersting to verify the relationship between the external sfincthere and the prostate. As reported in https://www.kenhub.com/en/library/anatomy/urethral-sphincters:

"The main action of the urethral sphincter complex is to compress the urethra. This is important as it provides control over the urinary continence. The internal sphincter's smooth muscle resting state is one of contraction or 'closure', in which urine is prevented from passing through the internal urethral orifice into the urethra. The external sphincter ES is also thought to contribute to resting closure, although it's most important feature is augmenting closure to prevent urination or voluntary opening to allow voiding."

According s Yucel et al : "The smooth and striated muscle components of the urethral sphincter complex USC are inseparable in both sexes."

In Journal of UrologyReview May 2008

The Male Urethral Sphincter Complex Revisited: An Anatomical Concept and its Physiological Correlate

M. M. Koraitim

https://doi.org/10.1016/j.juro.2008.01.010 is reported :

Citation: *Luisetto M, Mashori Gulam Rasool, Gamal A, Cabianca L, Latyshev O. There is a Relationship Between in Efficiency of External UretralSfincther and BPH? The Growth Factor and Pharmacological – PhytotherapicRole : The Inversion of The Classic Paradigm as Hypotesys of work.Sali Jour Uro. 2024;1(2):1-5.*
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***Corresponding author:** Luisetto M.IMAacademyAppliedpharmacologistitaly29121

“The male urethral sphincter complex USC is composed of an inner lissosphincter of smooth muscle and an outer rhabdosphincter of skeletal muscle. It extends in the form of a cylinder around the urethra from the vesical orifice to the perineal membrane. While the rhabdosphincter RS is most marked around the membranous urethra and becomes gradually less distinct toward the bladder, the lissosphincter has its main part at the vesical orifice and is thinner in its further course in the urethra.”

(The rabdosfincthere is the external)

The internal sfincthere is primary muscle involved in prohibiting of the release of the urine , the extnernal is secondary.

Euorpean urology 2007

Editorial – referring to the article published on pp. 1736–1743 of this issue Are We Ready for a Home-Grown Urinary Sphincter?

Arnulf Stenzl, Karl-D. Sievert

“the pelvic sphincter and central nervous system CNS are different in bipeds than in quadrupeds”

Anatomical Science International https://doi.org/10.1007/s12565-023-00717-7

REVIEW ARTICLE Pelvic floor and perineal muscles: a dynamic coordinationbetween skeletal and smooth muscles on pelvic floor stabilization Satoru Muro • Keiichi Akita March 2023

“The pelvic floor PF is a structure unique to humans formed by upright bipedal walking . In quadrupeds, the weight of the abdominal viscera rests on theabdominal wall; in humans, it is directed toward the pelvic

outlet. This necessitates that the human pelvis must have a mechanism to resist gravity while maintaining function asan exit for reproduction and excretion. The pelvic floor PF is the bearer of this mechanism; that is, the structure that supportsthe abdominal and pelvic organs against gravity.The pelvic floor PF is responsible for lower urinary tract function (storing and eliminating urine), defecation , and sexual function (erectile function and ejaculation in men,and sexual sensation and arousal in women) “

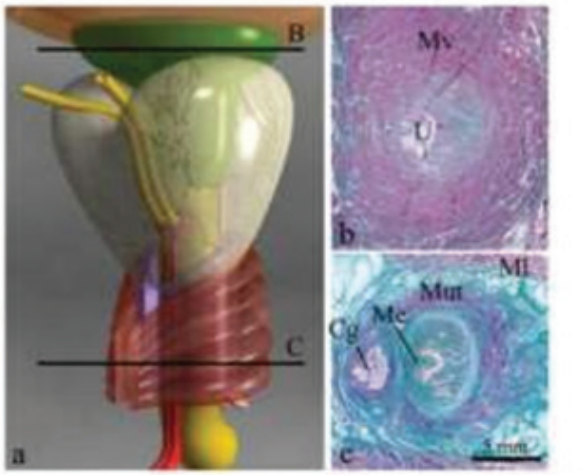


Figura 1.12: (a) rappresentazione tridimensionale della muscolatura dell'uretra posteriore; in verde è rappresentato lo sfintere liscio, in rosso lo sfintere uretrale esterno, in viola la muscolatura liscia dell'uretra membranosa, in giallo l'uretra e in grigio la prostata; (b) sezione trasversale dell'uretra prostatica; (c) sezione trasversale dell'uretra membranosa.
U: uretra Mv: sfintere liscio, Mur: sfintere uretrale esterno; Mi: muscolo elevatore dell'ano, Me: muscolo eiaculatore, Cg: ghiandole di Cowper (Stolzenburg, 2002)

Fig. n 1 from

file:///C:/Users/annao/Downloads/Andretto_Sofia_Analisi_del_comportamento_meccanico_dei_tessuti_e_della_configurazione_dell'uretra_maschile.pdf

“the rabdosfincthere have a horseshoe form .

In the human uretra , the composition of the wall change durin the various age : in child the striated muscle is about 79% and in the advanced age the 35,5% .”

According X Wang et al “There is a close relationship between prostatic zones and urethral sphincter complex USC .”

Review article November 1, 2015

Regeneration of Degenerated Urinary Sphincter Muscles: Improved Stem Cell-Based Therapies and Novel Imaging Technologies

Bastian Amend, Martin Vaegler, Kerstin Fuchs, J. G. Mannheim, S. Will, U. Kramer, Melanie L. Hart, Wouter Feitz, C. Chapple, Arnulf Stenzl, and Wilhelm K. Aicher

https://doi.org/10.3727/096368915X6862

“most promising candidates for sphincter regeneration: muscle-derived satellite cells as precursor cells for repair of the rhabdosphincter RS, which is a striated muscle, and MSCs, derived from bone marrow or adipose tissue for general muscular regeneration and repair of the lissosphincter (a smooth muscle)”

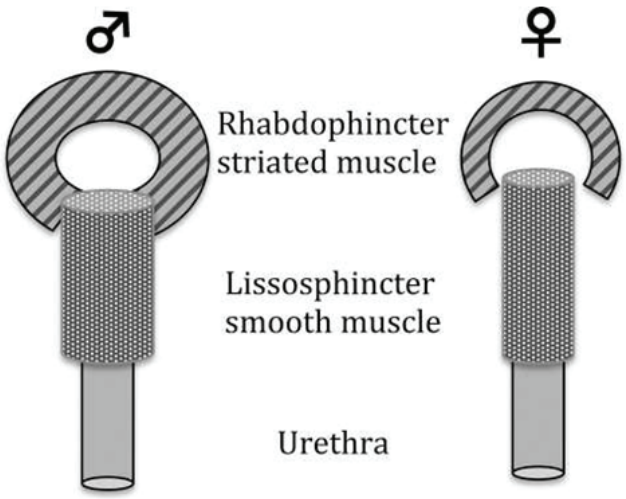


Fig. n 2 Schematic overview on the male (left) and female (right) urinary sphincter complex. The urethra (gray tubing) is surrounded by a tubular muscle layer with longitudinal and circumferential muscle fibers

built by smooth muscle cells and is called lissosphincter LS (dotted structure). The lissosphincter is enforced by an Ω-shaped muscle, built by striated muscle fibers, called the rhabdosphincter RS (striated Ω). The whole sphincter complex is stronger (thicker) in males compared to females but shorter. From

https://doi.org/10.3727/096368915X6862

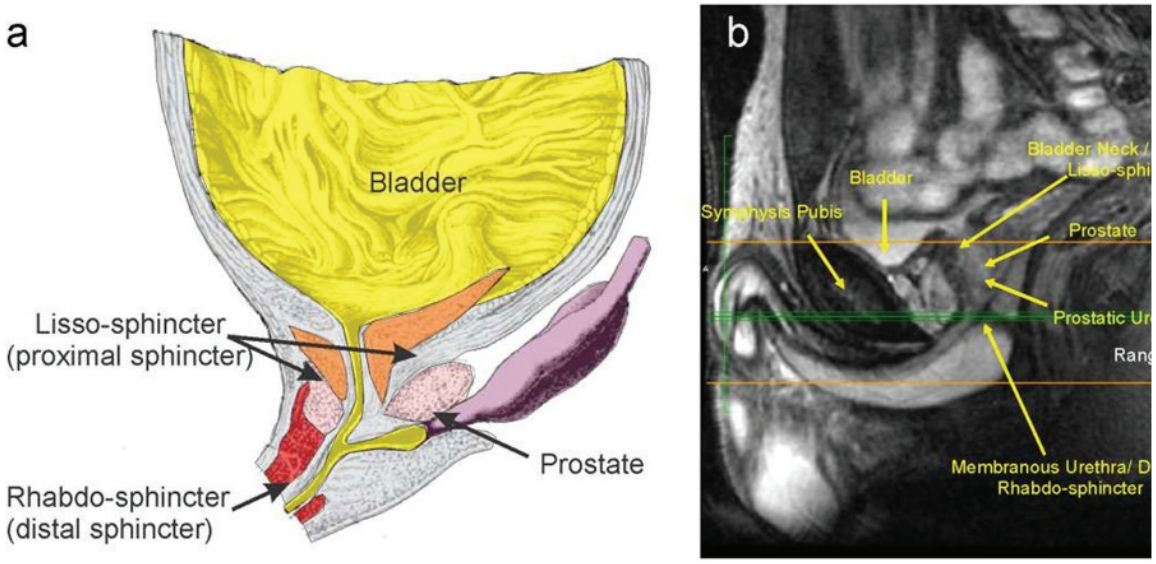


Fig n. 3 from https://doi.org/10.1002/jmri.26017 Urethral sphincters, namely the proximal lisso-sphincter and the striated external (EUS) or rhabdo-sphincter, as well as pelvic floor muscles, play an important role in urinary incontinence

Original Research

Exploration of male urethral sphincter complex using diffusion tensor imaging (DTI)-based fiber-tracking Shantanu Sinha , Usha Sinha , V. Malis , V. Bhargava , Kyoko Sakamoto , M. Rajasekaran

March 2018 https://doi.org/10.1002/jmri.26017C

"injury to the lisso-sphincter LS resulted in incontinence (postprostatectomy incontinence). The presence of the intact rhabdo-sphincter muscle does not guarantee continence and its loss does not cause incontinence in the presence of an intact lisso-sphincter."

In Diagnostic Ultrasound: Abdomen and Pelvis, 2016 Prostate Function:

"Main function is to add nutritional secretions to sperm to form semen during ejaculation

Also plays role in controlling the flow of urine; prostate muscle fibers are under control of involuntary nervous system NS and contract to slow and stop urine"

Naunyn Schmiedebergs Arch Pharmacol. 2021 Jan doi: 10.1007/s00210-020-02044-4

Purinergic smooth muscle contractions in the human prostate: estimation of relevance and characterization of different agonists

Annabel Spek et al

"Elevated prostate smooth muscle tone may contribute to urethral obstruction in BPH, resulting in impairments of urinary flow and bladder emptying, and finally in LUTS suggestive of a BPH ."

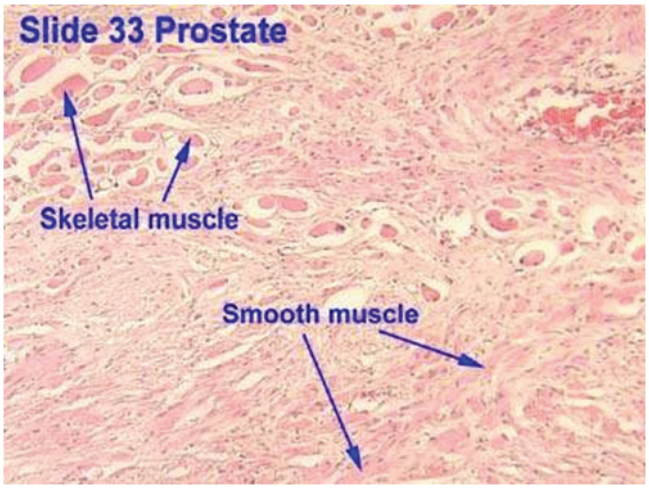


Fig n 4 Prostate and prostatic urethra: this section smooth muscle and skeletal muscle are both present. Compare and contrast the 2 types of muscle. The smooth muscle is present as an integral part of the prostate surrounding the islands of epithelium and the skeletal muscle SM is present off to one side of the tissue section (apparently a small portion of one of the skeletal muscles in the lower abdominal wall). Most of the skeletal muscle cells (skeletal muscle fibers) are cross sectioned .From

https://www.ouhsc.edu/histology/Text%20Sections/Muscle.html

From https://www.kenhub.com/en/library/anatomy/the-prostate-gland

"The hallmark histological feature of the prostate is the myoelastic/fibromuscular stroma in which there are clusters of smooth muscles mixed with elastic fibers EF . This surrounds the glandular tissue/ parenchyma of the prostate, which is responsible for the production of approximately 27% of seminal fluid."

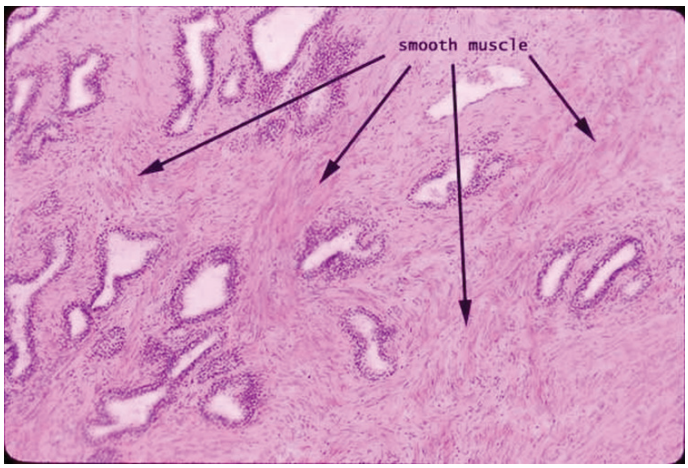


Fig. n 5 from https://histology.siu.edu/erg/RE043b.htm The prostate consists of irregular glands embedded in an extensive fibromuscular stroma

https://www.informedhealth.org/how-does-the-prostate-work.html

"The muscles of the prostate also ensure that the semen is forcefully pressed into the urethra and then expelled outwards during the ejaculation."

U.S. flag An official website of the United States government NIH NLM Bookshelf

In brief: How does the prostate work?

Sept. 2022

"The prostate gland is surrounded by a capsule of connective tissue containing many smooth muscle fibers and elastic connective tissue, it feels very elastic to the touch when it is examined. There are also many

smooth muscle cells inside of the prostate. During the ejaculation these muscle cells contract and forcefully press the fluid that has been stored in the prostate out into the urethra."

The prostate: History, Morphology, Functional Anatomy.

G. Passavanti

" functions of the prostate: regulating the composition and volume of the

ejaculate, controlling the cycle of continence/miction, through adjustments in the resistance to urinary transit at the level of the prostatic urethra; this is also closely connected to the functioning of the bladder neck.

In patients with LUTS, this smooth muscle component has a stronger impact on the tone of the bladder neck BN and the prostatic urethra, making obstructive symptoms more likely.

the tone of this smooth muscle component is more intense in older patient (>55 aa); These patients show a hyperplasia of the smooth muscle component as well as of thefibrous-fibroblastic element. The tone / contractions of these smooth muscle fibrocells cause and influence LUTS .

The contraction of smooth muscles is mainly controlled by the orthosympathetic system (alpha1-adrenergic).

In rest conditions, the activity of smooth muscle SM cells is not completely blocked: a minimal tone is always present, significantly less intense than in the active phase; activator cells show a

lower action potential and the contractions propagate to a limited number of other cells .

This basic tone inevitably influences the resistance to urinary transit at the level of the prostatic urethra PU.

In the young adult this plays an important though not decisive role, contributing to urinary containment capacity. In the older patients with LUTS, this tone, caused by a higher number of smooth muscle SM cells and by their greater contractile recruitment, is stiffer and influences the very obstructive symptom “

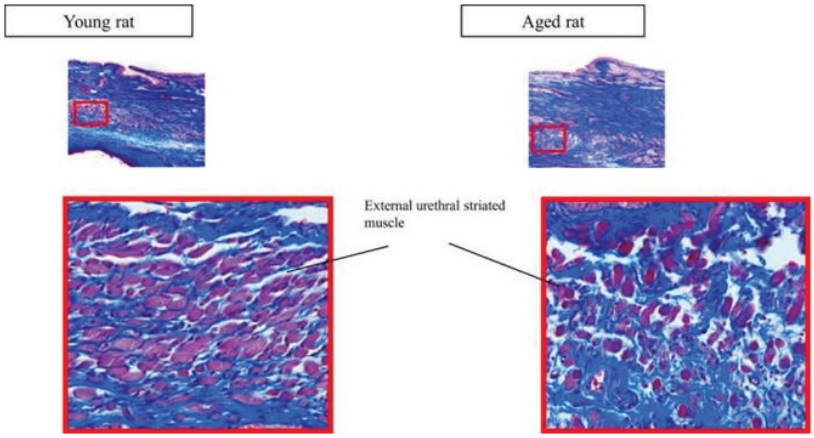


Fig . n 6 Masson's trichrome staining of the urethra. EUS atrophy and fibrous tissue hyperplasia are

observed in the submucosal layer in aged rats compared with young rats. EUS, external urethral sphincter From doi: 10.14814/phy2.14643

Braz. J. Pharm. Sci. 58 2022 https://doi.org/10.1590/s2175-97902022e21063 copy Aging-associated prostate smooth muscle hypercontractility in rats

Tabatha Danielle da Silva Lopes ,R. Bazuco Fritoli,F. Henrique da Silva,F. Beraldi Calmasini

“BPH is a multifactorial disease, highly associated with aging and characterized by increased prostate smooth muscle SM contractility.”

It is present in a significative nember of men at 40 years, and 90% in 80 decades of age.

BPH is more common in Western societies compared to the Asian. It is less common in those who eat large amounts of vegetables.

DHT deidrotestosterone is involved in prostate growth, it is produced into the prostate starting from circulating TST bt the enzyme 5 alfa reductase.

DHT bind and activate the nuclear androgen receptors (that regulate the expression of the gene that support the growth and surviving of epitelial and stromal prostatic cells).

But the level of DHT in men with or without BPH not differ in significative way so other factor are involved in BPH.

BPH involve the internal transitional zone TZ , increase the prostate volume, with nodules iperplastics that have an variable composition of glandular elements and of fibromuscolar stroma.

Benign Prostatic Hyperplasia

Michael Ng; S. W. Leslie; Krishna M. Baradhi. Oct 2024.

“BPH refers to the nonmalignant growth or hyperplasia of prostate tissue and is a common cause of LUTS in older men. Disease prevalence DP has been shown to increase with advancing age. The histological prevalence of BPH at autopsy is as high as 50% to 60% for males in their 60s, increasing to 80% to 90% of those older than 70 years of age. The development of BPH is characterized by stromal and epithelial cell proliferation in the prostate transition zone TZ , which surrounds the urethra. This produce urethral compression and bladder outflow obstruction,(clinical manifestations of LUTS, urinary retention, or infections due to incomplete bladder emptying) . BPH arises due to the loss of homeostasis between the prostatic cellular proliferation and apoptosis or cell death. This imbalance favors cellular proliferation without intervention. There is an increased numbers of prostatic periurethral epithelial and stromal cells, which can be seen histopathologically. The etiology of BPH is influenced by a wide variety of risk factors, in addition to the direct hormonal effects of TST on the prostate tissue. Men who are castrated before

puberty or who have an androgen-related disorder do not develop BPH.

Non-modifiable and modifiable risk factors also

contribute to BPH. These include diabetes, diet, genetic factors, localized inflammation, obesity, and metabolic syndrome.

Diabetes and the use of antidiabetic medications, like insulin, appear to increase the risk of BPH, LUTS.

Beta-carotene, carotenoids, and vitamin A seem somewhat protective, while excessive alcohol ingestion, heavy caffeine intake, and high-dose supplemental vit. C tend to increase BPH risk and symptoms. No prepared dietary supplement has been proven to help BPH in randomized, controlled studies.

Genetic predisposition to BPH has been demonstrated in cohort studies. First-degree relatives in 1 study demonstrated a 4-fold increase in the risk of BPH compared to the control. These findings have

demonstrated consistency in twin studies looking at the disease severity of BPH, with higher rates of LUTS seen in the monozygotic twins.

Localized inflammation is often associated with BPH, at least histologically. While the exact etiology is unclear, possible causes include increased detrusor voiding pressure, obesity, low-grade or chronic prostatitis, compression of the prostatic ducts, and autoimmune disorders AD.

Obesity is associated with an increased risk of BPH in observational studies.The exact cause is unclear but is likely multifactorial, as obesity makes up 1 aspect of metabolic syndrome. (Proposed mechanisms include increased levels of systemic inflammation and higher levels of estrogens).

Metabolic syndrome MS refers to conditions that include hypertension, glucose intolerance/ insulin resistance, dyslipidemia. Meta-analysis has demonstrated those with metabolic syndrome MS and obesity have significantly higher prostate volumes. Studies looking at men with elevated glycosylated hemoglobin

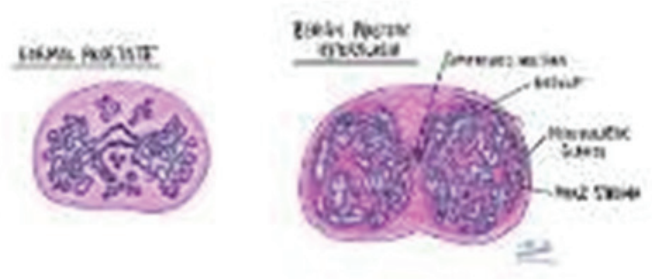
levels have demonstrated an increased risk of LUTS. Limitations of these studies are that there were no subsequent significant differences in prostate symptom scores, and the effect of diabetes on LUTS has been shown to be multifactorial."

Hyperplasia is generally considered a responce to stimulus, inflamation ,hormone effect and other . IPB Is a kind of iperlasia. (because prostate is a gland the phenomena involved its cells)

According the famous Pascal's principle: in fluid (gas or liquid) mechanics, statement that, in a fluid at rest in a closed container, a pressure change in one part is transmitted without loss to every portion of the fluid and to the walls of the container.

This concept must to be applied to the all uretral sfichtere complex (internal , prostate and exthernal part) and expecially related a compensatory role .

BPH : hyperplastic process with an increase of the cell number on hystoloy (hyperplasia) . This happen in both in the periuretral and transition zone .



Fi n. 7 from https://www.mypathologyreport.ca/it/diagnosis-library/benign-prostatic-hyperplasia/

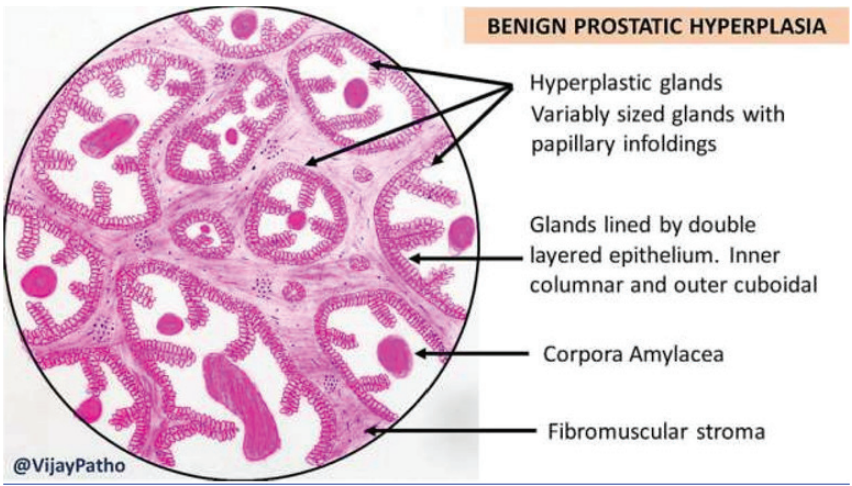


Fig .n. 8 from https://ilovepathology.com/benign-prostatic-hyperplasia/

Review Curr Urol Rep. 2008 Jul; doi: 10.1007/s11934-008-0048-6.

Growth factors in benign prostatic hyperplasia: basic science implications M Scott Lucia , J. R Lambert

“The histopathology of BPH strongly implicates local paracrine and autocrine growth factors GF and inflammatory cytokines in its pathogenesis. A complex milieu of growth-regulatory proteins includes members of the fibroblast, insulin-like, and transforming growth factor families. It appears that these

proteins and downstream effector molecules, in addition to a variety of interleukins IL , are overexpressed in BPH and, working together, create a landscape of increased stromal and epithelial growth EG and

mesenchymal transdifferentiation that leads to disease progression. Inflammation, commonly present in

BPH, may contribute to tissue injury, and cytokines CK produced by inflammatory cells may serve to drive local growth factor GF production and angiogenesis in the tissues as a "wound healing" response.”

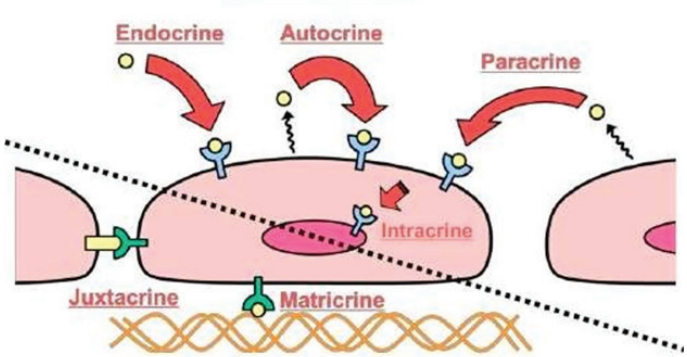


Fig n. 9 from DOI: 10.3390/ijms13056053 Modes of action of growth factors. Growth factors GF interact with their receptors in a diffusible manner (by endocrine, paracrine, autocrine and intracrine pathways) or in a nondiffusible manner (by juxtacrine and matricrine pathways)

Ageing and local growth factors in muscle

S. D. R. Harridge

Jan. 2003 https://doi.org/10.1034/j.1600-0838.2003.20235.

“local growth factors GF produced within the muscle may play important roles in both repair, adaptation and ageing. many tissues including muscle, produce IGF-I for autocrine and paracrine actions”

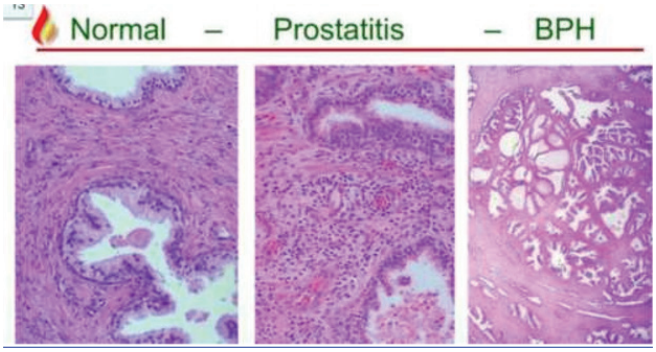
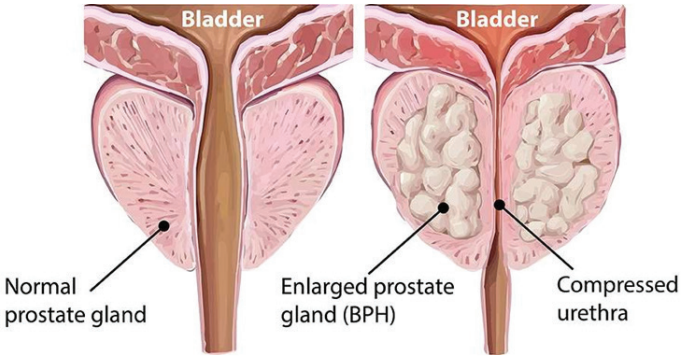


Fig n. 10 https://image.slidesharecdn.com/bph3prostate-150925003320-lva1-app6891/85/Pathology-of- Prostate-Benign-13-320.jpg



Fi n 5 from https://www.saintjohnscancer.org/urology/conditions/benign-prostatic-hyperplasia/

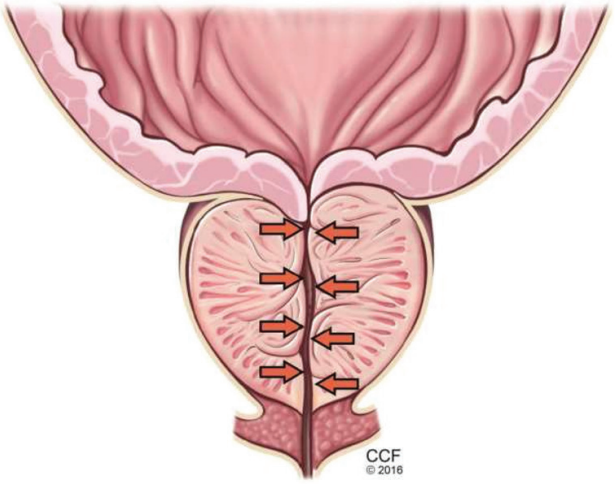


Fig. n. 11 from cleveland clinic journal of medicine

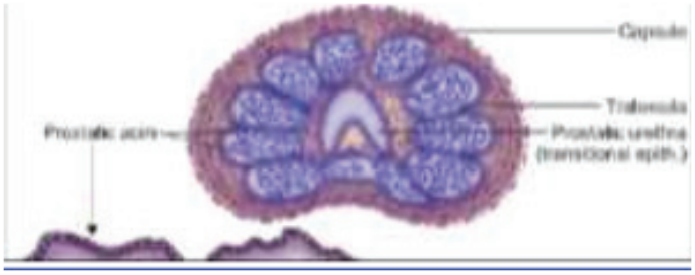


Fig. n 12 From H.HASSAM et al structure of prostate gland.

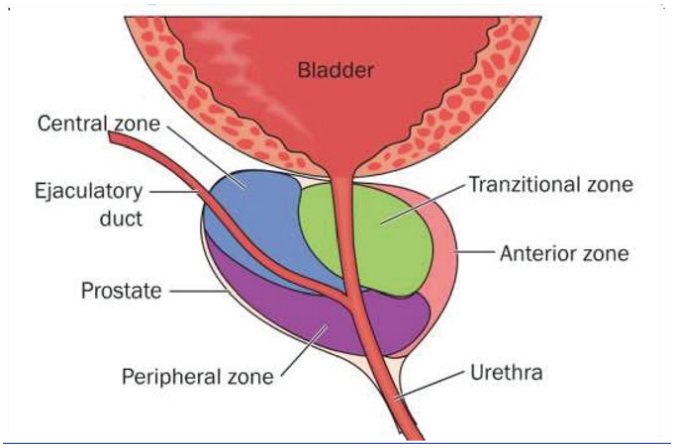


Fig n 13 from https://www.prostatelasercenter.com/blog/prostate-zones-what-you-should-know/

MANAIA, J. H. M.; COSTA, W. S.; SAMPAIO, F. J. B.; FIGUEIREDO, M. A.; CARDOSO, G. P. BABINSKI, M. A.

High concentration of reticular fibers in periurethral region of the prostatic urethra from patients with BPH as revealed by stereology. Int. J. Morphol., 2012.

“the lack of relationship between the total prostatic volume and BOO suggests that the symptoms

and urodynamic outcomes of the infra-vesical obstruction from HPB is more associated to the enlargement of the prostatic transitional zone PTZ than to the total prostatic volume. BPH nodules cause compression forces

in prostatic urethra and consequently induces a remodeling process of the extracellular matrix EM with significant increase of reticular fibers in prostatic urethra ”

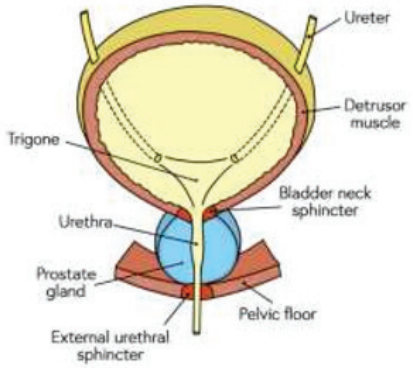


Fig n 14 from https://www.futurelearn.com/info/courses/understanding-continence- promotion/0/steps/46067

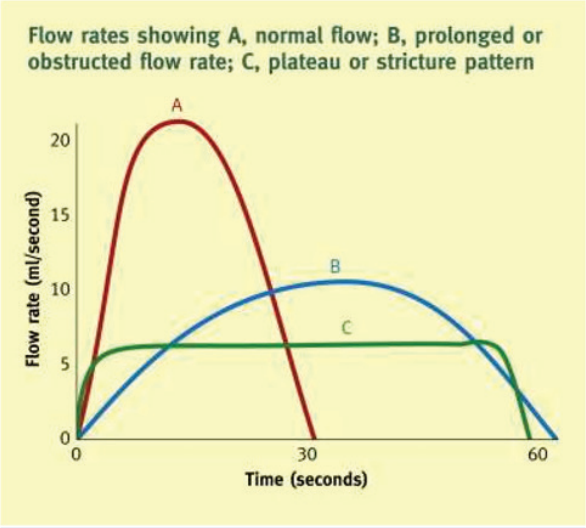


Fig n. 15 from https://www.sciencedirect.com/topics/medicine-and-dentistry/urine-flow-rate

Mean flow rate in men aged 14-45: 21 ml/s Average flow rate in men aged 46-65: 12 ml/s Mean flow rate in men aged 66-80: 9 ml/s

Related the effect of phytotherapy it is of interest to see:

https://silvershell.com.tr/wp-content/uploads/2022/08/Ref.-64.-Safarinejad-et-al-2005.pdf

“Peak flow rates improved by 3.4 mL/s for placebo recipients and by 8.2 mL/s for treated

patients ($P < 0.05$). In Urtica dioica UD group, PVR decreased from an initial value of 73 to 36 mL ($P < 0.05$) Prostate size (as measured by TRUS) decreased from 40.1 cc to 36.3 cc in Urtica dioica UD group ($P < 0.001$), while no significant change was observed in the placebo group

Long term results: Those in the primary Urtica dioica UD group continued to have a favorable outcome, with all values remaining stable from the end of the double-blind study to the 18-month follow-up”

Continence

Volume 10, June 2024

What do we really know about the external urethral sphincter?

Karen D. McCloskey , A. Kanai , J. N. Panicker , H. Hashitani , Christopher H. Fry

https://doi.org/10.1016/j.cont.2024.101223

“The external urethral sphincter EUS , composed of skeletal muscle, along with a smooth muscle-lined internal urethral sphincter , have crucial roles in maintaining continence during bladder filling and

facilitating urine flow during voiding. Disruption of this complex activity has profound consequences on normal lower urinary tract function during the micturition cycle.

The US FDA approved the use of phosphodiesterase-5 inhibitor, tadalafil, and its recent (2021) combination with finasteride as a single pill for BPE/BPO”

Int J Clin Exp Med. 2015 Sep 15;

Normal anatomic relationship between urethral sphincter complex and zones of prostrate in young Chinese males on MRI

Xiangdong Wang , T. Liu , Jing Zhao , Jingyi Sun , Y. Chen , P. Sun , Xuesong Wang , Sheng Liu

“There is a close relationship between prostatic zones and urethral sphincter complex. Urethral sphincter complex USC is the anatomic landmark for well-developed posterior urethra in males.”

J Urol. 1984 Sep; doi: 10.1016/s0022-5347(17)49713-8.

Electromyography of the external urethral sphincter in patients with prostatic hyperplasia S Abe, K Kawabe, T Niijima, Y Shimada

Related the external urethral sfinchter:

“We analyzed quantitatively the action potential of external urethral sphincter EUS muscles by

electromyography in 9 patients with BPH and in 13 patients without micturition disturbances. In patients with BPH the motor unit potentials had a mean amplitude of 290 plus or minus 40 microV., duration 5.0 plus or minus 0.1 msec. and phases 3.9 plus or minus 0.1. The control group values were 310 plus or minus 20 microV., 5.5 plus or minus 0.1 msec. and 3.8 plus or minus 0.1, respectively.”

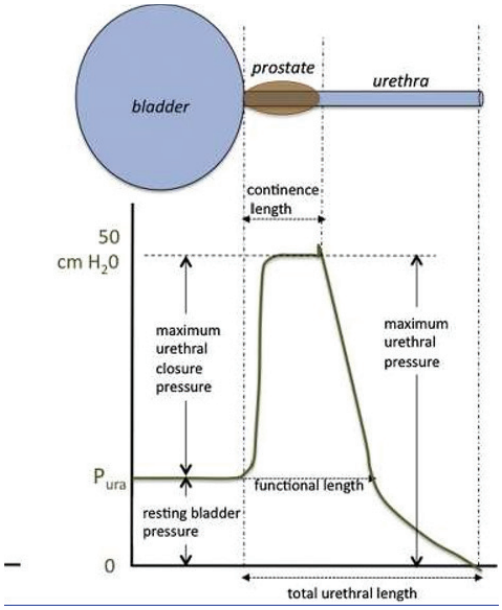


Fig n. 16 Urethral pressure profiles of the male lower urinary tract. From Animal Models of Lower Urinary Tract Dysfunction Rita I. Jabr, Christopher H. Fry, in Animal Models for the Study of Human Disease , 2013

The green traces show the minimum pressures required to open a closed urethra at various positions along the tract. The high-pressure sections show the continence regions. The y-axis values for Pura are indicative only, and may vary considerably around this value.

Utretral pressure profilometry : UPP is a graph indicating intraluminal pressure alon the length of urethra. The urethral pressure is the fluid pressure needed to just open a closed urethra .

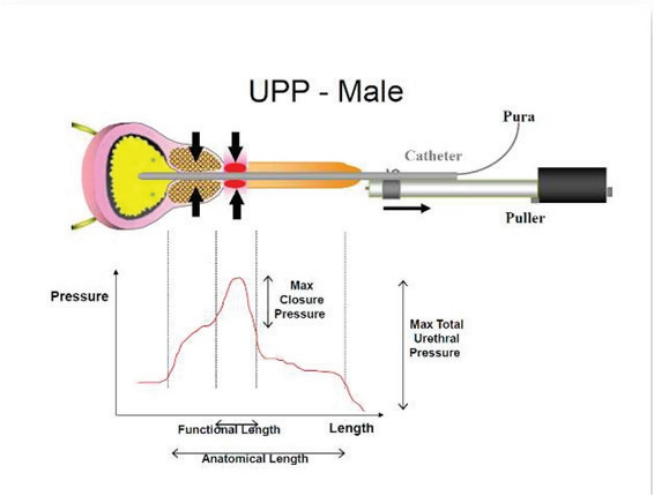


Fig.17 from https://www.urology.com.my/urodynamics-and-neuro-urology/

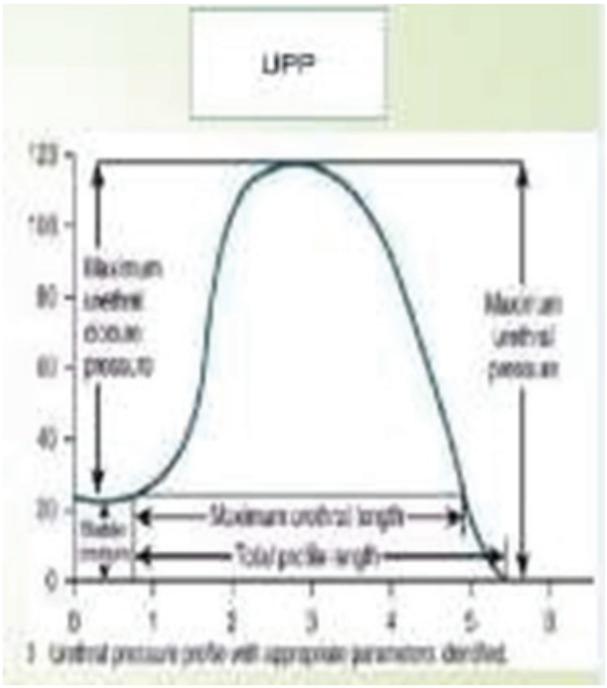


Fig. n 18 UPP: uretral pressure profilometry

Urethral closure pressure profile is given by subtraction of intravesciacal pressure from urethral pressure . Maximum urethral pressure is highest pressure measured along the UPP.

Maximum urethral closure pressure (MUCP) : maximum difference between urethral pressure and intravescical pressure.

Functional profile lenght : lenght of the urethra along with urethral pressure exceeds intravescical pressure in women .

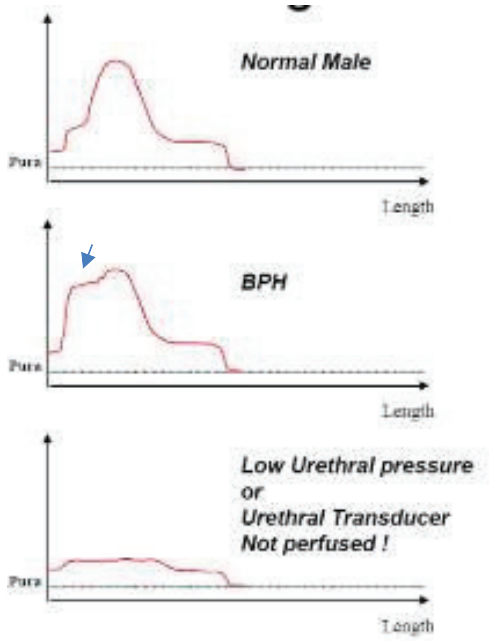


Fig .n. 19 UPP uretral pressure profile and pathologies from https://www.urology.com.my/urodynamics-and-neuro-urology/

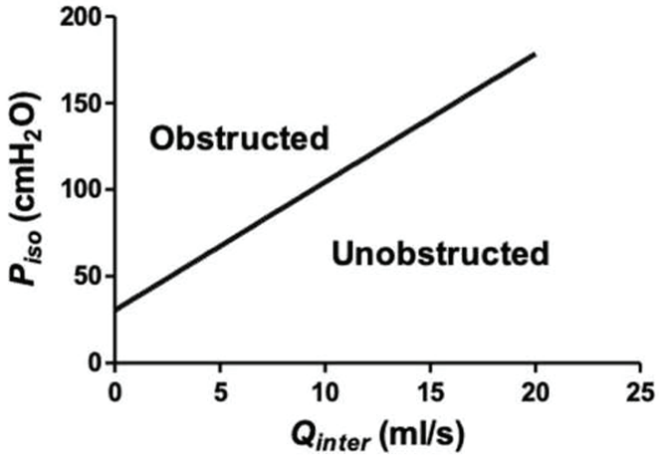


Fig n.20 Nomogram for Classifying Minimally Invasive Urodynamics Pressure-Flow Data

Urethral resistance pressure is the pressure existing in urethra during urination or other conditions generated by the detrusor muscle.

Oshiyama N, D'Ancona C, Bassani J

ICS-SUFU standard: Theory, terms, and recommendations for pressure-flow studies performance, analysis, and reporting, Part 2: Analysis of PFS,reporting, and diagnosis

Peter F.W.M. Rosier , A. Gammie , Juan P. Valdevenito , John Speich ,Phillip Smith , Sanjay Sinha ,

“the detrusor D can compensate for slowly increasing UR uretral reistance in men with a growing prostate over many years of time, by muscle contraction force adaption . As a consequence

of a growing prostate, the patients “move” to diminished flow rates (slower contraction) and higher pressures (with higher force). Incomplete voiding may develop when the detrusor is unable to further

compensate or loses the ability to contract sufficiently, which is commonly referred to as decompensating .

Incomplete voiding may be regarded as a sign of insufficient compensation or of decompensation

or inability to maintain force. A sudden increase in UR, caused, by surgery or (acute) inflammation around the bladder outlet, does not give the detrusor time to compensate and, may directly lead

to incomplete voiding or complete urinary retention UR .”

Int Braz J Urol. 2017 Mar-Apr; doi: 10.1590/S1677-5538.IBJU.2016.0308

Urethral pressure variation: a neglected contributing factor in patients with overactive bladder syndrome?

Ruth Kirschner-Hermanns , Ralf Anding , N. Gadzhiev, Ing Goping, A. Campbell, N. Huppertz

“Our study revealed that patients with OAB OVERACTIVE BLADDER have statistically significant higher range of urethral pressure variation than in SUI STRESS URINARY INCONTINENCE and MUI MIXED URINARY

INCONTINENCE patient groups, we found that in patients with OAB and concomitant DO DETRUSOR OVERACTIVITY urethral pressure variation range was even higher than without DO ($p<0.05$) .”

Material and methods

With an observational point of view various relevant literature are reported for the scope of this work All works comes from biomedical database.

Figure reported (1-23) help in better explain the meaning of this research.

An experimental project hypotesys is submitted in order to provide a global conclusion.

From literature Results :

according Vaki Antoniou et al

“1 double-blind RCT of 558 men demonstrated significant superiority of urtica dioica when evaluating the effect on IPSS scores (an 8-point reduction), post-void residual (37 mL reduction), and prostate size (4.8 cc reduction), compared to a placebo . A meta-analysis from 2016 concluded that the usage of urtica dioica UD for the treatment of LUTS in BPH is both efficacious and safe . In this meta-analysis, on average, IPSS scores were reduced by 18.1 and prostate volumes by 3.6 cc . All included RCTs in this meta-analysis did not report any side effects or adverse events .

The mechanism of action of UD has been shown to involve 5-alpha-reductase inhibitory activity on testosterone . Antiproliferative effects have also been demonstrated to affect just epithelial cells . It is further speculated to inhibit the growth of the prostate in BPH .”(1)

A. Ghorbanibirgani et al

“In a clinical trial, 287 BPH patients who had been treated with nettle (Urtica dioica UD) showed significant reduction in IPSS, serum PSA and prostate size . Researchers decided to carry out a new research aiming to investigate the efficacy of nettle on the reduction of clinical symptoms of BPH.”(2)

M. Reza Safarinejad :

“By intention- to-treat analysis, at the end of 6-month trial, 232 (81%) of 287 patients in the Urtica dioica UD group reported improved LUTS compared with 43 (16%) of 271 patients in the placebo group ($P <$

0.001). Both IPSS and Qmax showed greater improvement with drug than with placebo. The IPSS went from

19.8 down to 11.8 with Urtica dioica UD and from 19.2 to 17.7 with placebo ($P = 0.002$). Peak flow rates improved by 3.4 mL/s for placebo recipients and by 8.2 mL/s for treated patients ($P < 0.05$).”(3)

Miriam Saponaro et al

“This study aimed to evaluate the antioxidant and anti-inflammatory activity of a combined formulation of Serenoa repens SR and Urtica dioica UD in an in vitro human model of BPH. The results confirmed both the antioxidant and the anti-inflammatory effects of SR/UD. In fact, SR/UD simultaneously reduced ROS production, NF-κB translocation inside the nucleus, and, consequently, IL-6 and IL-8 production. The effect

of SR/UD was also tested in a human androgen-independent prostate cell model, PC3. SR/UD did not show any significant antioxidant and anti-inflammatory effect, but was able to reduce the NF-κB translocation

“(4)

N. D Patel et al

“Physical activity

Increased physical activity and exercise have been robustly and consistently linked with decreased risks of BPH surgery, clinical BPH, histological BPH and LUTS. A meta-analysis of 11 published studies (n = 43,083 men) indicated that moderate to vigorous physical activity PA reduced the risk of BPH or LUTS by as much as 25% relative to a sedentary life-style, with the magnitude of the protective effect increasing with higher levels of activity." (5)

Cheng-Ling Lee et al

"The pathophysiology of LUTS could include bladder dysfunction (bladder hypersensitivity, detrusor overactivity), bladder outlet obstruction, (bladder neck dysfunction, prostatic obstruction, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia), or a combination of these etiologies .

Growth factors

Various growth factors and their corresponding receptors have been identified in prostatic epithelium and stroma, which can stimulate or inhibit cell division and differentiation processes. These include epidermal growth factor EGF, fibroblast growth factor, and transforming growth factor-β, but this list is by no means exhaustive. Activation of these growth factors alone or in combination can induce stromal cell SC growth, followed by significant tissue remodeling, which is responsible for prostate enlargement "(6).

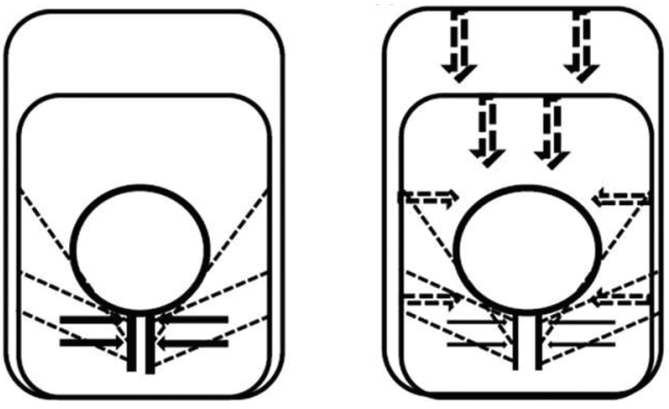


Fig.n. 21 Analogy demonstrating the compensation for decreased pelvic floor support in order to resist the downward pressure. (A) Under normal pelvic floor PF support (thick unbroken arrows), the reservoir function of the bladder is maintained by well-functioning sphincter and abdominal muscle relax. (B) Under weak pelvic floor support (thin unbroken arrows), the weak sphincter function is compensated by the increasing tension (thin double broken arrows) of the circumferential muscles, fasciae, and ligaments connecting to the pelvic floor PF (thin dotted line). This process manifests as tightness of the pelvic floor and a slight rise in abdominal pressure.From DOI: 10.5213/inj.1630392.196

Lancet. 1999 Sep 11 doi: 10.1016/S0140-6736(99)02588-X.

Urinary incontinence in the elderly and age-dependent apoptosis of rhabdosphincter cells H Strasser, M Tiefenthaler, M Steinlechner, G Bartsch, G Konwalinka

"With advancing age, a progressive and age-dependent decrease of the density of striated muscle cells can be observed in the rhabdosphincter RS . This continuous loss of striated muscle cells due to apoptosis may finally lead to urinary incontinence"

Tahara H et al

"Unexpected rich urethral sphincter US volume in the elderly people might suggest the compensatory hypertrophy against the overactivity of the aging bladder" (7)

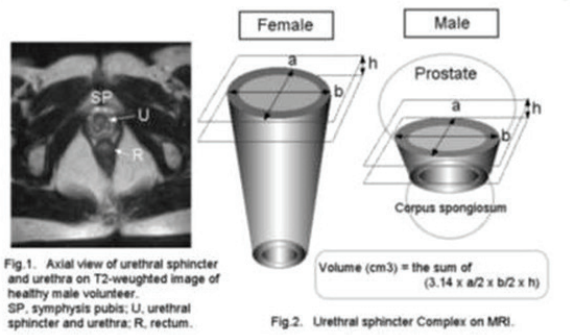


Fig.1. Axial view of urethral sphincter and urethra on T2-weughted image of healthy male volunteer. SP, symphysis pubis; U, urethral sphincter and urethra; R, rectum.

Fig.2. Urethral sphincter Complex on MRI.

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1. Maximum urethral closure pressure and sphincter volume in women with urinary retention. J Urol 2002: 167: 1348-51.

Fig.n. 22 from Tahara et al

Ragionieri et al

"Structural differences also exist, due to the mechanics of the urinary system US , as in humans, besides pressure generated by the bladder wall, urethra also operate gravitational forces that

are different in relation to body size, vertical/horizontal stance and lifestyle (frequency of bladder emptying, house training, rapid flow, or spurts for marking).

In both species, the portion of the UM (urethral muscle) proximal to the bladder forms a short internal leaflet continuing,without distinction, the innermost layer of smooth muscle SM ,and an external layer that is continuous with the muscle surrounding the caudal part of the pelvic urethra. The internal layer of striated muscle SM , in pig, is composed of very small myofibers surrounded, as in humans , by an abundant interstitium composed of collagen with intermingled elastic fibers. In this leaflet, the % of slow-twitch

(type I) fibers is about 20%. A similar proportion was found in dog , while in man type I fibers represented the dominant population . In pigs, the 2 layers of striate muscle begin to overlap in correspondence of the body of the prostate, and together form a sort of complete sphincter caudally to the body of the prostate. More caudally, the inner layer thins and disappears. Almost all of the myofibers of the external layer are fast-twitch, more compact and nearly

twice as large as those of the inner layer. This external layer might correspond to the 'much bulkier external component' of the UM described in humans and, also in man, the part of UM caudal to the body of the

prostate is composed almost exclusively of fast-twitch fibers.

Some differences in the morphology and structure of the UM in the 2 species seem due to the

morphology of the accessory genital glands that develop from the urethral wall and to the different effect of gravity between quadruped and bipedal mammals on the mechanics of the urinary system"(8)

Nathan Lawrentschuk et al

"This concept has been further refined in that obstructive symptoms are thought to result not only from mechanical obstruction due to glandular enlargement, but also dynamic obstruction DO secondary to contraction of the smooth muscle of the prostate, urethra and bladder neck."(9)

Saeid Golbidi et al

"the function of the external sphincter ES may be impaired due to diabetic neuropathy and also lead to urinary incontinence "(10)

A. Erdem Canda :

"diabetes can lead to functional and anatomical abnormalities of the external urethral sphincter. EUS"(11)

Guiming Liu el al

"Morphometric analysis showed atrophy of the EUS after 20 week but not 6 weeks of DM induction"(12)

Basu Chakrabarty et al

"Spontaneous myogenic contractions have been shown to be significantly upregulated in prostate tissue collected from men with BPH, an extremely common disorder of ageing male."(13)

Nobuo Moriyama et al

"These results suggest that there are no significant differences in responsiveness of α-adrenoceptor

agonists and the smooth muscle SM contents in longitudinal and circumferential directions to urethra, for human hypertrophied prostate."(14)

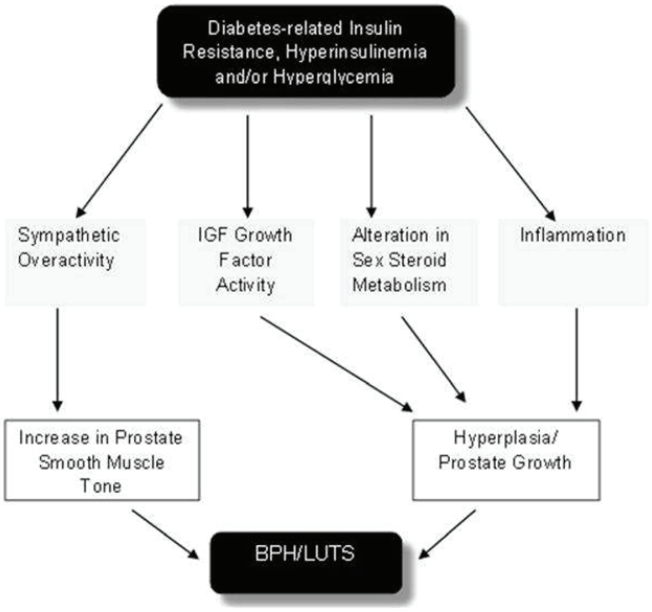

Fig. n. 23 Hypothesized mechanisms of diabetes, hyperglycemia, and insulin resistance in the pathogenesis of BPH/LUTS from doi: 10.1007/ s11934-014-0462-x

B. N Breyer et al :

“Hypothesized Mechanisms

Multiple pathways may explain the association of diabetes-induced insulin resistance and hyperglycemia with BPH/LUTS . Hyperinsulinemia is associated with increased sympathetic nerve activity . This increased nerve activity may contribute to increased prostate smooth muscle tone and subsequent bladder outlet obstruction BOO. Increased outlet resistance can lead to obstructive symptoms OS as well as potential

future irritative symptoms. Increased insulin concentrations secondary to diabetes may have a trophic affect that leads to enlarged prostate size . McVary et al. demonstrated that autonomic nervous system NS

hyperactivity was associated with increased LUTS and prostate size in a cohort of 38 men , Dysregulation of the IGF axis has been implicated in the development of BPH and prostate cancer . The IGF axis regulates

the physiologic and pathophysiologic growth of many organs including the prostate. Because of its structural similarity to IGF, insulin combines to IGF receptor to enter prostate cells, possibly causing

receptor activation to induce growth and proliferation. Other possibility is as insulin levels increase, IBFBP-1 declines, increasing the bioavailability of IGF. insulin may increase the transcription of genes/ translation of proteins involved in sex hormone metabolism influencing the prostatic hormonal milieu . Diabetes-related insulin resistance/hyperinsulinemia/ hyperglycemia-induced obesity may cause hormonal changes.

Hyperinsulinemia is associated with lower levels of sex hormone-binding globulin SHBG, increasing the

amount of sex hormone entering prostatic cells thereby influencing growth. the chronic pro-inflammatory state associated with metabolic syndrome, hyperglycemia, and hyperinsulinemia may contribute to BPH/ LUTS .” (15)

M. Hagovska et al

“the aim of this study was to evaluate the effect of combining pelvic floor PF muscle training with the urgency suppression technique (PFMT-st) and silodosin in comparison with silodosin in men with BPH and OAB after 12 weeks of treatment. The addition of PFMT-st to silodosin treatment significantly improved OAB in men with BPH”. (16)

From https://www.nuhospitals.com/blog/6-things-no-one-tells-you-about-prostate-enlargement-prevention/ Dr. V. Krishnamoorthy

“Prostate Enlargement Exercise:

Physical activity PA plays a pivotal role in maintaining prostate health. From pelvic floor exercises to aerobic activities, identify a tailored exercise regimen that contributes to your overall wellness.”

https://americanprostatecenters.com/blog/6-exercise-tips-for-a-healthy-prostate

“Kegel exercises are simple yet effective, and can greatly benefit men looking to protect their prostate health”

According by Dr Antoine Hakime | Nov 20, 2024 Exercises to reduce prostate volume: Kegel exercises “The most common Kegel exercises KE are specifically designed to strengthen the pelvic floor muscles. Yoga and specific postures

Yoga can reduce stress and improve flexibility, which helps relieve tension around the prostate. Postures such as the Bridge Posture (Setu Bandhasana), which strengthens the pelvic muscles and improves

circulation, or the Cobra Posture (Bhujangasana), which stimulates the pelvic organs, are particularly

recommended. The child's pose (Balasana) is also ideal for releasing tension in the lower back and pelvis”

Exp Gerontol. 2021 Jan:143:111152. doi: 10.1016/j.exger.2020.111152. Epub 2020 Nov 13.

Aerobic exercise ameliorates benign prostatic hyperplasia in obese mice through downregulating the AR/androgen/PI3K/AKT signaling pathway

Sha-Sha Wang 1, Kai Li 1, Zhiwei Liu 1, Shukang Gui 1, Nian Liu 1, Xiangyun Liu 2

DOI: 10.1016/j.exger.2020.111152

“These data demonstrate that aerobic exercise AE may alleviate BPH in obese mice through regulation of the AR/androgen/PI3K/AKT signaling pathway.”

"IGF-I and IGF-II were identified as potent mitogens and were previously associated with an increased risk of cancer development including the prostate cancer"(17)

Experimental project hypotesys

In order to verify the effect played by various therapeutic strategies 60 patients with IPB , overactive bladder and minctionary urgency must to be divided in group:

20 patients under finasteride -dutasteride therapy prescribed by phisicinas 20 patients using Serenoa R and Urtica dioica (phytotherapy)

20 patients that use KEGEL EXERCISE alone Time of observation : 1- 3 month

To be measured at month 1-2-3 the uroflussometry , the residual volume after mintioning , prostate volume , quality of life with a specific approved questionary . (evaluated by urologist).

To be verified if there is significative difference between in this 3 category of patients and the role played by the physiotherapic exercise a part from any phamacological -phytoterapic intervention.

Discussion

According https://www.kenhub.com/en/library/anatomy/urethral-sphincters: "The main action of the urethral sphincter complex is to compress the urethra."

The internal sfinthere is a continuation of the detrusor bladder muscle, it is involuntary . The external uretral sfinthere is of striate muscle (voluntary).

The internal sfincthere is primary muscle involved in prohibiting of the release of the urine , the external is secondary.

In quadrupeds, the weight of the abdominal viscera rests on the abdominal wall; in humans, it is directed toward the pelvic outlet.

In the human uretra , the composition of the wall change during the various age : in the child the striated muscle is about 79% and in advanced age the 35,5% ."

The prostate is placed between this two muscle and have inside smooth muscle fiber (specific role in ejaculation) .

The muscles of the prostate also ensure that the semen is forcefully pressed into urethra and then expelled outwards during the ejaculation.

Prostate muscle fibers are under control of involuntary nervous system and contract to slow and stop urine

Accordin Nathan Lawrentschuk, Gideon Ptasznik, and Sean Ong. 2021 :

" in that obstructive symptoms are thought to result not only from mechanical obstruction due to glandular enlargement, but also dynamic obstruction secondary to contraction of the smooth muscle of the prostate, urethra and bladder neck."(9)

BPH is a multifactorial disease, highly associated with aging and characterized by increased prostate smooth muscle contractility.

Between the BPH risk factors is is possible to see :

Aging,androgens, estrogens ,apoptosis disfuntions,stromal epitelial interactions, grow factors.

EUS (external uretral sfinchtere) atrophy and fibrous tissue hyperplasia are observed in the submucosal layer in aged rats compared with young rats

According S.Abe about external urethral sphincter muscles by electromyography:

"In patients with BPH the motor unit potentials had a mean amplitude of 290 plus or minus 40 microV., duration 5.0 plus or minus 0.1 msec. and phases 3.9 plus or minus 0.1. The control group values were 310 plus or minus 20 microV., 5.5 plus or minus 0.1 msec. and 3.8 plus or minus 0.1, respectively."

Luts are also linked to "poorly relaxed urethral sphincter condition" .

OVB is linked also to weakeness or spasm of pelvic muscle floor

"Also plays role in controlling flow of urine; prostate muscle fibers are under control of involuntary nervous system and contract to slow and stop urine"

from https://www.kenhub.com/en/library/anatomy/the-prostate-gland:

"The hallmark histological feature of the prostate is the myoelastic/fibromuscular stroma in which there are clusters of smooth muscles mixed with elastic fibers. This surrounds the glandular tissue/parenchyma of the prostate, which is responsible for the production of approximately 27% of seminal fluid."

Annabel Spek et al :

“Elevated prostate smooth muscle tone may contribute to urethral obstruction in benign prostatic hyperplasia (BPH),

The muscle of the prostate act as an reinforce to the internal uretral sfinchtere .

(https://www.benessereurinario.it/apparato-urinario/prostata/come-fatta-e-come-funziona-la-prostata/)

There are difference in bipede or quadrupede animals in the sifincthere units anatomy .(8)

The ipotonicity of the external urethral sfinctere (a voluntary muscle) produce the need that other structure act in supporting (and this structure can be upper the EUS.)

Whit advancing age, a progressive and age-dependent decrease of the density of striated muscle cells can be observed in the rhabdosphincter.

Shantanu Sinha et al : “the presence of the intact rhabdo-sphincter muscle does not guarantee continence and its loss does not cause incontinence in the presence of an intact lisso-sphincter”

According S. H. SHIN “Under weak pelvic floor support , the weak sphincter function is compensated by the increasing tension of the circumferential muscles, fasciae, and ligaments connecting to the pelvic floor”

The prostate is a gland and growth factor can produce iperplasia with more closing of the uretra channel. In BPH patogenesys are involved various growth factors (autocrine or paracrine).

According article Ageing and local growth factors in muscle Stephen D. R. Harridge 2003 :

“local growth factors produced within the muscle may play important roles in both repair, adaptation and ageing. many tissues including muscle, produce IGF-I for autocrine and paracrine actions”

(The histopathology of BPH strongly implicates local paracrine and autocrine growth factors and inflammatory cytokines in its pathogenesis).

The diabetes can cause external urethral sfincthere (atrophy)

“Spontaneous myogenic contractions have been shown to be significantly upregulated in prostate tissue collected from men with BPH”(13)

“there are no significant differences in responsiveness of α-adrenoceptor agonists and the smooth muscle contents in longitudinal and circumferential directions to urethra, for human hypertrophied prostate.”(14)

The pharmacological effect played by Finasteride , dutasteride but also of Serenoa R and urtica dioica are clearly showed by literature and used in the management of IPB.

The diabetes/ insuline resistance conditions play a role in BPH : increase sympatic overactivity with

increased smooth prostate fiber tone, inflamation, alterations in sex hormone methabolism and in IGF growth factor activity

Conclusion

The exact causes of BPH are unknown at today so it is of interest to submit a new hypotesys.

Related the sex hormonal theory this not explain totally this process : the level of DHT in men with or without BPH not differ in significative way so other factor must to be involved in BPH.

The Nodules iperplastics have a variable composition : glandular elements and of fibromuscolar stroma.

The exthernal uretral sfincthere electromyography in BPH patient show an abnormal activity level . According literature there is a role of prostate also in the urinary continence function.

Generally IPB is considered a pathology that produce uretral obstrucion and reduced flux but it must to be better verified the role played by the functionality of the external urethral sfincthere and the compensation

Inside the global unit Urethral sfinctere (internal , Prostate smooth fiber , external Urethral sfinctere). And for the scope of this work to verify also the movens played by Prostate smooth fibers in IPB process.

The prostate inside have smooth fibers that help in semen eiaculation so it can be considered not only a simple gland but with a specific muscolar role.

This 2 function Can be considered linked together ?

What happen if increase the need of muscular contraction to the gland ?(ipetrophy?).

And what is the effect played by growth factor in the gland and into the smooth fiber inside?

The reduced activity of the external sfincthere can produce the need of intervention by the prostatic uretra and this overload of additional work produce increase in growth factors : the autocrine contribute

to the effect of iperplasia. (oncological process can be involved also ?)

So it is right to change the paradigm : IPB as secondary effect as compensation of the exthernal uretral sfincthere ?

Moderate to vigorous physical activity reduced the risk of BPH

Aerobic exercise may alleviate BPH in obese mice through regulation of the AR/androgen/PI3K/AKT signaling pathway.

The reabilitation with Kegel exercise acting on the external uretral sfinchtere make possible to improve OVB and minctionary urgency.

And in therapy of the IPB are used also alfa antagonist to relax the smooth fibers of the Prostate and urethra .

The literature reported and figure help in verify all the pathogenetic movens.

If confirmed this pathoenetic movens the therapeutic implication can be relevant .

As final conclusion it is suggestet to consider the unit internal urethral sfinctere-prostate muscle -external urethral sfinthere as an linked structure that globally contribute to urine continence mechanism:

if malfunction of the external sfincthere the prostate can act in compensation . The IPB can be considered as secondary to this process.

Even if many elderly develop BPH not all are subjected. In animal world : In elderly dogs a % show BPH also.

In humans (bipede) the ipetrophya is in concentric way instead in the dogs happen in eccentric way and this can be related the different need of the bipede vs quadrupede mammals vs gravity forces.

Conflict of interest:no

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