Chapter 20
What is the prostate and what are its functions?

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Male accessory sex glands

The prostate gland is one of the male accessory sex glands. To appreciate its function, one must understand the role of accessory sex glands and the production of seminal fluid. The accessory sex glands consist of the prostate gland, the paired seminal vesicles, located at the base of the bladder, and the bulbourethral glands (a.k.a. Cowper's gland) directly connected to the urethra. Collectively, the main function of the sex accessory tissues is to create the seminal plasma, the medium in which sperm are delivered in the ejaculate. The sex accessory tissues produce high concentrations of prostaglandins, fructose, citric acid, polyamines, zinc, and enzymes such as proteases and acid phosphatases. The function of seminal fluid is twofold; 1) it serves as a buffered, nutrient transport medium for sperm as they are deposited in the female vagina, and 2) it retains sperm within the vagina for an optimum time period to permit proper activation of sperm capacity to fertilize and entry into the upper female genital tract.

While seminal plasma substances are not essential for fertilization of the egg by mature sperm, it is clear that seminal plasma enhances the *in vivo* fertilizing capacity of sperm. The slightly alkaline (7.2 - 7.8) pH of seminal plasma neutralizes the acidic vaginal environment. Seminal fructose provides energy for sperm, prostaglandins aid in smooth muscle contractions of the female genital tract and assist in sperm transport, and specific proteins coat the sperm surface and prevent premature activation of factors necessary for egg penetration. Zinc and IgA act as bacteriostatic factors, while anti-agglutination proteins prevent sperm cells from clumping together.

During emission and ejaculation, sperm move from their storage site in the epididymis through the vas deferens, propelled by peristaltic contractions of the vasa musculature. This is coordinated

with contractions from the accessory sex glands and the combined contents – the semen – are expelled through the urethra. However, the accessory sex glands do not contract simultaneously but rather in a specific sequence. With adequate sexual stimulation, a small initial fraction from the bulbourethral gland is released prior to ejaculation to lubricate the urethra. When ejaculation begins, a sperm-rich fraction is expelled first containing sperm from the vas deferens along with prostatic secretions. This fraction is ~0.5 ml in volume or 25% of the ejaculate, the bulk of this volume coming from the prostate gland. The last and largest fraction of the ejaculate comes from the seminal vesicles and varies between 1.0-2.5 ml or 75% of seminal volume. Spermatozoa and the epididymal fluid bathing them make up less than 5% of the volume of the ejaculate.

Soon after ejaculation, the semen coagulates, forming a gelatinous clot that restricts free movement of spermatozoa. Coagulation occurs by coagulating factors and unique enzymes produced by the seminal vesicles, similar to the thrombin coagulating system found in blood. After 15-30 minutes, the coagulated semen begins to liquefy as a result of proteolytic digestion by enzymes produced in the prostate gland. These prostatic enzymes include a chymotrypsin-like enzyme termed seminin, urokinase, and distinct plasminogen activators. The liquefaction process permits the slow release of sperm from the coagulum, allowing them to be transported into the cervix and eventually upstream to the ovulated egg. Overall, the process of coagulation / liquefaction allows for appropriate exposure of the sperm cells to seminal fluid factors that stimulate motility and enhance fertilizing capacity and then permits an orderly entry of sperm cells into the upper female genital tract.

Prostate gland anatomy

The prostate is a small walnut-sized gland that resides at the base of the bladder surrounding the urethra (Fig. 1). In its center, the urethra makes a 70º turn at a site referred to as the verumontanum. The seminal vesicle ducts and vas deferens merge cranial to the prostate to form paired ejaculatory ducts that transverse the prostate and empty into the urethra at the level of the verumontanum. Below this site, 20-30 excretory ducts from the prostate enter the urethra and deposit prostatic secretions during ejaculation. This later region of the urethra is referred to as the prostatic urethra. Although the prostate gland is not lobular, there

are distinctive regions or zones based on anatomic site, histologic appearance and propensity for disease. The central zone, lies between the ejaculatory ducts from the bladder base to the verumontanum and represents ~20% of the glandular volume. The peripheral zone surrounds the central zone and extends downward to the prostate apex, comprising 70% of prostatic volume. The tubuloaveolar glands in these regions empty into the prostatic urethra via the aforementioned 20-30 ductules within the peripheral zone. The transition zone (~10% volume) lies adjacent to the proximal urethra just above the verumontanum and is in contact with the central and peripheral zones at this site. The proximal urethra is surrounded by a smooth muscle sphincter, the preprostatic sphincter, which contracts during ejaculation preventing retrograde flow of semen into the bladder. It is noteworthy that benign prostatic hyperplasia (BPH) develops in the transition zone surrounding the proximal urethra whereas most prostate cancers develop within the peripheral zone.

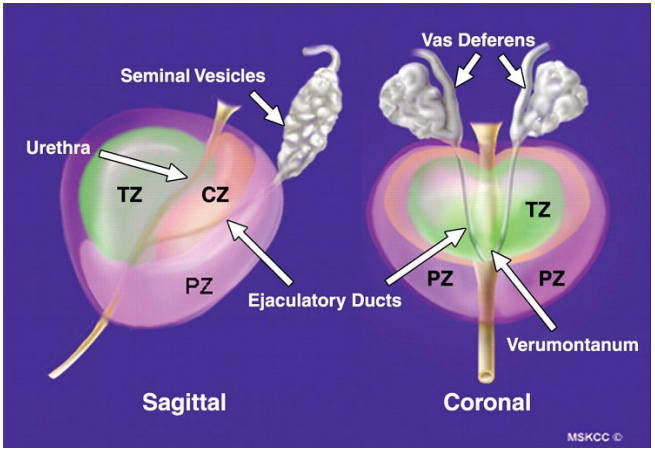

Figure 1. Schematic representation of the prostate gland. PZ: Peripheral zone. TZ: Transition zone. CZ: Central zone. (Reprinted with permission from Currin S. et al, Am J Roentgenol 2007; 188: 3737).

Prostate growth control

Prostate development, function and homeostasis throughout life are entirely dependent on androgens. The primary source is testosterone produced by the testes although adrenal androgens can also contribute to prostate health. Of note, the prostate gland has high expression of reductase enzymes that rapidly and irreversibly convert testosterone to dihydrotestosterone (DHT). Since DHT has a higher affinity for the androgen receptor, this allows for greater androgenic action within the prostate gland without over-androgenizing other peripheral organs that utilize testosterone.

Diseases of the prostate gland

The prostate gland is widely known for its propensity to develop diseases that interfere with quality of life and, in some cases, are fatal. This is unique among the male accessory sex glands and may be related to its embryologic origin from the endodermal urogenital sinus in contrast to the other accessory sex glands derived from the mesodermal Wolffian ducts. Three major prostatic diseases, in decreasing order of frequency, are prostatitis, BPH and prostate cancer. These are diseases of the aging male, most often appearing after the age of 50. A brief overview of these conditions is presented below and some will be discussed in greater detail in chapters of their own (Chapters 56-59). Prostatitis, an inflammatory condition of the prostate gland, can be both acute and chronic and affects ~50% of men during their lifetime. Interestingly, less than 10% of cases are due to bacterial infections and the etiology of the majority of prostatitis is unknown. The primary symptom of this disease is pelvic pain and treatments may include antibiotics, alpha-blockers, anti-inflammatory drugs, muscle relaxants, heat therapy or repetitive prostatic massage.

Benign prostatic hyperplasia or BPH is a noncancerous enlargement of the prostate gland due to its continued growth with aging. BPH occurs in 40-50% of men over 50 years of age and reaches 80% by 80 years of age. Since the prostate surrounds the urethra, BPH can decrease urine flow rate by increasing the flow-resistance within the urethra and may lead to various lower urinary tract symptoms such as urinary frequency and urinary retention. Treatments are necessary in ~25% of patients and include surgery (e.g. TURP) as well as medical management with alpha-adrenergic blockers and/or 5α–reductase inhibitors.

Prostate cancer, an adenocarcinoma, is the most common non-cutaneous cancer in American men and the second leading cause of cancer-related deaths in the United States. Risk factors include aging, family history and ethnicity with African-American men having a 2:1 incidence ratio compared to Caucasians and Asian men having the lowest incidence world-wide. African men have the highest mortality rate due to prostate cancer in the world. Prostate cancer has a life-time risk of 1 in 6 men in the USA with an incidence of 1 in 45 between 40-60 years and 1 in 7 between 60-80 years. While up to 50% of cancers remain latent, i.e. do not progress beyond the prostate gland, the remainder progress at variable rates which can lead to distant metastasis and death. At present, it is not possible to distinguish between these cancer types during early stage disease making treatment choices difficult. Early detection of prostate cancer has increased due to monitoring of prostate specific antigen (PSA) levels in the blood which can detect ~70-80% of cancers. Treatments are typically age and stage-dependent and include watchful waiting, active surveillance, surgery (prostatectomy) or radiation for early stage disease (i.e. confined to prostate). Side effects of surgical and radiation therapy can include incontinence and impotence. When prostate cancer reemerges or is diagnosed at the metastatic stage, androgen-deprivation therapy (ADT) without or with chemotherapy (e.g. taxanes) is the first line of therapy for this later-stage disease. Like the prostate gland itself, prostate cancer initially depends on androgens to grow. Unfortunately, as the disease progresses, particularly with extended ADT duration, it becomes independent of androgens with no curative treatments available. With second and third generation ADT modalities, ~30% of metastatic disease will emerge as neuroendocrine (small cell) prostate cancer with no available treatments at present. Side effects associated with ADT include sexual dysfunction, infertility and muscle and bone wasting. In the past decade, several new treatment approaches have emerged for advanced prostate cancer therapy including immunotherapy, PARP inhibitors, immune checkpoint blockade, advanced radiation approaches (^{177}Lu-PSMA-617; radium-223) and novel approaches continuously under development. The goal is to prolong life and maintain a high quality of life so that men continue to live with the disease and not die from it.

Suggested reading

Aaron L, Franco OE, Hayward SW. Review of Prostate Anatomy and Embryology and the Etiology of Benign Prostatic Hyperplasia. Urol Clin North Am. 2016;43(3):279-88.

Prins GS, Lindgren M. Accessory Sex Glands in the Male. In: Plant TM, Zeleznik A, editors. Knobil and Neill's Physiology of Reproduction, 4th ed. San Diego: Academic Press; Vol 1, chapter 18, pp. 773-803, 2015.

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