Casual Friday Presents

BPH: Benign Prostatic Hyperplasia

A BIOGENETIX CLINICAL PRESENTATION

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Benign prostatic hyperplasia (BPH) refers to the nonmalignant growth or hyperplasia of prostate tissue and is a common cause of lower urinary tract symptoms (LUTS) in older men. Disease prevalence 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.[1]

Several definitions exist in the literature when describing BPH. These include bladder outlet obstruction, LUTS, and benign prostatic enlargement (BPE). BPH describes the histological changes, BPE refers to the increased size of the gland (usually secondary to BPH), and bladder outlet obstruction is defined as the blockage to urinary flow.[2][3] Those with BPE who present with bladder outlet obstruction are also termed benign prostatic obstruction.[4]

Lower urinary tract symptoms (LUTS) describe the urinary abnormalities shared by disorders affecting the bladder and prostate, typically caused by BPH. These terms have largely replaced those historically termed "prostatism."

The development of BPH is characterized by stromal and epithelial cell proliferation in the prostate transition zone, which surrounds the urethra. This leads to urethral compression and bladder outflow obstruction, which can result in clinical manifestations of LUTS, urinary retention, or infections due to incomplete bladder emptying.[5] Long-term, untreated disease can lead to the development of chronic high-pressure retention (a potentially life-threatening condition) and long-term or permanent changes to the bladder detrusor muscle.

BPH treatment options range from watchful waiting to various medical and surgical interventions. Risk factors may be divided into non-modifiable and modifiable. Other factors such as age, genetics, geographical location, and obesity have all been shown to influence the development of BPH.[6][7]

Age is a significant predictor of the development of BPH and subsequent LUTS. Fifty percent of men older than 50 show evidence of BPH, and the association with the development of LUTS increases linearly with age.[33][34] This is supported by studies that have demonstrated increases in prostate volume with age (2% to 2.5% increase in size per year).[35]

In the US, studies have shown BPH prevalence to be as high as 70% in those between 60 and 69 years of age and more than 80% in those over 70 years.[36] In a Boston area community health survey, the prevalence of male LUTS alone significantly increased with age from 8% (30 to 39 yrs) to 35% (60 to 69 yrs). Other US population-based studies have shown 56% of men between 50 and 79 years reported BPH symptoms.[37][38]

At a population level, the reported prevalence of BPH increased dramatically between 1998 and 2007 in the US, with the number of cases nearly doubling.[39] These increases are attributed to an aging population, with those older than 80 years projected to be 19.5 million in 2030 (up from 9.3 million in 2003).[40] As the worldwide population grows older, the number of symptomatic BPH cases is expected to rise.

International studies have suggested that Western populations have significantly higher prostate volumes than those from other parts of the world, particularly Southeast Asia.[41] Further studies looking at the correlation of prostate volume with LUTS found that lower prostate volumes did not necessarily correlate with symptoms, as higher mean IPSS was observed in a cohort of Indian men compared to similar Western populations.[42]

BPH arises due to the loss of homeostasis between prostatic cellular proliferation and apoptosis or cell death. This imbalance favors cellular proliferation without intervention. The result is increased numbers of prostatic periurethral epithelial and stromal cells, which can be seen histopathologically.[5] The etiology of BPH is influenced by a wide variety of risk factors, in addition to the direct hormonal effects of testosterone on prostate tissue. Men who are castrated before puberty or who have an androgen-related disorder do not develop BPH.

There is conflicting data on the role of non-steroidal anti-inflammatory medications (NSAIDs) in promoting BPH, with some studies indicating a positive association and others discounting any association.[8][9][10] Allopurinol is somewhat protective for BPH, possibly secondary to reduced oxidative stress from hyperuricemia effects.[11]

Testicular androgens are required to develop BPH as dihydrotestosterone (DHT) promotes tissue growth and cellular proliferation by interacting directly with prostatic epithelium and stroma.[5][12] Testosterone is converted to DHT by 5-alpha-reductase 2 in prostatic stromal cells and accounts for 90% of total intraprostatic androgens.[7] DHT directly influences prostatic stromal and adjacent cells, which affect cellular proliferation and apoptosis.[13] Interestingly, there does not appear to be any relationship between testosterone or DHT levels and the development of symptomatic BPH.[14]

Risk Factors

Non-modifiable and modifiable risk factors also contribute to the development of BPH. These have been shown to include diabetes, diet, genetic factors, localized inflammation, obesity, and metabolic syndrome.[7]

- **Diabetes and the use of antidiabetic medications**, particularly insulin, appear to increase the risk of BPH, LUTS, and prostatic surgery.[15][16]

- **Dietary factors** also appear to influence the development of BPH. Beta-carotene, carotenoids, and vitamin A seem somewhat protective, while excessive alcohol ingestion, heavy caffeine intake, and high-dose supplemental vitamin C tend to increase BPH risk and symptoms.[17][18][19] No prepared dietary supplement has been proven to help BPH in properly performed, randomized, controlled studies.

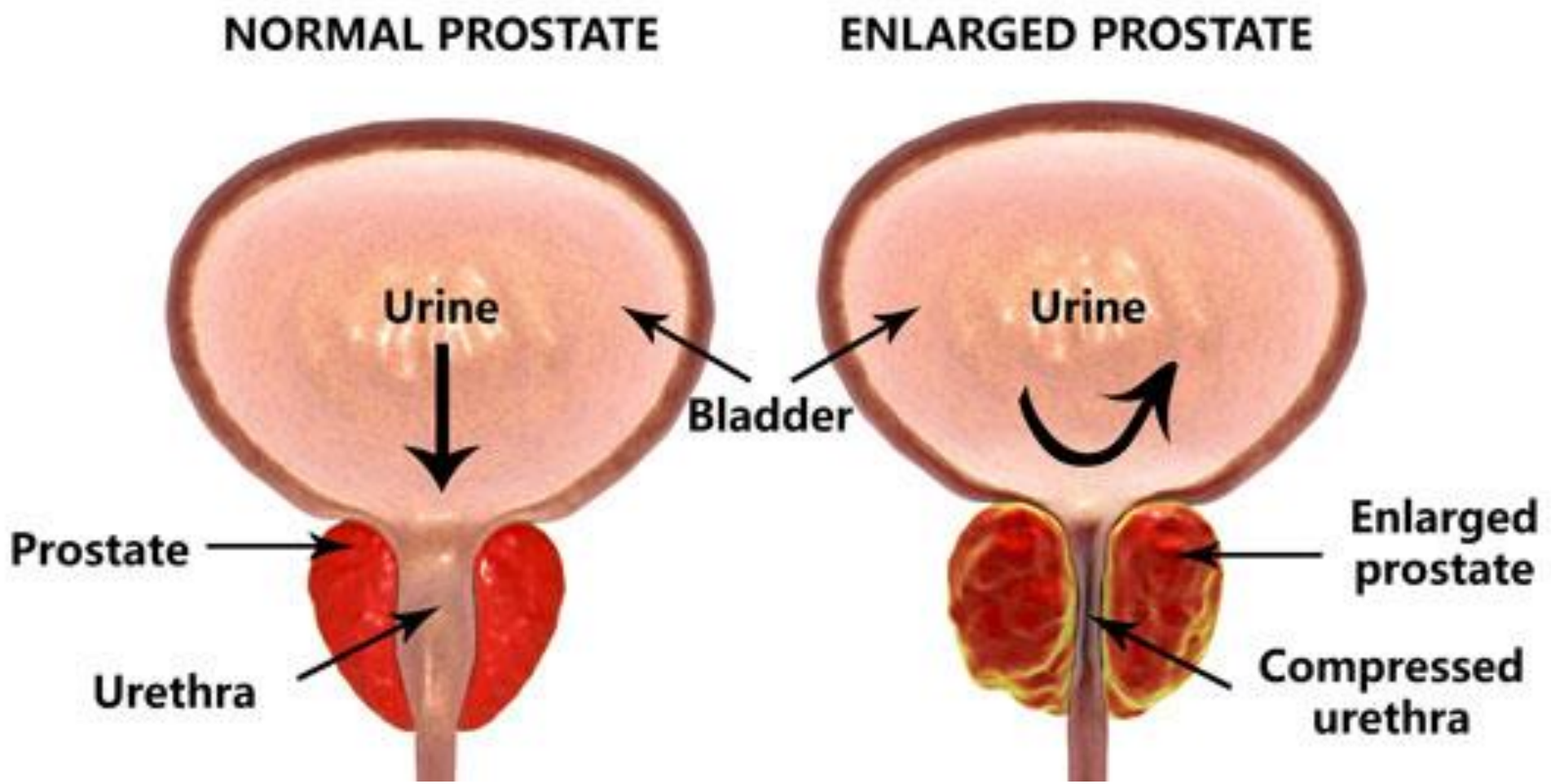
- **Genetic predisposition** to BPH has been demonstrated in cohort studies. First-degree relatives in 1 study demonstrated a 4-fold increase in the risk of BPH compared to the control.[20] These findings have demonstrated consistency in twin studies looking at the disease severity of BPH, with higher rates of LUTS seen in monozygotic twins.[21][22]

- **Localized inflammation** is often associated with BPH, at least histologically.[23][24][25] 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. This would suggest that the use of NSAIDs could be used to treat symptomatic BPH. Three randomized studies have confirmed that NSAIDs can improve BPH symptoms, but the difference was relatively modest at <3 points (International Prostate Symptom Scores [IPSS]) and <1 mL/s improvement in urine peak flow rate.[26]

- **Obesity** is associated with an increased risk of BPH in observational studies.[27][28] 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.[29][30]

- **Metabolic syndrome** refers to conditions that include hypertension, glucose intolerance/insulin resistance, and dyslipidemia. Meta-analysis has demonstrated those with metabolic syndrome and obesity have significantly higher prostate volumes.[31] Further studies looking at men with elevated glycosylated hemoglobin levels (Hba1c) have demonstrated an increased risk of LUTS.[15] 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.[31][32] Further studies are therefore required to establish causation in these individuals.

BENIGN PROSTATIC HYPERPLASIA



https://auspecialists.com/wp-content/uploads/2019/08/bph.jpg

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Finasteride as a main therapeutic:

It works by blocking the body's production of dihydrotestosterone (DHT), a male hormone that can cause the prostate to enlarge.

1.DHT's Role: DHT is derived from testosterone and plays a significant role in prostate growth.

2.5-alpha reductase: This enzyme converts testosterone into DHT.

3.Finasteride's Action: Finasteride inhibits the activity of 5-alpha reductase, specifically type 2, the predominant enzyme in the prostate.

4.Reduced DHT, Reduced Prostate Size: By blocking the production of DHT, finasteride helps to shrink the prostate and improve urinary flow.

Benefits of finasteride for BPH:

•Reduces prostate size: Finasteride can significantly reduce the volume of an enlarged prostate.

•Improves urinary symptoms: It can help relieve symptoms like frequent and difficult urination, as well as the sudden inability to urinate (acute urinary retention).

•Reduces the need for surgery: Finasteride can decrease the chance that surgery will be needed to treat BPH.

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55 yo male

Hormone Testing Summary

Key (how to read the results):

Sex Hormones

Estradiol(E2)

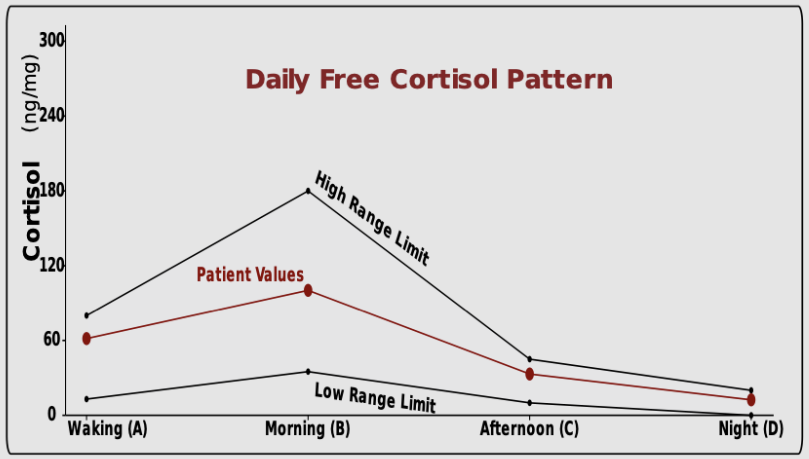
Testosterone

Testosterone

Age	Range
18-25	35-115
26-40	30-95
41-60	25-80
>60	20-60

Adrenal Hormones

See pages 4 and 5 for a more complete breakdown of adrenal hormones



Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500

Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

24hr Free Cortisol
(A+B+C+D)

cortisol metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

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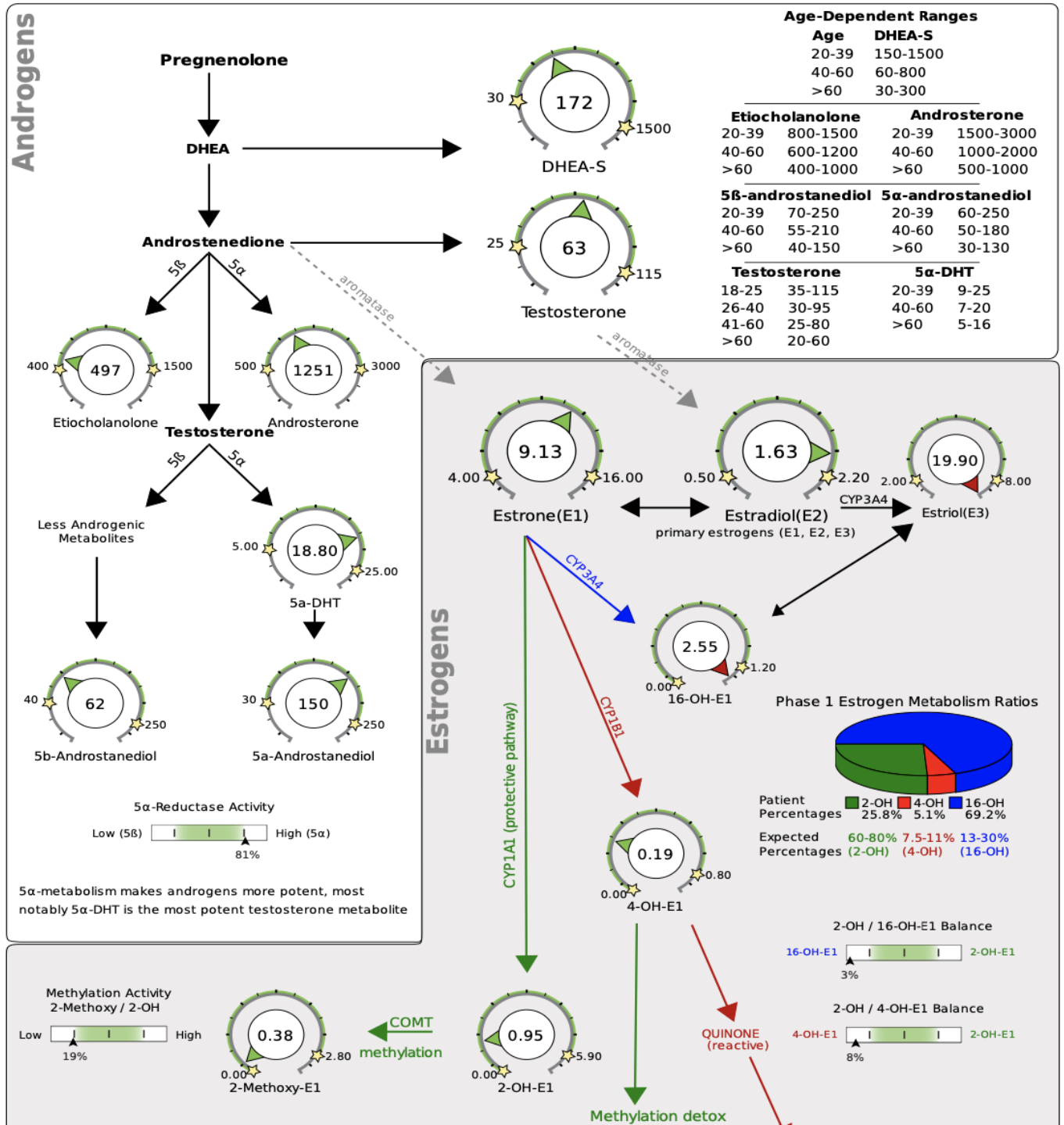
Androgens
Pregnenolone
DHEA
Androstenedione
Testosterone
5ß
5α
aromatase
172
30
1500
DHEA-S
63
25
115
Testosterone
497
400
1500
Etiocholanolone
1251
500
3000
Androsterone
Less Androgenic Metabolites
18.80
5.00
25.00
5a-DHT
62
40
250
5b-Androstanediol
150
30
250
5a-Androstanediol
5α-Reductase Activity
Low (5ß)
High (5α)
81%
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Age-Dependent Ranges
Age DHEA-S
20-39 150-1500
40-60 60-800
>60 30-300
Etiocholanolone
20-39 800-1500
40-60 600-1200
>60 400-1000
Androsterone
20-39 1500-3000
40-60 1000-2000
>60 500-1000
5ß-androstanediol
20-39 70-250
40-60 55-210
>60 40-150
5α-androstanediol
20-39 60-250
40-60 50-180
>60 30-130
Testosterone
18-25 35-115
26-40 30-95
41-60 25-80
>60 20-60
5α-DHT
20-39 9-25
40-60 7-20
>60 5-16
Estrogens
9.13
4.00
16.00
Estrone(E1)
1.63
0.50
2.20
Estradiol(E2)
primary estrogens (E1, E2, E3)
CYP3A4
19.90
2.00
8.00
Estriol(E3)
CYP3A4
2.55
0.00
1.20
16-OH-E1
CYP1B1
CYP1A1 (protective pathway)
0.19
0.00
0.80
4-OH-E1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages
2-OH 25.8%
4-OH 5.1%
16-OH 69.2%
Expected Percentages
60-80% (2-OH)
7.5-11% (4-OH)
13-30% (16-OH)
2-OH / 16-OH-E1 Balance
16-OH-E1
2-OH-E1
3%
2-OH / 4-OH-E1 Balance
4-OH-E1
2-OH-E1
8%
Methylation Activity
2-Methoxy / 2-OH
Low
High
19%
0.38
0.00
2.80
2-Methoxy-E1
COMT
methylation
0.95
0.00
5.90
2-OH-E1
QUINONE (reactive)
Methylation detox

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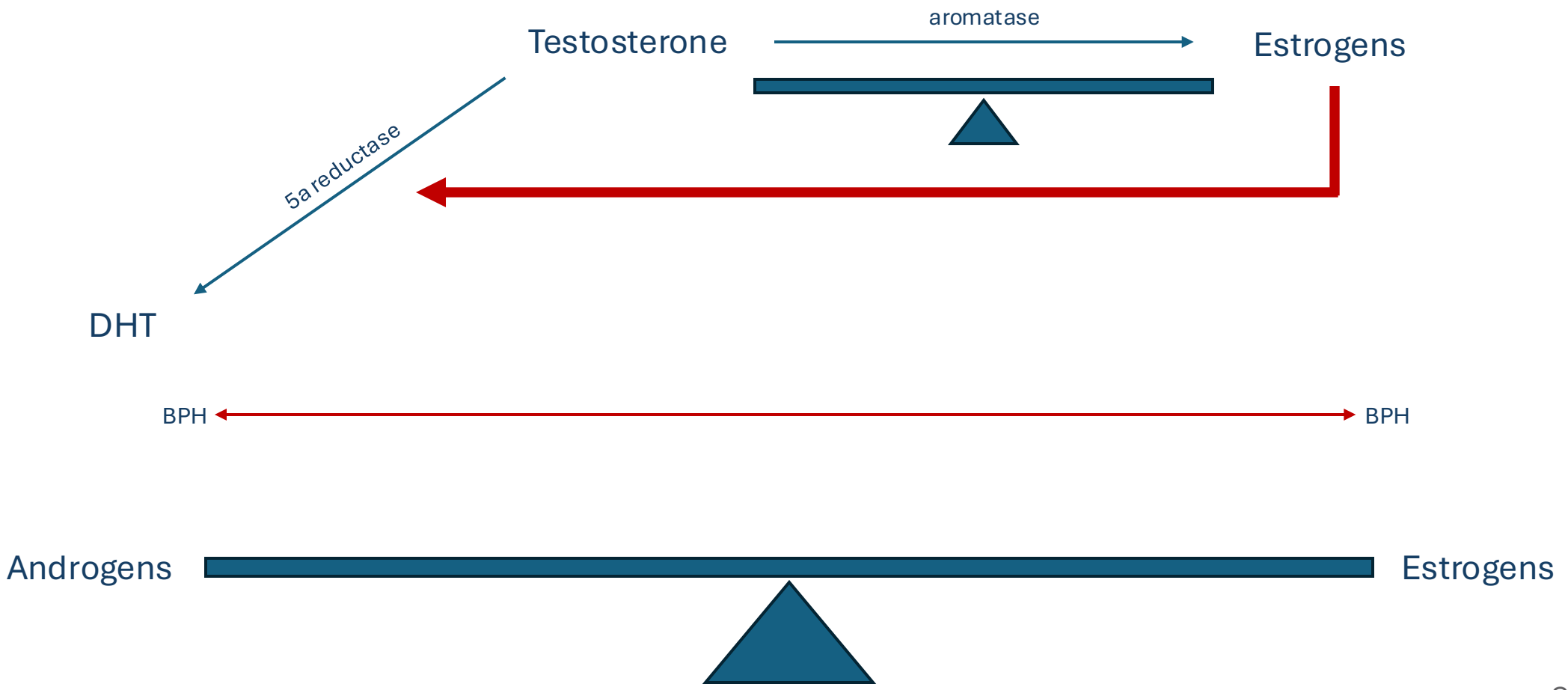
BPH: A hormone balancing act.



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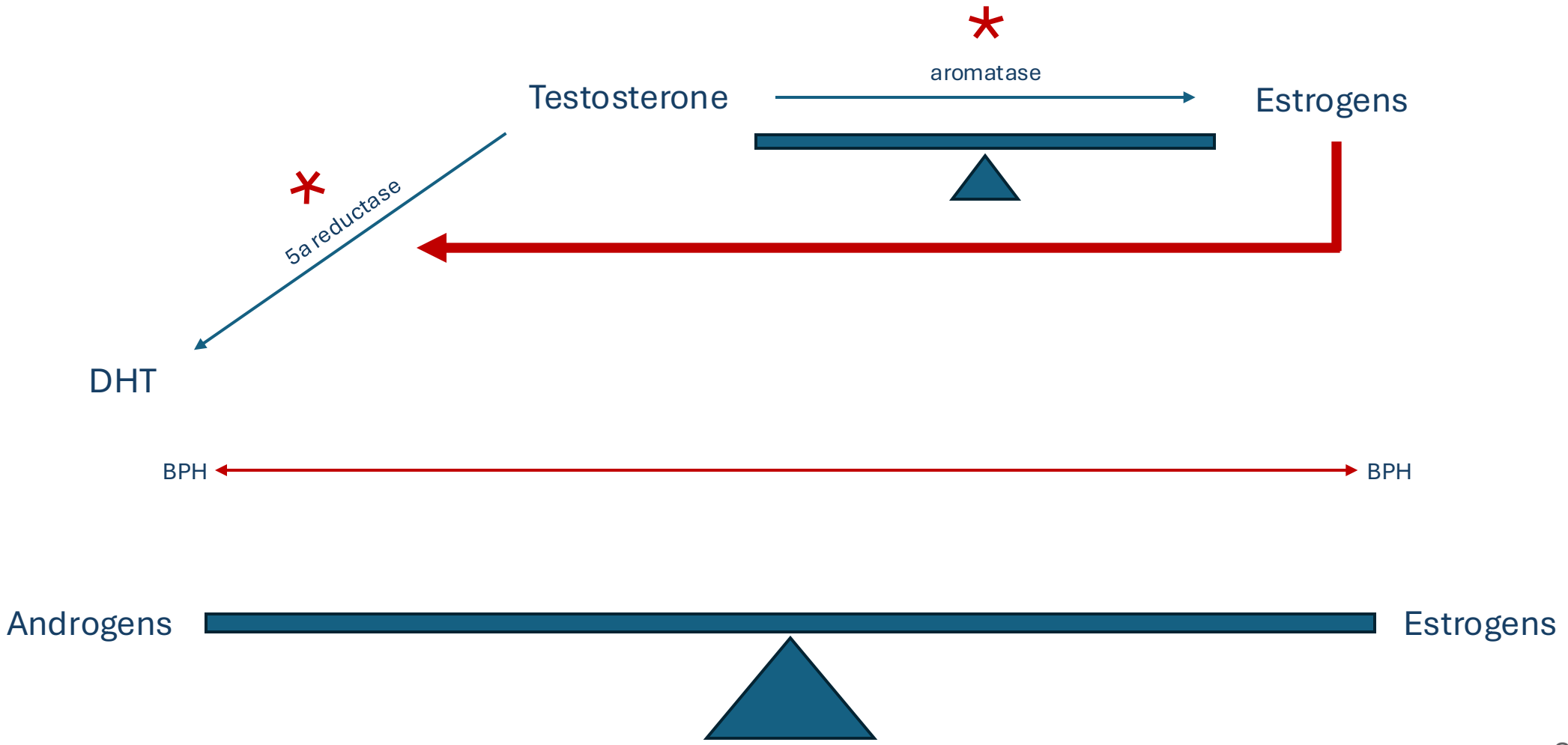

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5a reductase

Saw Palmetto
Pygeum
Nettle Root
Cranberry
Green Tea (egcg)
Zinc

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aromatase

Chrysin
Cruciferous vegetables
Mushrooms
Green Tea (egcg)
Blueberries
Cherries

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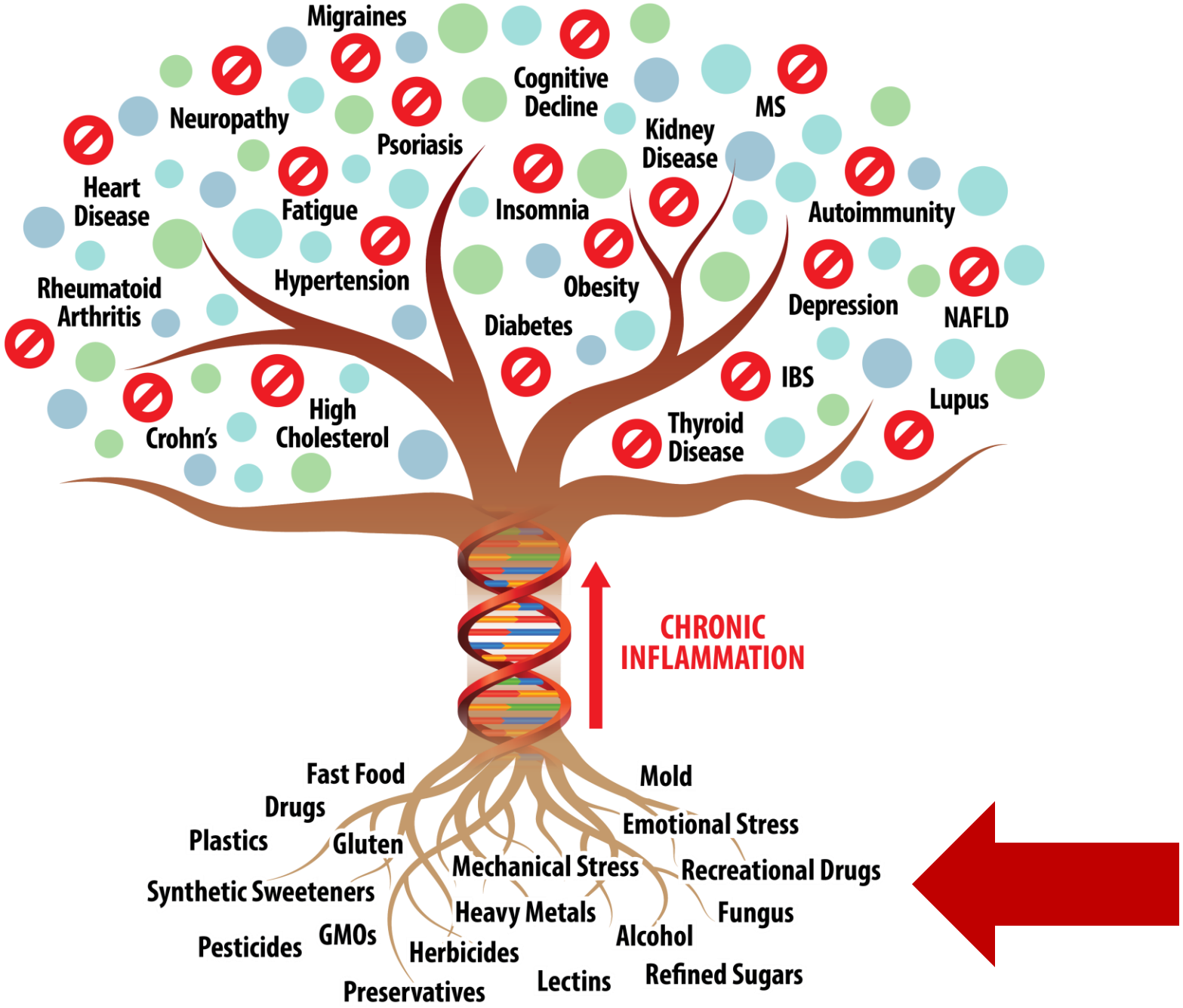
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

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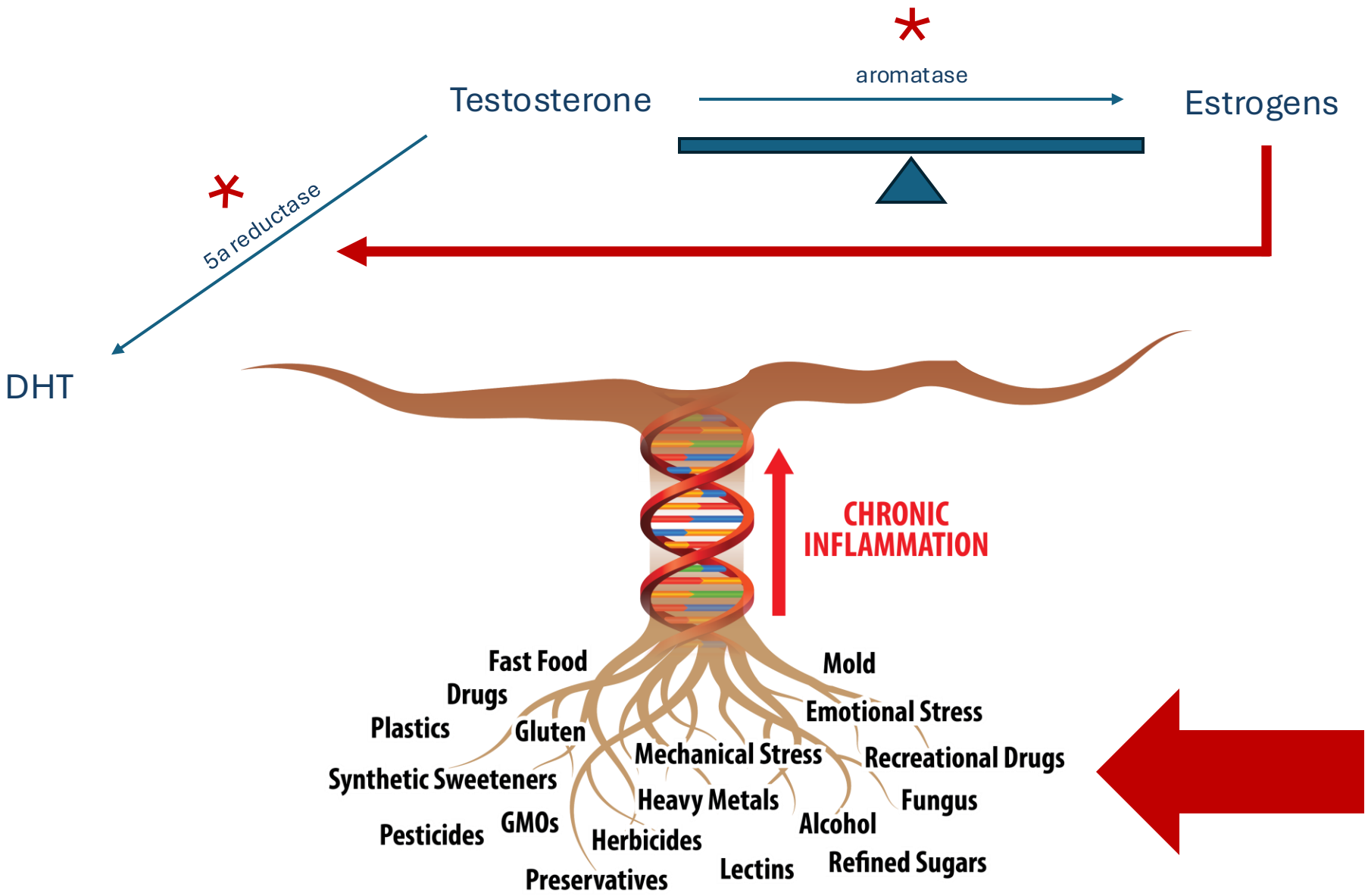
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aromatase
Testosterone
Estrogens
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5a reductase
DHT
CHRONIC
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What about mycotoxin?

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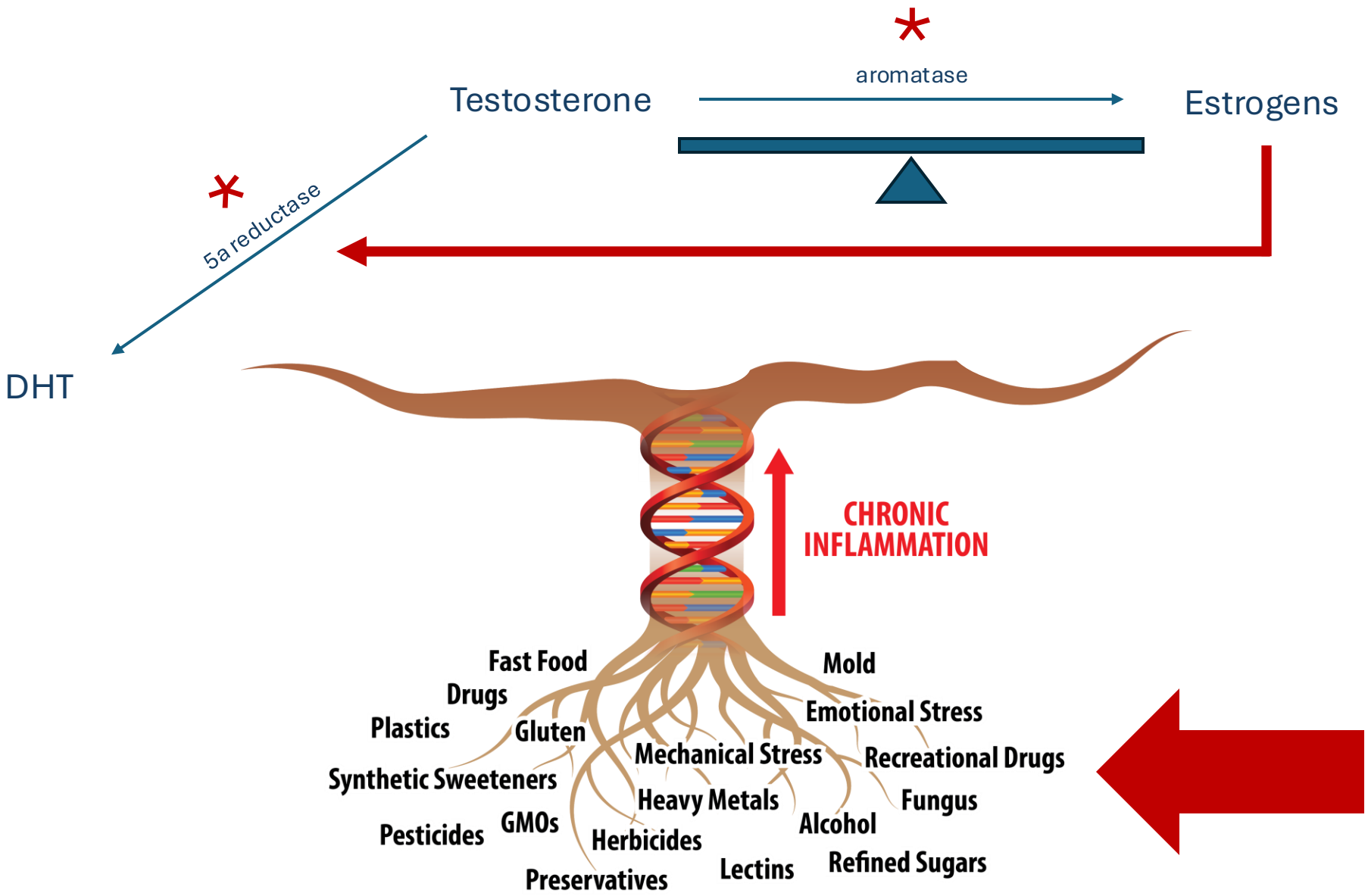
Toxins (Basel). 2018 Feb 28;10(3):98. doi: 10.3390/toxins10030098

Estrogen Receptor α Is Crucial in Zearalenone-Induced Invasion and Migration of Prostate Cancer Cells

Karolina Kowalska [1,2], Dominika Ewa Habrowska-Górczyńska [1,2], Kinga Anna Urbanek [1,2], Kamila Domińska [2], Agnieszka Wanda Piastowska-Ciesielska [1,2,*]

Zearalenone (ZEA), a mycotoxin produced in the genus *Fusarium*, binds to estrogen receptors (ER) and is therefore regarded as an endocrine disruptor. ZEA has also been found to modulate the proliferation and apoptosis of prostate cancer cells in a dose-dependent manner. This study evaluates whether the effect of a low dose of ZEA (0.1 and 0.001 nM) on the invasion and migration of prostate cancer cell line PC3 is associated with ERs expression. The invasion and migration was evaluated by modified Boyden chamber assay, scratch assay, gelatin zymography, Real Time qPCR (RTqPCR) and Western blot. The involvement of ERs was evaluated with the selective ER antagonists: estrogen receptor α (ERα) antagonist 1,3-*bis* (4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy) phenol]-1H-pyrazole dihydrochloride (MPP) and estrogen receptor β (ERβ) antagonist 4-[2–phenyl-5,7–*bis* (trifluoromethyl) pyrazolo [1,5-a]-pyrimidin-3-yl] phenol (PHTPP). ZEA was found to modulate cell motility dependent on estrogen receptors, particularly ERα. Increased cell migration and invasion were associated with increased MMP-2 and MMP-9 activity as well as the up-regulation of the EMT-associated genes vimentin (*VIM*), zinc finger E-box-binding homeobox 1/2 (*ZEB1/2*) and transforming growth factor β 1 (*TGFβ1*). In conclusion, ZEA might modulate the invasiveness of prostate cancer cells dependently on ERα expression.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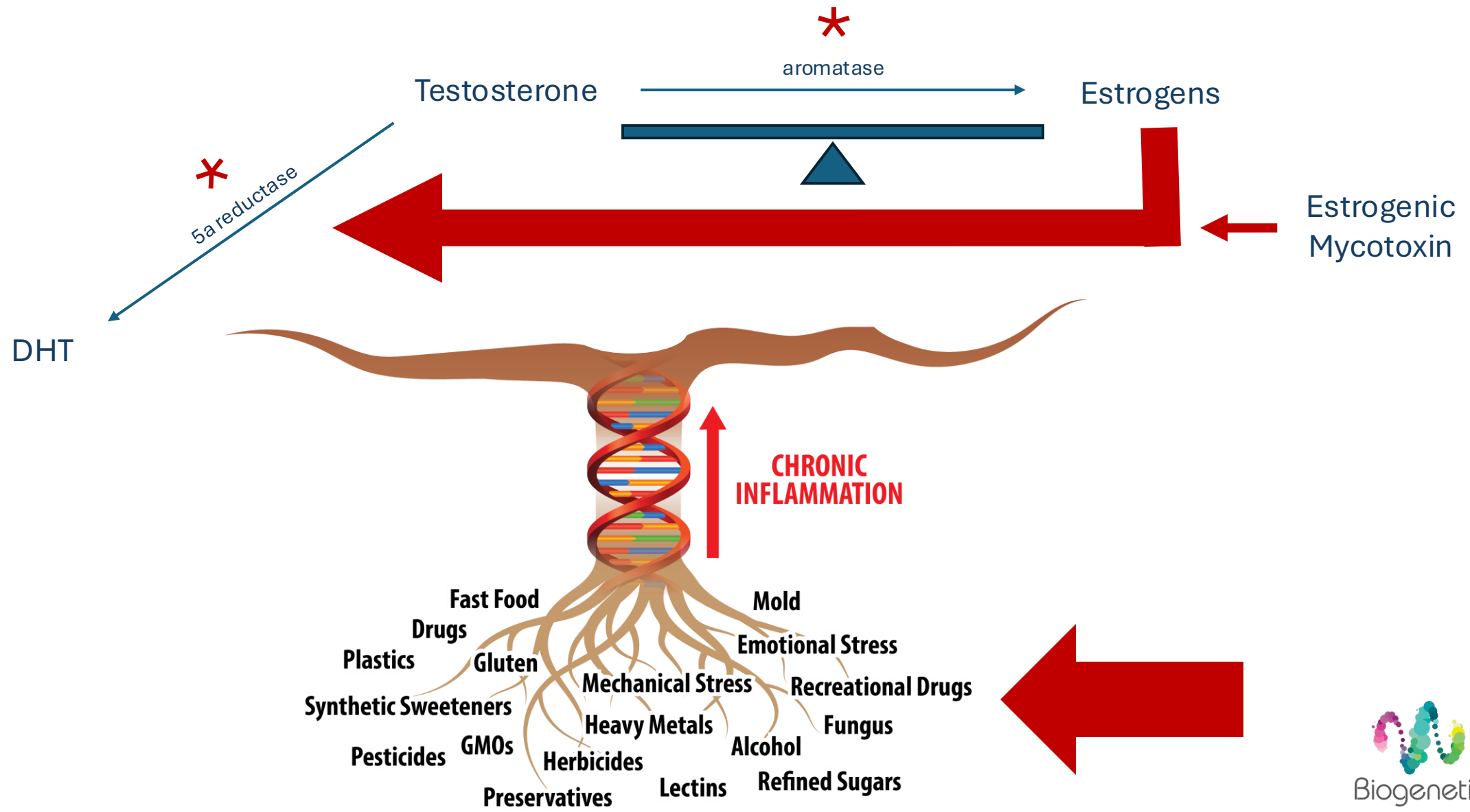
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