The Global Decline of Testosterone & Sperm in the Western World: The Health, Social & Cultural Impact

ABSTRACT

Evidence suggests that testosterone and sperm levels are lowering in men across the globe.

Testosterone and healthy optimal blood levels have a profound relationship with optimal health in men. Lowering testosterone levels are related to diseases such as cardiovascular disease,[1] osteoporosis,[2] Alzheimer's disease,[3] and diabetes.[4] In addition, and less commonly known, testosterone is responsible for healthy neurological function[5] and improved psycho-social and behavioral dynamics.[6]

Research has begun to reveal a measurable decline in both testosterone[7] [8] [9] and sperm production,[10] [11] and sperm quality[12] [13] in men in industrialized countries across the world. Despite research that refuted this assertion, additional recent French research retorts back to the original premise that testosterone levels are declining.[14] We are seeing the physical impact of this testosterone decline in male strength levels including grip strength[15], a global rise in testosterone deficiency correlated obesity,[16] and the psychological impact in terms of mood disorders.[17] It is important to note that some small sample size research suggests we do not see the same age-related decline of testosterone levels in non-industrialized countries.[18] [19] [20] The global health and social impact of this trend in industrialized countries is not to be underestimated, but rather understood and coupled with ardent strides to provide resourceful medical solutions.

This article begins with a cursory review of the physiological implications of testosterone effects in the male spanning the entire life cycle including the anatomy and physiology in the developing male, the mature male, and the geriatric male. It also explores the health consequences of lowering testosterone and sperm in men.[21] The causative factors of this decline are intriguing and numerous, including in utero influences,[22] lifestyle considerations,[23] [24] co-morbid disease relationships,[25] nutritive and exercise preferences, environmental toxin exposure to endocrine disrupting chemicals,[26] iatrogenic pharmaceutical causes,[27] [28] psycho-social influences,[29] [30] and even cultural norms.[31]

This article will provide naturopathic medical solutions offering effective clinical interventions.

- High Fat Diet: It is suggested that a diet rich in cholesterol, saturated fat, and fat soluble vitamins optimize healthy testosterone levels in the long term.[32] [33] [34] [35]
- High Intensity Exercise: High intensity exercise with heavy weights stimulates testosterone production.[36]
- Lifestyle Modifications: Including sexual practices and meditation.

- Behavioral Considerations: The Naturopathic Doctor and functional medicine clinician are in a unique situation to provide counseling suggestions towards optimal testosterone production.
- Botanical Medicine: Various botanical medicines have been shown to increase both total and free testosterone levels.[37] [38] [39]
- Light Therapy: A 100 year science that influences testicular function.
- Hydrotherapy: An ancient therapy with modern applications and efficacy.
- Exogenous Bioidentical Testosterone Replacement: Natural bioidentical testosterone replacement therapy has been shown to be a safe and effective choice for hormone and health optimization.[40] [41]

INTRODUCTION

PHYSIOLOGY OF TESTOSTERONE IN MEN

Production and Synthesis

Testosterone in the male is largely produced by the testes through the hypothalamic-pituitary-gonadal axis and secondarily in the adrenal cortex through the hypothalamic-pituitary-adrenal axis. However, and less known and appreciated, the active biosynthesis of testosterone and other steroids also occurs in the brain. This synthesis is controlled by an enzyme known as Steroidogenic acute regulatory protein (StAR) and can be synthesized directly from cholesterol or derived from deoxycorticosterone or progesterone which enter through the blood stream into the nervous system.[42]

Physical Effects

The physiological effects of testosterone in the male are vast. They are typically categorized as Anabolic and Androgenic effects. The anabolic effects of testosterone influence skeletal muscle growth, skeletal bone density, bone strengthening, linear bone growth, and neurotrophic effects, all through an enhancement of protein synthesis and cell regulatory mechanisms. The androgenic effects of testosterone lead to the development of male Secondary Sexual Characteristics. These characteristics of testosterone are the more widely known and understood influences of testosterone in the developing male. Testosterone is responsible for influencing the maturation of the penis, increased facial and body hair, and enhancement of the larynx leading to a deepening of the voice. Skeletal changes influence the jaw, chin, and nose, all leading to an adult appearance that is distinctly male.

Mental & Emotional Effects

Because of the influence of testosterone on the brain, we see considerable androgenic effects that influence neurological function including cognition, emotions, and behavior.[43] [44] One specific area of the brain that has a significant response to testosterone and androgens is the hippocampus.[45] The hippocampus region of the brain

is located within the medial temporal lobe and comprising an important part of the emotion-regulating limbic system. The hippocampus is associated with long-term memory and spatial navigation, the later ability being generally more developed in males. This hippocampal influence of testosterone is important in the developing male as well as the adult and aging male.

Social/Behavioral Effects

Behavioral endocrinology has studied the effects of testosterone on behavior. In general, we see the importance of testosterone as a social behavioral stimulus. Testosterone influences aggression and social dominance, assertiveness, risk-taking behavior, to name just a few more classically known relationships. But less understood, particularly by the general physician and within the lay public, is the positive effects of testosterone on promoting promoting pro-social behaviors such as honesty and rule following.

UNIT 1: THE GLOBAL STATE OF TESTOSTERONE

DISEASES ASSOCIATED WITH LOWERING TESTOSTERONE IN THE AGING MALE

Cardiovascular Disease

Men tend towards a higher incidence of cardiovascular disease than women, including myocardial infarction and stroke. Previously, it was assumed that because men have more testosterone than women, that the testosterone was to blame. This has been consistently challenged. Low testosterone is increasingly being linked to cardiovascular disease and this is a current understanding.[46] [47] Even with regression analysis studies, it has been demonstrated that when the effects of such comorbid conditions are controlled for the relationship between coronary artery disease and lower testosterone levels remains.[48]

Diabetes

The link of testosterone deficiency and diabetes has been well know. In fact, a recent 2014 meta-analysis including four prospective studies demonstrated that testosterone deficiency is associated with a three- to four-fold increased risk of diabetes mellitus.[49]

Obesity

A high BMI is related to lowered testosterone levels. Several review studies support the notion that restoration of normal testosterone levels in obese men is related to improved weight loss, reduction in waist circumference and BMI, and improvement in body composition including lowered body fat percentage and increased muscle mass.[50] [51] [52] Additionally, being overweight and obese were associated with an increased prevalence of azoospermia or oligozoospermia in a recent meta-analysis study.[53]

Metabolic Syndrome

Metabolic Syndrome is defined by the International Diabetes Federation as central obesity, hypertriglyceridemia, low high-density lipid cholesterol, hypertension, or insulin resistance, and has been highly associated with testosterone deficiency.[54] [55]

Osteoporosis

The prevalence of male osteoporosis is very low under age 70, yet rises significantly to an estimated prevalence of 22.6% in the very aged (>90 years old)[56] with the lifetime risk of fracture at ≥50 years being 50% for women and 20% for men.[57] [58] Testosterone affects bone growth and remodeling and Late Onset Hypogonadism (LOH) is related to bone loss in the aging male.[59] Testosterone Replacement Therapy (TRT) and the normalization of testosterone serum blood levels has been shown to improve bone deposition and lower fracture risk.

Age Related Cognitive Decline

Testosterone is associated with age related cognitive decline in the aging male. Testosterone levels have been associated with an increase in the brain amyloid load, a major Alzheimer's disease risk factor.[60] TRT has been shown to improve cognition in older men.[61]

Depression & Anxiety

The aging male has an increased risk of depression and anxiety, the most common psychiatric disorders. Hypogonadal men have an increased risk of depressive and anxiety disorders.[62] TRT has been shown to improve cognition in aging men with depression and anxiety.[63]

EVIDENCE FOR GENERATIONAL TESTOSTERONE DECLINE BY COUNTRY

Testosterone Decline in the US

It is generally understood that as U.S. men age, total testosterone levels decline at about 1% annually and free testosterone at about 2% annually.[64] Additionally, a thorough 2007 analysis of data from the Massachusetts Male Aging Study (MMAS) by Travison et al.[65] demonstrated that population-level declines are greater than the declines in testosterone typically associated with age. Evidence demonstrated that from the late 1980s through 2004 total and bio-available testosterone decreased an average of 1.2 and 1.3 percent, respectively, when comparing one age cohort to the next of the same age. For example, men 65-69 years of age, average total testosterone levels fell from 503 ng/dL (nanograms/deciliter) in 1988 to 423 ng/dL in 2003. This suggests that some factor *other than age* may be contributing to the declines in testosterone over

time. The key purpose of this article is to propose possible etiologies for this decline and supply potential medical solutions.

Testosterone Decline in the UK

A recent study[66] using data from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) concluded that there is an age-related decline in salivary testosterone levels in men and women, which cannot be explained by an increase in ill health. [67] The study perhaps offers some explanation to this trend, finding significant age-independent associations between lower salivary testosterone and higher BMI, poorer self-reported general health, mobility problems, longstanding illness, and co-morbid conditions such as cardiovascular disease and depression.

Testosterone Decline in Finland

There is evidence of a testosterone decline in Finnish men. The study concluded that the more recently born Finnish men have lower testosterone levels than their earlier born peers. As an example, serum testosterone levels decreased in men aged 60–69 years from 21.9 nmol/l [632 ng/dl] (men born 1913–1922) to 13.8 nmol/l [398 ng/dl] (men born 1942–1951).[68]

Testosterone Decline in Denmark

There is evidence showing lowering testosterone levels in Denmark. In this study, testosterone and SHBG were analyzed in 5350 male serum samples from four large Danish population surveys conducted in 1982-1983, 1986-1987, 1991-1992, and 1999-2001. They discovered that when appropriately age-matched, testosterone and SHBG serum levels were lower in the more recently born/studied men.[69]

Testosterone Levels in Men by Country

A 2010 study[70] showed differences in testosterone levels among different countries. They evaluated 5003 ambulatory, community-dwelling men at least 65 yr of age from Japan, Hong Kong, Sweden, Tobago, and the United States. Asians have the highest levels of testosterone, but interestingly, Asian Americans have similar, if not slightly lower levels of testosterone as compared to US Males. This could indicate that environmental factors, such as diet, exercise, and cultural norms, play a role in testosterone levels among men.

Testosterone & Sperm Levels in India

Males from India in the US have been shown to have lower testosterone levels seems to have a generalized lowering of testosterone and virility. One study demonstrated that “men from the Indian subcontinent are smaller, manifest lower levels of circulating free testosterone, lower mean PSA levels and lean body mass, but are comparable to white Caucasian men in terms of SHBG, estradiol, levels of visceral fat and CAG repeat

length. These data suggest that Indian men manifest a lower level of virilization compared to white Caucasian males and that this might be due to lower mean circulating testosterone levels rather than higher AR CAG repeat length or SHBG."[71] As far as sperm health in men residing in India, a recent report on the status of infertility found that nearly 50% of infertility is related to reproductive anomalies or disorders in the male.[72]

EVIDENCE FOR MALE SPERM DECLINE

Male Fertility Rates

The prevalence of couple infertility is very high and in many countries affects one in seven couples, with the most commonly identified cause being low sperm levels in males. Studies have shown that in young men 18–25 years of age infertility is as high as 15–20%.[73] [74]

The World Health Organization (WHO) defines infertility as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse." As per the WHO, the overall prevalence of primary infertility ranges between 3.9% and 16.8%.[75]

Specifically in men, sperm analysis for fertility is broken down into various parameters. The World Health Organization's 5th edition of normal semen analysis values are shown below. It is important to note that these are minimal values and many fertility specialists seek optimal levels higher than the WHO values. A mixture of normal, suboptimal, or frankly low measurements in any of these parameters can lead to the diagnosis of subfertility.

Semen Analysis Parameter	Normal Values
Volume	1.5 ml or more
pH	> or equal to 7.2
Sperm concentration	15,000,000/ml or more (Up to 300 million/ml)
Total motility	40% or more
Progressive motility	32% or more
Morphology	4% or more normal forms (Strict criteria)
Vitality	58% or more live

White blood cells	Less than 1,000,000/ml

It is important to note that most fertility experts believe that sperm count needs to be at least 40 million/mL to be fertile for men.[76] Therefore, the WHO sperm concentration parameters could be too low. It also brings attention to the observation that sperm counts have been lowering globally, leading the WHO to lower the minimal accepted sperm concentration from 20 million/mL in 1999 to 15 million/mL in 2010.

Sperm counts and quality do seem to be lowering. Sixty-one studies in the US found a 50% decline in sperm density between 1938 and 1990 determined in two meta-analyses [77] [78] demonstrating a gradual decrease in sperm quality since the 1970s, particularly of sperm count. A French study[79] in 2013, based on sperm samples from 26,609 healthy men, found a substantial decline in average sperm counts between 1989 and 2005, from 73.6 million to 49.9 million per millilitre.

The evidence that sperm counts and quality are lowering is copious and a full assessment of this data is beyond the scope of this paper. However, the topic of global lowering sperm counts is controversial. The conclusion in a short paper written in The Handbook of Andrology entitled “Is there a decline in sperm in men?” leaves us with an all too common conclusion in the scientific world, citing the inability to conclude anything. The authors summarize “…it seems impossible at present to scientifically conclude that there is or is not a worldwide secular decline in human sperm counts or male fertility. However, the regional differences in sperm counts have yet to be explained and deserve further investigation.”[80]

The Sperm Decline Controversy

Although several studies have suggested that there has been a decline in overall sperm quality, others found no significant decline in sperm quality over time.[81] [82] But the concern about lowering sperm all began in 1992 when Carlsen, et al. published a landmark meta-analysis of 61 studies finding a significant global decline in the average sperm concentration from 113 to 66 million/ml among men with no history of infertility, between 1938 and 1991.[83] The scientific debate quickly ensued. However, five years later, Swan et al. got involved and through their reanalysis of 56 studies, it was confirmed that a significant decline in sperm density was discovered in the United States and Europe.[84] In an extended meta-analysis of 101 studies, Swan et al. again confirmed a decline in sperm density from 1934 to 1996.[85] Finally, a recent study by Rolland et al. from France in 2013, also concluded a trend of lowering sperm in their population.[86]

Lowering Sperm in France

The findings from Rolland et al. in 2013 were extremely significant. The sample size was massive, with 154,712 men included in the study. The observation period was 17 years, from 1989 to 2005. They concluded that the sperm concentration for a 35-year-

old man went from an average of 73.6 million/ml [69.0-78.4] in 1989 to 49.9 million/ml [43.5-54.7] in 2005. This study is also significant because of its scope, in that “it is the first study concluding a severe and general decrease in sperm concentration and morphology at the scale of a whole country over a substantial period.”

Lowering Sperm in Italy

One Italian study of 1068 males from 1981 to 1995 from a semen bank found that the mean concentration of spermatozoa in semen has shrunk from 88 x 10(6)/ml in 1981 to 61 x 10(6)/ml in 1995, a reduction of 30.7%. Additionally, mean total motility diminished from 74 to 66%, and the mean percentage with typical morphology has fallen from 76 to 63%. The authors provided a proposed etiology, arguing that it could be due to the increased use of pollutants during the study period in urban and rural areas.[87]

Lowering Sperm in the UK

A study from 1996 in a group of over 500 Scottish men born between 1951 and 1973 found that when the four birth cohort groups were compared, a later year of birth was associated with a lower sperm concentration, a lower total number of sperm in the ejaculate, and a lower number of motile sperm in the ejaculate. The median sperm concentration fell from 98 million/ml among donors born before 1959 to 78 million/ml among donors born after 1970. The total number of sperm in the ejaculate fell from 301 million to 214 million, and the total number of motile sperm in the ejaculate fell from 169 million to 129 million.[88]

This was followed up by a 2007 study in Northern Scotland based on a population of 500,000 studying specifically 4832 men with sperm counts above 20 million/mL from 1994 to 2005. They concluded that in fact sperm density is lowering although motility was not affected.[89] These studies are by no means conclusive, but it continues to support the trend of lowering sperm. Something is occurring, and we should continue to be vigilant.

Sperm Quality in Spain & Testis Cancer Risk

Indeed, the idea that sperm levels are lowering globally is controversial and there are examples where this is not always the case. Spain is one such exception.[90] In a study of 273 men from the Almeria region in the Southern Spain both semen count and testosterone levels were optimal and unchanged over a time period from November 2001 to December 2002. Spanish men have a low risk for testis cancer in comparison to other European countries.[91] This results of this study is consistent with the testicular dysgenesis syndrome (TDS) concept that suggests a link between risk of impaired semen quality and increased risk of testicular cancer.

CAUSES FOR LOWERING TESTOSTERONE & SPERM

In Utero Influences on Male Testosterone Levels

2D:4D Ratio

A potential biomarker for understanding the influence of testosterone on both men and women is the 2D:4D length ratio. In men, the ratio tends to be lower than women. The 2D:4D ratio has been studied and purported to be correlated with the level of circulating prenatal testosterone, i.e. the more circulating maternal testosterone, the lower the 2D:4D ratio in the fetus, and the higher the levels of testosterone, sensitivity to testosterone, and response to behavioral correlates such as assertiveness, aggression, competitiveness, and fertility, among other things.[92] In cardiovascular disease, men with lower 2D:4D ratios, and therefore generally higher testosterone levels and higher affinity to the androgen receptor (AR), have a lower risk for cardiovascular disease than men with higher ratios.[93] A Chinese studying 2012 demonstrated that lower 2D:4D ratios are associated with higher fertility rates.[94] Manning and Barley reported in 2000[95] on 2D:4D ratios in men and women across nine populations from the highest mean ratio of approximately 1.0 to the lowest mean ratio of approximately 0.93. In order of highest to lowest ratio: Poland, Spain, England, Hungary, Hungary Gypsy, Germany, Indian, Zulu, Finland, Jamaica.

There is controversy with this measurement as a definitive of correlation to maternal exposure to testosterone and as a potential biomarker of the physiological influences of testosterone.[96] Additionally, there is controversy over whether 2D:4D ratio can estimate adult circulating sex hormone levels.[97] However, the work of John Manning, et. al. as far back as 1998 is considerable and his team has lead the research in this field. As recently as 2011, Manning and his group revised their working theory to include the influence of prenatal estrogen exposure.[98] They conclude that the there is a correlation with a low 2D:4D ratio as a biomarker for the *balance* between free testosterone (FT) and free estradiol (FE) signaling in a narrow time window of fetal digit development. High testosterone with low estrogen tends towards a lower 2D:4D ratio and low testosterone with high estrogen leads to a higher 2D:4D ratio. Their hypothesis and conclusions seem to be more elegant and global in perspective as they consider the results within the context of more than one endocrine parameter. They additionally clarified that the relative levels of prenatal FT and FE have “organizing effects” on the brain and other organ systems, which are not evident in the adult unless the subject is in a “challenging” situation, such as an aggressive, competitive, or sexual encounter.[99]

The 2D:4D ratio has been shown to be negatively related to testosterone levels and sperm counts and positively related to estrogen concentrations in both men and women.[100] The lower the 2D:4D ratio, the higher the testosterone levels, including the affinity to the androgen receptor, and the higher the sperm count in men. Conversely, the lower the 2D:4D ratio, the lower the estrogen levels. There is also evidence that the 2D:4D ratio will predict the genetic polymorphism CAGn, which correlates to androgen receptor sensitivity. The lower the 2D:4D ratio, the lower the CAGn, and the greater the affinity of androgens to the androgen receptor.[101] However, other reports have not found this consistent correlation.[102] [103]

The body of evidence is large enough to surmise that there is a relationship with sex hormones and 2D:4D, however controversial it remains. The clinical benefit to the 2D:4D ratio could be in helping to determine an estimate of the likely response to hormone replacement therapy. If the 2D:4D ratio implies AR sensitivity, this can help to guide the clinician along with the other subjective and objective parameters that are typically employed.

Endocrine Disruptor Chemicals (EDCs) in Utero

In industrialized countries, xenobiotic chemical exposure to EDCs is ubiquitous. It is not a matter of if an individual has bioaccumulated EDCs, it is more of a matter of amount and chemical type and how this is affecting the biology of the exposed.[104] Knowing the full biological effects of these chemicals is difficult, particularly in humans. In respect to the United States, of the 87,000 chemicals registered for commerce, only one-tenth have been tested for potential health effects.[105] And of those that have been tested, only a portion have been assessed for reproductive health effects. Although there are many studies that demonstrate the association of endocrine disruptor chemicals on sperm count, motility, and morphology in the developed male, to date there are only four papers[106] [107] [108] [109] explicitly studying xenobiotic prenatal exposure to potential endocrine disrupting compounds relative to semen quality in adult men. A recent meta analysis in 2016, through its exclusion criteria, found limited data to support a "substantial role in the development of male reproductive disorders through prenatal and perinatal mechanisms."[110] This of course does not mean that they concluded there is no evidence. And none the less, the relationship of EDCs and poor heath outcomes has mounting evidence in Europe, with a recent study concluding "that endocrine disrupting chemical exposures in the EU are likely to contribute substantially to disease and dysfunction across the life course with costs in the hundreds of billions of Euros per year."[111] Finally, the conclusions of The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals in December of 2015 clearly listed among the strongest translational evidence that of the negative effects of EDCs on male reproduction.[112]

Endocrine Disruptor Chemical (EDCs) Exposure in Males

EDCs affect multiple endocrine pathways but they particularly influence and disrupt the synthesis of sex steroids such has testosterone through steroidogenesis and overall reproduction since most effects are through the disturbance of estrogen or androgen-mediated processes.[113] [114] EDCs affect hormone receptors altering the synthesis, transport, and metabolism of endogenous hormones including testosterone.[115] [116] There is even mounting evidence that EDCs are affecting genetic systems [117] [118] and perhaps most alarming, the epigenetic consequences[119] that may lead to a "Pottenger's Cats" type of transgenerational inheritance of disease.[120] Studies[121] [122] are concluding that EDCs are at least in part to blame for the increasing incidence of human reproductive diseases and the decline in worldwide reproductive function.

An excellent online resource exists that helps to understand the critical embryological stages in the developing fetus and how chemical exposure influences health, with a specific focus on five major known EDCs including bisphenol A, dioxin, pthalates, chlorpyrifos, perflourinated compounds (PFCs).[123] Additionally, another online resource provides a detailed list of several EDCs and its negative affects to various endocrine systems including lowering and disrupting the function of androgens and testosterone.[124]

Most Common EDCs

Various substances are thought to cause endocrine disruption, including pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, plastics such as bisphenol A (BPA) and phthalates. These substances are collectively known as Endocrine Disruptor Chemicals (EDCs). EDCs are found in many everyday products including plastic bottles, the lining of metal food cans, food additives, household items such as flame retardant clothes and toys, detergents, personal cosmetics, and pesticides. EDCs interfere with the synthesis, secretion, transport, activity, or elimination of natural hormones. This interference can block or mimic hormone action, causing a wide range of effects.

EDC's and Testosterone

Exposure to EDCs starts early. We see that early phthalate exposure leads to lowering testosterone in boys. One study on phthalates observed a 24 percent to 34 percent drop in testosterone levels in boys ages 6 to 12.[125]

EDCs and Sperm

EDCs affect sperm at all levels of sperm development, leading to varying issues. Evidence points to the development of Reactive Oxygen Species as a potential mechanism for lowering sperm and affecting motility and morphology.[126]

Lifestyle Considerations

Results and analysis of the Massachusetts Male Aging Study has shown that lifestyle choices affect testosterone levels in men. Good health, defined as absence of chronic illness, prescription medication, obesity, or excessive drinking, added 10–15% to the level of several androgens.[127]

Alcohol Intake, Testosterone Levels, and Sperm Parameters

The idea that alcohol intake is related to lowered testosterone and poor sperm morphology is well known, but controversial. It seems that amount of alcohol is the most important in terms of total and free testosterone. Men who drink moderate amounts of alcohol have higher levels of testosterone and free testosterone compared to men who do not. However, consistent alcohol drinking and those considered alcoholics have low

testosterone. In respect to sperm count and morphology, Overall, most studies demonstrate a correlation with low testosterone, and poor sperm morphology, with review studies[128] and US and European population studies supporting this premise.

Marijuana Intake (Cannabinoids) Lowers Testosterone Levels

Several studies have shown that cannabinoids interfere with the testicular production of testosterone. High levels of THC cause the body to produce lower levels of testosterone.[129] [130]

Co-morbid disease relationships

As previously stated in this article, there are multiple associated diseases with testosterone deficiency. They present as both cause and effect to testosterone deficiency in the aging male. Again, these include cardiovascular disease, obesity, diabetes and metabolic syndrome,

One additional disease state not previously mentioned is thyroid function. The effects of thyroid hormone alterations on the reproductive system have been studied extensively in human and animal models that generally demonstrate that changes from normal thyroid function result in decreased sexual activity and fertility.[131]

Nutrition and Testosterone Levels in Men

Fat intake is crucial for the formation of testosterone and other androgens in men.

A recent cross-sectional study[132] among 209 healthy male volunteers conducted in the Murcia Region of Spain explored the relationship of fatty acid intake, testosterone levels and testicular volume. They found that high intakes of monounsaturated fatty acids, primary examples being plant-based oils such as olive or canola oil, was associated with lowered levels of calculated free testosterone, total testosterone, and inhibin B. Additionally, they found that a high intake of polyunsaturated fatty acids, particularly of omega-6 polyunsaturated fatty acids, also sourced primarily from plant-based oils, lowered luteinizing hormone (LH) concentrations. In addition, the intake of trans fatty acids was associated with lower total testosterone and calculated free testosterone concentrations. Trans fatty acid sources being primarily found in processed and packaged foods. Finally, higher intake of omega-3 polyunsaturated fatty acids related to higher testicular volume while the intake of omega-6 polyunsaturated fatty acids and *trans* fatty acids related to lower testicular volume. Omega-3 fatty acids are abundant in fatty fish such as mackerel and salmon and vegetarian sources such as chia and hemp seeds.

Sedentary Trends

Grip Strength is Lowering

With an increasing tendency towards a lack of physical education in schools, video game use, and obesity, we are seeing a trend towards a lack of physical prowess. Indeed, children are getting weaker. A recent study[133] showed that millennials showed that hand grip strength is lowering in comparison to data from the 1980s.

Obesity, Testosterone & Sperm

The unfortunate trend of obesity continues to increase in both the US and Europe. Testosterone levels are lower in obese men.[134] This creates a cycle of promoting obesity because testosterone influences metabolic rate and lipolysis.

Autoimmunity

Autoimmunity is responsible for a multitude of diseases. As laboratoryPreliminary info suggesting autoantibodies to gonadotrophs leading to lowered testosterone levels.[135]

Iatrogenic Pharmaceutical Causes

Several medications may contribute to the development of testosterone deficiency.

- 5α-reductase inhibitors for prostate enlargement.[136]
- Cancer treatments such as alkylating agents, decrease Leydig-cell function and spermatogenesis.[137]
- Oral glucocorticoids inhibit the HPG axis, lasting up to 12 months after cessation of therapy.[138]
- Anabolic steroids prior to TRT can negatively impact the HPG axis for up to two to three years and even permanently in some cases.[139] [140] (These effects, however, would be from extreme doses of not just testosterone, but the other more powerful anabolic agents, used chronically without cycling, and without proper Post Cycle Therapy which includes testicular enhancing and estrogen lowering medications such as clomiphene, anastrozole, and tamoxifen.)
- Opioid analgesics temporarily suppress the HPG axis.[141]
- β-blockers and statin medications induce mild to moderate reductions in serum testosterone levels.[142]

Social Influences and Cultural Norms

Men are having less sex

Sexual activity increases testosterone levels.[143] [144] And higher testosterone levels influence the desire to want to engage in more sexual activity.[145] [146] Testosterone also regulates sexual desire and enzymes crucial for the erectile process such as nitric oxide synthase (NOS) and phosphodiesterase type 5 (PDE5).

Men are having less sex, perhaps as both cause and result of lowering testosterone. A recent study published in the Archives of Sexual Behavior found that American adults

had sex about nine fewer times per year in the early 2010s compared to the late 1990s.[147] And they compared the generations and we see that men born in the 1930s had more sex than men born in the 1990s, or the so-called Millenial Generation. They offered up two possible reasons for the decline: One, there is an increasing number of individuals without a steady or marital partner and two, a decline in sexual frequency among those with partners. Men with higher testosterone levels seek out a relationship. If testosterone levels are indeed lowering, then this could offer a partial explanation for the decline in monogamist relationships. And of course, if testosterone levels are lowering, then generalized libido is lowered and sexual frequency will lower, even in a committed relationship. Despite all the declines, one age group showed no interest in slowing down: people over 70. They had sex nearly 11 times during 2014, up from an average of 9.6 times in 1989.

Undemanding Social Environments & Limited Self Reliance

In the US and in Europe, the conveniences of modern life is potentially influencing testosterone. Men are not tested and have little reason or need to rely on themselves and their own abilities. Social structures are constantly in place to take care of basic needs, and more. This cultural norm is becoming the consciousness of society.

SOCIAL AND BEHAVIORAL INTERACTIONS WITH TESTOSTERONE

Testosterone & The Permissive Effect of Hormones[148]

Hormones are permissive in their effects. They potentiate a given reaction and a given behavior. A prime example of this is testosterone levels and aggression. It is true that testosterone levels are higher in men. And men clearly are responsible for more aggression in comparison to women, by far. However, the levels of testosterone do not correlate to violence and aggression in a linear fashion, suggesting there are other things at play with aggression.

Male violent offenders do not necessarily have more testosterone than their male non-violent counterparts, on an individual to individual basis. Experimental biologists have demonstrated this idea. In a famous study, male baboons would be put into a small group of five and given ample time to work out a hierarchy of dominance. Once they had worked out top to bottom, one to five ranking, the number three baboon would be given supraphysiological levels of testosterone, several orders higher than normal. But despite far more testosterone, it would not lead the baboon to challenging number one and two for dominance at all. Nothing would change. However, that baboon would become more aggressive to number four and five, demonstrating the “permissive effect” of potentiating an already established social neuro-association.

Multiple studies show that initial testosterone levels measured in males placed in groups are not predictive of aggression. But higher testosterone levels may be a *result* of the aggressive behavior. Another study also demonstrates the idea that testosterone is permissive in its effect. If you measure aggression in a male and then castrate that

male, aggression will plummet to near zero. If you replace the testosterone to pre-castration levels, aggression will resume at the same intensity. However, if you only give 20% of pre-castration levels, the same amount of aggression will resume. Even if you give double the amount of testosterone of pre-castration levels, you will observe the same level of aggression.

This permissive effect of testosterone is relevant to this discussion for several reasons:

1. This is important for its clinical implications of using testosterone replacement therapy. It shows that giving testosterone with physiological levels as is done in medically supervised testosterone replacement therapy, the level of aggression that may result from the therapy, is going to be from potentiating what is already present in that individual and his social settings. This author has observed this phenomena multiple times clinically, in both men and women.
2. One key point of this article is to explore the behavioral aspects of testosterone and its resultant social and cultural implications. As we explore the effects of testosterone, or the lack thereof, whether positive or negative, they should be seen as comprehensive and systems-based versus as a singular, reductionistic reaction occurring within a biological vacuum.
3. The concept of the permissive effect of testosterone is supportive of the idea that we should view testosterone and its effects as a comprehensive grouping of "androgenicity" that considers multiple anthropomorphic and behavioral aspects of the male and how this relates to health.

Testosterone & Status Seeking Behavior

Testosterone seems to be related more to status seeking behavior than to aggression in and of itself.

One study[149] shows that the typical trait of male dominance behavior only occurs when testosterone is high and cortisol is low due to the blocking and inhibitory effects of cortisol. Saliva hormone levels from 57 subjects were taken before and after the respondents participated in a one-on-one competition and were given the opportunity to compete again after winning or losing. Of those who lost, 100 percent of the subjects with high testosterone and low cortisol requested a rematch to recapture their lost status. However, 100 percent of participants with high testosterone and high cortisol declined to compete again, implying that cortisol levels block and/or regulate the effects of testosterone.

Implicit Power Motivation & Testosterone

Implicit Power Motivation is defined as "a recurrent concern with and the ability to derive reward from having physical, mental, or emotional impact on other individuals or groups of individuals and to find the experience of others having impact on themselves to be aversive."[150] To further explain the details behind Implicit Power Motivation, an excerpt from a research article[151] by will be very helpful and enlightening:

> "As the definition of n Power denotes, power-motivated individuals are concerned with having impact over others, and they derive reward and reinforcement from having this impact. Power-motivated individuals are more likely to be successful in managerial positions and to have productive, vibrant careers. They tend to be perceived by others as competent and persuasive. However, they also tend to make autocratic business decisions without utilizing the opinions of coworkers of lower status. Power-motivated individuals take bigger risks in gambling situations to garner attention and are more likely to own ostentatious products. Later in life, they often become more generative. Power-motivated presidents are more likely to be considered "great" presidents and are also more likely to go to war with other nations. Power-motivated individuals are also more likely to be violent with their significant others, to abuse alcohol, to be politically radical, and to be sexually promiscuous."

This article also goes on to state, "While n-Power and testosterone are positively correlated, correlations are in the low positive range, which suggests that n Power and testosterone are not the exact psychological and biological equivalents of each other. *Individuals' n-Power is shaped by many factors including life experiences in asserting dominance, parenting styles, and heritability, in addition to biological factors like testosterone.*"

Testosterone & Lying, Antisocial Behavior, Egoism, and Aggression

Conventional wisdom, sometimes the opposite of reality, has associated men with lying and antisocial behavior with the resultant cause being that they possess high amounts of testosterone. This wisdom is being challenged. A study in 2010 published in Nature[152] showed that when women were given testosterone it increased their tendency towards "fair bargaining" which reduced bargaining conflicts and increased the efficiency of social interactions. Aside from this very telling result, a more intriguing result was found. *Subjects who believed they received testosterone behaved unfairly whether they received it or not.*

In a double-blind placebo controlled study[153] in 91 men administered physiologic exogenous testosterone or a placebo, then given the task to self-report in a simple task, in which their payoff depended on a self-reported outcome of a die-roll. The men could increase their payoff by lying without fear of being caught. Both groups lied, or embellished their results to achieve a higher payoff. But the men that received testosterone administration substantially decreased their lying.

Sociopolitical Associations with Testosterone

A recent study[154] from Brunel University London concluded that physically weaker men tend towards socialist concepts, such as redistribution of wealth versus stronger men tending towards capitalist concepts, such as the idea that people should keep what they earn. The study included 171 men aged 18 – 40, examining their overall physical strength, bicep circumference, weight, and height, with measurement of time each

subject spent at a gym, and directly examined their political tendency towards either capitalist or socialist ideologies. They found that the more physically strong the men were, the less they believed in socialist policies, and the more they believed certain social groups should be dominant, *whether they are financially rich or poor*.

Brunel University's senior lecturer in Psychology in the College of Health and Life Sciences Michael Price has said in regards to the study results, "It could be the result of men calibrating their egalitarianism to their own formidability. It could be the case that less egalitarian men strive harder to become muscular. Or there could be a third variable at play affecting both egalitarianism and muscularity."

Another study from 2013 entitled *The Ancestral Logic of Politics: Upper-Body Strength Regulates Men's Assertion of Self-Interest Over Economic Redistribution* further supports the idea that muscular strength is associated with a more egalitarian worldview.[155] With an even larger sample size, including both men and women, in three different countries [Argentina (113 males, 110 females; mean age = 21 years, SD = 3.03), the United States (211 males, 275 females; mean age = 19 years, SD = 3.35), and Denmark (421 males, 372 females; mean age = 48 years, SD = 13.91)], the study concluded that "men with greater upper-body strength more strongly endorsed the self-beneficial position: Among men of lower socioeconomic status (SES), strength predicted increased support for redistribution; among men of higher SES, strength predicted increased opposition to redistribution."

These studies are important as they are also a direct result of the influence of testosterone and ancient evolutionary programing on how cultural and social norms are created and persist. It is clearly understood that upper body strength and time spent exercising is associated with overall higher testosterone levels and superior androgenicity. If testosterone levels in men are indeed lowering globally, as this paper posits, then this has a direct and indirect affect on how men navigate the political and social landscape, creating policies and worldviews that affect us all. Depending on your evolved political and social perspectives, this may be good or bad. Either way, male testosterone physiology is part of the influence.

Social Assertiveness and Testosterone Levels

The opposite of love is not hate, it is indifference, and vice versa. The opposite of aggression is not passivity, it is assertiveness. It is important to distinguish the difference between assertiveness and aggression, as our society often has difficulty in telling them apart. To be assertive is to be self-confident and self-assured. Testosterone is in part responsible for potentiating a sense of self-worth, ability, and self-reliance. This may be evident in how men direct their physiology of testosterone through how they move their body through specific intention.

One particular study measured this effect. The study design model showed that holding a power pose that consists of an open armed posture for two, 1-minute sessions leads to a 13% increase in Testosterone and a simultaneous ~20% drop in Cortisol. The

psychological effects of this pose have been shown to increase social dominance and leadership traits.[156]

UNIT 2: TESTOSTERONE AND ANDROGENICITY ENHANCEMENT

THERAPEUTIC GOAL OF ANDROGENICITY

A Global Clinical Definition of Androgenicity

Typically, the word androgenic implies “any substance that controls the development and maintenance of masculine characteristics.” This definition is limited for at least two reasons: One, it leaves out the accepted definitions of “masculine characteristics”, and two, it limits the functions of testosterone to only men, where we know that women have similar effects from testosterone as men.

When physicians asses male hypogonadism or Late Onset Hypogonadism, clinical determinations are largely based around the testosterone levels. Subjective symptoms of the patient is considered but there is still a large focus on serum (or saliva) total and free testosterone levels, with attempts towards properly assessing minimal cut off ranges. This singular and reductionistic approach is limited clinically and potentially misses other neuroendocrine relationships to testosterone and the concept of androgenicity.

This author proposes the term “Androgenic” as referring to “The complex physiological state of induction by testosterone and any other hormone, of all anatomical, physiological, psychological, social, and cultural implications of testosterone.”

The clinical assessment and determination of androgenicity has several proposed physiological impact measurements of testosterone. These should be considered in both diagnosis and monitoring of therapy. These include:

- Total Testosterone levels
- Free T Levels
- Estradiol levels
- Total estrogen levels
- E2:TT ratio <3%
- Total Testosterone:Cortisol Ratio 80:1 to 100:1, no more than a 10 to 30% change from baseline 24 to 48 hours post intense exercise, to determine recovery (mental health, exercise/performance recovery)
- DHEA:Cortisol Ratio: 5:1 to 6:1
- Androgen Receptor Considerations
- The androgen ratio and genital ratio as proposed by Endobiogeny
- Erectile Function Scale
- Grip strength
- Bone density

- Muscle mass
- Body fat percentage
- Psychological Assessment
- QoL (Quality of Life) Assessment

Considering Androgen Receptor Sensitivity

Clinically, Androgen Receptor sensitivity should be considered where possible. It is used clinically currently, but not is the context of testosterone replacement therapy or within the context of the proposed definition of androgenicity provided in this article. The opinion of this author is that the androgen receptor sensitivity and number will be considered more in the future for testosterone assessment and treatment, particularly when practical laboratory assessments become more accessible and popular. Some detail will now be given to this topic.

The Androgen Receptor (AR), is located within the nucleus on the X chromosome at q11-q12.[157] Exon 1 of the AR gene contains a polymorphic nucleotide sequence of CAG (Cytosine, Adenine, Guanine) repeat, which usually varies in number from 10 to 35.[158] The AR is expressed in a diverse range of tissues leading to androgens having significant biological actions in bone, muscle, prostate, adipose tissue and the reproductive, cardiovascular, immune, neural and haemopoietic systems.[159] The general mechanism is for either testosterone or its more potent androgenic metabolite dihydrotestosterone (DHT) to bind to the AR at the DNA level, resulting in nuclear transcription and gene expression.[160] Evidence suggests that CAG number is inversely correlated to the transcriptional activity of the AR.[161] A CAG sequence repeat less than 22 is considered low and tends towards a higher affinity of the AR to its ligand testosterone or DHT.[162] Above 22 is considered high and repeats above 40 are associated with Kennedy Syndrome with decreased virilization, testicular atrophy, reduced sperm production, and infertility.[163]

The CAG repeat is associated with various disease states. CAGn (n= number) is inversely associated with prostate cancer risk,[164] and benign prostatic hyperplasia with CAG sequences less than 19.[165] Androgen insensitivity, whether from endocrine disruption[166] or from a low CAGn, has also been suggested as a risk factor for testicular cancer, although this remains very controversial at this stage.[167]

The clinical relevance of the CAG repeat with men undergoing Testosterone Replacement Therapy (TRT) is significant and promising and in one particularly study of hypogonadal men has shown to be predictable to clinical outcomes.[168] However, another study in younger eugonadal men who were chemically induced into hypogonadism demonstrated little to no association with an androgenic response and the CAG repeat.[169] The issue with this later study could be that they used younger healthy men and only induced the hypogonadism chemically. The shorter length of the AR gene CAG repeat is associated with an improved metabolic effect of TRT, including improved levels of BMI, fasting glucose, systolic blood pressure, and percentage of hypertension.[170] [171] The clinical relevance of using the AR CAG polymorphism supports

the premise of focusing on androgenicity of the patient versus solely on testosterone levels.

The therapeutic goal during any clinical intervention including testosterone replacement or natural testosterone enhancement should be to consider the influence of the AR. The cellular density of the AR and the sensitivity of AR play an integral role for the ultimate therapeutic goal of becoming androgenic. If testosterone levels are adequate, but the AR is either limited and/or insensitive, then the physiological effects of testosterone will be limited. Additionally, if the AR is influenced to be both more dense and sensitive, even lower testosterone serum levels will have more of a physiological effect.

It is an extremely exciting and promising area of research and potential clinical significance in the arena of ligand-independent actions of the AR. We typically assume that the AR needs testosterone or DHT (i.e. ligand-dependent) to bind to the receptor to initiate action. This is not necessarily the case. Ligand-*independent* activation of the AR by a number of different growth factors has been demonstrated, mostly with prostate cancer models, via phosphorylation of the AR or following interaction with co-activators.[172] This research is still very new, but its implications potentially supports the idea of androgenicity explained in this article. Testosterone alone is not enough to consider clinically when assessing the effectiveness of the goal of androgenicity in the male.

FUNCTIONAL MEDICAL APPROACHES TO TESTOSTERONE ENHANCEMENT & ANDROGENIC OPTIMIZATION

LIFESTYLE MODIFICATIONS

Diet Considerations for Enhanced Testosterone & Sperm: A Position for Saturated Fats vs Veganism

Testosterone is enhanced with increased dietary saturated and polyunsaturated fats.[173] [174] [175] including dietary supplementation of omega 3 fatty acids.[176] Sperm count and quality is also enhanced by increased dietary saturated and polyunsaturated fat consumption.[177] [178] [179]

We are seeing an increasing trend towards vegetarianism, a practice that not only tends to limit protein consumption and saturated fats, but also tends towards high amounts of unfermented soy products, something that is capable of lowering testosterone and negatively affecting sperm.

A survey by Vegan Life Magazine and the Vegan Society[180] found among almost 10,000 people across England, Scotland, and Wales, that at least 542,000 people in Britain are following a veganism, an increase of 350 percent over the last decade. Interestingly, 42% of those vegetarians were aged 15 to 34.

A vegetarian diet increases Sex Hormone Binding Globulin, thereby lowering bioavailable free testosterone.[181] [182]

Dietary protein is important, but in fact, evidence suggests that a very high protein diet with low carbohydrates will lower testosterone.[183]

However, the protein source perhaps is more important, with one study showing that testosterone levels increased when dietary protein sourced from meat was replaced with dietary soy protein.[184]

The review of this above evidence suggests that the traditional ancestral diet recommended by the observational research of Weston A. Price, would tend to fit the dietary requirements for optimal testosterone and sperm production.

The Ancestral Diet

The prominent dentist Weston A. Price known for his theories on the relationship between nutrition, dental health, and physical health. In 1939, he published his seminal volume *Nutrition and Physical Degeneration*, detailing his intercontinental travels studying the diets and nutrition of various cultures comparing them to the ills of a typical Western diet.

The dietary guidelines proposed by Price and extolled by Sally Fallon and Mary Enig on the Weston A Price Foundation website:[185]

- Eat whole, unprocessed foods.
- Eat beef, lamb, game, organ meats, poultry and eggs from pasture-fed animals.
- Eat wild fish (not farm-raised), fish eggs and shellfish from unpolluted waters.
- Eat full-fat milk products from pasture-fed cows, preferably raw and/or fermented, such as raw milk, whole yogurt, kefir, cultured butter, full-fat raw cheeses and fresh and sour cream.
- Use animal fats, such as lard, tallow, egg yolks, cream and butter liberally.
- Use only traditional vegetable oils—extra virgin olive oil, expeller-expressed sesame oil, small amounts of expeller-expressed flax oil, and the tropical oils—coconut oil, palm oil and palm kernel oil.
- Take cod liver oil regularly to provide at least 10,000 IU vitamin A and 1,000 IU vitamin D per day.
- Eat fresh fruits and vegetables, preferably organic. Use vegetables in salads and soups, or lightly steamed with butter.
- Use whole grains, legumes and nuts that have been prepared by soaking, sprouting or sour leavening to neutralize phytic acid, enzyme inhibitors and other anti-nutrients.
- Include enzyme-rich lacto-fermented vegetables, fruits, beverages and condiments in your diet on a regular basis.
- Prepare homemade stocks from the bones of pastured chicken, beef and lamb fed non-GMO feed, and wild fish, and use liberally in soups, stews, gravies and sauces.
- Use filtered water for cooking and drinking.

- Use unrefined salt and a variety of herbs and spices for food interest and appetite stimulation.
- Make your own salad dressing using raw vinegar, extra virgin olive oil and a small amount of expeller-expressed flax oil.
- Use traditional sweeteners in moderation, such as raw honey, maple syrup, maple sugar, date sugar, dehydrated cane sugar juice (sold as Rapadura) and stevia powder.
- Use only unpasteurized wine or beer in strict moderation with meals.
- Cook only in stainless steel, cast iron, glass or good quality enamel.
- Use only natural, food-based supplements.
- Get plenty of sleep, exercise and natural light.
- Think positive thoughts and practice forgiveness.

The Ancestral Diet and its focus on optimal fat intake is in line with the nutritional research on testosterone optimization.

High Intensity Exercise

According to the Bureau of Labor Statistics[186], the most popular types of exercises in the US are cardiovascular and low intensity types of exercise. Weight lifting was relatively popular, but is performed by only 8.9% of the population 15 years and older. Cardiovascular exercise will increase testosterone levels, but this has been found in overweight subjects who lose weight during the testing.[187] It seems that excessive cardiovascular exercise (sustained steady state exercise) over several years lowers testosterone levels[188] [189] [190] and libido in men.[191] Comparisons have been made between high intensity exercise versus sustained stead state exercise with the former clearly having considerable advantages in creating a more anabolic state including higher total and free testosterone levels.[192]

High intensity exercise with heavy weight loads using compound multi-joint movements stimulates post-exercise testosterone production.[193] [194] The general exercise prescription to achieve this post-exercise testosterone increase is two to three multi-joint exercises such as back squats, deadlifts, or power cleans, or many others, completing 6 sets of 6-8 repetitions, with rest periods of 60 to 90 seconds between straight sets, finishing the entire workout within 20 to 30 minutes.

Sexual Practices

Having More Sex

Sexual arousal is enhanced through the act of sex. In other words, having sex makes you want to have sex. Sexual activity also increases testosterone.

Ejaculation Frequency & Abstinence [195] [196]

In the orgasm response, testosterone acts to stimulate the androgen-dependent neural circuitry by enhancing the ability of the neural circuitry to work. Testosterone is not the direct stimulant for orgasm. It holds the door open, allowing other hormonal and neural processes to take place. This is demonstrated in complete orchiectomy. Since antiquity, some Roman eunuchs would retain the ability to achieve erection and have intercourse, providing valuable services to Roman women.[197]

Orgasm is facilitated by dopamine, the main neurotransmitter involved in orgasm. Conversely, serotonin is the main inhibitor of orgasm. When orgasm takes place, dopamine is significantly elevated, along with prolactin and serotonin, both inhibitors of orgasm. Dopamine is making it feel good, but prolactin and serotonin act as mediators to lower the response, otherwise orgasm and the dopamine response would become potentially addictive.

The neurochemical processes that occur post-orgasm are vast. Brain androgen receptors decrease, and serotonin and opioids increase. This neurochemical inhibition lasts for up to two weeks post ejaculation, leaving many feeling depressed and ironically potentially distant from their partner. However, oxytocin is also elevated post ejaculation, which helps to enhance pair-bonding and modulates the inhibition of dopamine.

We know that abstinence from ejaculation can help to increase testosterone levels.[198] [199] And increasing sex and the anticipation of sex also increases testosterone. Therefore, a good strategy to increase testosterone and improve the overall sexual experience is to increase the frequency of intercourse and/or masturbation, but abstain from ejaculation. Since oxytocin appears to be the antidote to post-orgasm neurotransmitter inhibition, one effective strategy towards testosterone optimization and health would be to engage in more affectionate, non-goal-driven (i.e. ejaculation) lovemaking.

Meditation

Meditation increases testosterone levels and lowers cortisol. Incorporating meditation into a daily regimen is very easy for

Improving the T:C Ratio

Testosterone functions more optimally when it operates within a milieu of balance with other neuroendocrine stimuli. These neuroendocrine stimuli either enhance or inhibit the effects of testosterone. Cortisol is a known inhibitor of testosterone function at the Androgen Receptor and also inhibits testicular production of testosterone.

It is proposed that the ratio of testosterone to cortisol (T:E) is related to exercise recovery. Hypercortisolemia is associated with catabolic states which decreases the ability for the body to recover from intense exercise.

Independent of the focus on exercise recovery, utilizing the T:E clinically may help to guide the functionally-minded clinician toward optimal outcomes for hypogonadal patients.

Botanical Medicine

Various botanical medicines have been shown to increase both total and free testosterone levels as well as possess aphrodisiac effects including enhanced sexual desire and erectile function enhancement. Some of the more common ones are Tribulus terrestris, Withania somnifera, Eurycoma longifolia, Avena sativa, Ginko biloba, Lepidium meyinii, and Psoralea coryifolia. Due to the scope of this article, two of the most common and most effective, in the experience of this author, will be focused on: Tribulus terrestris and Eurycoma longifolia.

TRIBULUS TERRESTRIS

Tribulus terrestris is an annual herb belonging to the Zygophyllaceae family. It is most often used for infertility and loss of sexual desire. The main active phytoconstituents of this plant include flavonoids, alkaloids, saponins, lignin, amides, and glycosides. The plant parts have different pharmacological activities including aphrodisiac, antiinflammatory, antimicrobial and antioxidant potential. It has potential application as immunomodulatory, hepatoprotective, hypolipidemic, anthelmintic and anticarcinogenic activities.[200] [201]

Testosterone Enhancing Effects of Tribulus Terrestris:

The limits of Tribulus terrestris is that it is a botanical that largely acts as an aphrodisiac. An aphrodisiac includes effects that increase libido or psychological arousal, increase in the effectiveness of erection, and increase in sexual sensation and resultant pleasure. A review article in 2014 did not find Tribulus terrestis to increase total testosterone levels in humans by itself, but rather in combination, supporting the synergistic effect and approach to botanical medicine applications. However, it was suggested that positive aphrodisiac effects from Tribulus terrestris could be from enhanced effects on nitric oxide and therefore vasodilation of the penis.[202] A more recent review article in 2016 from the Journal of Ethnopharmacology, and far more extensive in scope, concluded “Analysis of phytochemical and pharmacological studies in humans and animals revealed an important role for TT in treating erectile dysfunction and sexual desire problems; however, empirical evidence to support the hypothesis that this desirable effects are due to androgen enhancing properties of TT is, at best, inconclusive, and analysis of empirical evidence from a comprehensive review of available literature proved this hypothesis wrong.”[203] This suggests that Tribulus terrestris does not enhance the levels of testosterone but has the ability to enhance aspects of androgenicity, such as its aphrodisiac properties. However, there is some evidence that it is increasing total testosterone and free testosterone levels.

In a small study of 30 men presenting to an outpatient clinic that used a larger dose of 250 mg three times a day did show a statistically significant difference in the level of testosterone (total and free) and improvement in erectile dysfunction.[204] Animal models have shown some limited effect on increasing testosterone levels.[205] [206] Tribulus Terrestris has also been shown to increase the Androgen Receptor density in rat models in the muscle and liver[207] and in brain tissue leading to increased sexual behavior and intracavernous penile pressure.[208] In an controlled trial in post menopausal women, Tribulus terrestris did show an increase in sexual response and total and free testosterone.[209] In another study[210] using 250 mg of TT once daily in women did not find an increase in total and free testosterone. In fact they both lowered, but there was an increase in DHEA levels and improvement in sexual desire.

Sperm Enhancing Effects of Tribulus Terrestis:

Where Tribulus seems to potentially lack in actual testosterone level enhancement, it does have stronger evidence towards enhancing sperm morphology and motility. Human semen in vitro studies[211] and animal model studies[212] [213] have demonstrated positive results in sperm quality.

A study[214] using Androsten® (250 mg of Tribulus terrestris dried extract per capsule) in sixty-five men with abnormal semen evaluation, demonstrated significant enhancement in sperm concentration, motility and liquefaction time. Protodioscin, the main phytochemical agent of the Tribulus genus, acts on sertoli cells, germ cell proliferation and growth of seminiferous tubules.

Evidence suggests that TT may have antioxidant effects to Reactive Oxygen Species (ROS) that help with sperm viability, even after cryopreservation.[215] We do know that sperm quality is enhanced with antioxidant therapy such as glutathione administered parenterally (600 mg daily IM).[216] [217]

EURYCOMA LONGIFOLIA

Eurycoma longifolia, also known as Tongkat Ali in Malaysia and Pasak Bumi in Indonesia is a shrub tree that grows up to 10 meters in height and has long green pinnate leaves. The active ingredients are called quassinoids and are found in the root. Eurycoma longifolia is in high demanded and various preparations are currently available in the form of raw crude powder where the root is dried and ground. Typically, and most preferred, it is prepared as an extract directly from the root. Eurycoma longifolia has been shown to possess anticancer,[218] antibacterial,[219] cytotoxic,[220] aphrodisiac,[221] and antimalarial effects.[222]

Several recent review studies have demonstrated a positive effect of Eurycoma longifolia on male sexual health.[223] [224] [225] [226]

Eurycoma longifolia has adaptogenic effects, tempering the effects of stress and the resultant psychological responses of tension, anger, and confusion.[227] There is also evidence of androgenic and anabolic effects to bone tissue in orchodectimized rats.[228]

Testosterone Enhancing Effects of Eurycoma longifolia

There is evidence for Eurycoma longifolia increasing free testosterone levels by lowering Sex Hormone Binding Globulin (SHBG).[229] [230]

Estrogen in excess levels can act as a negative feedback loop for testosterone production and spermatogenesis at the testicular level. One elegant rat model study demonstrated that Eurycoma longifolia was able to reverse the negative effects of estrogen treated rats and improve spermatogenesis.[231]

There is also strong evidence that Euycoma longifolia does increase testosterone levels. Rat models have shown an increase in testosterone.[232] [233] One human study[234] of 76 patients suffering from late-onset hypogonadism (LOH) were given 200 mg of a standardized water-soluble extract of Eurycoma longifolia for one month. Before treatment 35.5% of the chosen patients had symptoms consistent with LOH, but had normal testosterone levels. After treatment 90.8% of the patients showed normal values.

Sperm Enhancing Effects of Eurycoma longifolia

Rat models show an increase in sperm count and morphology.[235]

Light Therapy

Light therapy is a very intriguing prospect for testosterone production and sexual enhancement. As people tend to work indoors more, we are exposed to light less.

Low level laser (LLL) at a wavelength of 670 nm seems to have some effect on increasing testosterone levels.[236] Studies suggest that low doses of laser light have a positive effect on spermatogenesis[237] and motility.[238] with the proposed mechanism of action being on increasing mitochondrial ATP production due to the hypothesis that poor sperm motility is due to mitochondrial dysfunction.[239]Indeed, if light therapy is stimulating mitochondrial function, this would include Leydig cell stimulation, leading to enhanced testosterone production. In a human trial, low level infrared laser improved both testosterone and sperm parameters in approximately 50% of 188 men studied.[240]

Therapeutically and clinically speaking, red or infrared light from an LED source (600-950nm) can be safely applied to the testes achieving benefit of increased testosterone and enhanced sperm. If sunlight is used on the testes, it should be done for short periods of time, less than 15 minutes, with the obvious precaution of avoiding sunburn. Additionally, testicular function is optimal at less than body temperature, approximately 95 degrees F. This is why Infrared and Low Level Laser are optimal due to the limited heat projection.[241]

Hydrotherapy

Hydrotherapy is the very foundation of naturopathic medicine and a therapy that is as old as humanity itself. Its systemic effects affect numerous biological systems proven with consistent scientific evidence.[242]

In respect to the male gonads, there is evidence that heat exposure to the testicles lowers sperm production and lowers testosterone levels.[243] When the testicles are kept colder than body temperature they function more optimally. We have seen evidence that sperm quality and Luetinizing Hormone and Follicle Stimulating Hormone are all enhanced during the colder winter months.[244]

Regularly using cold showers can help to lower testicular temperature and enhance sperm.

EXOGENOUS TESTOSTERONE REPLACEMENT THERAPY

Introduction to Testosterone Replacement Therapy

Review article research supports the benefits of testosterone replacement therapy (TRT).[245] Specifically, there are scientifically established benefits of TRT summarized from a recent review article,[246] supported by the literature, listed below.

<u>Established Benefits of Testosterone Replacement Therapy:</u>

- Improved Sexual Desire and Erectile Function
- Improved Energy, Mood and Vitality
- Increased Lean Body Mass
- Reduced Waist Circumference
- Reduced Total Body Fat Mass
- Increased Bone Mineral Density
- Increased Insulin Sensitivity
- Reduced Blood Glucose and HbA1C

Testosterone Replacement Therapy & Cardiovascular Risk

The recent concern over TRT and increasing the risk for cardiovascular disease including myocardial infarction and stroke has been incorrectly inflated.

In fact, we see that TRT is beneficial to cardiovascular disease outcomes and lowering the associated risk factors for CVD. TRT has been associated with improved lipid profiles with reductions in total and LDL cholesterol.[247] [248] Trials using TRT have demonstrated excellent reductions in systolic and diastolic blood pressure over periods from 6 months up to 10 years.[249] [250] The notion that testosterone replacement, administered to achieve optimal physiologic levels, causes cardiovascular disease, is

counterintuitive at the very least, with ample evidence to the contrary. Additionally, it is understood that TRT directly treats the conditions of diabetes, metabolic syndrome and obesity, all known risk factors associated with CVD.

Testosterone Replacement Therapy & Prostate Cancer Risk

Another controversy, that thankfully is not as controversial as it once was, is the fear that testosterone increases the risk for prostate cancer.[251] Old dogma dies hard, but it eventually dies. As far back as the 1940's, it has been taught that testosterone increases the risk for prostate cancer. Aside from the counterintuitive notion that the incidence of prostate cancer is virtually nonexistent in very young men with ample testosterone, there is no direct evidence that testosterone has carcinogenic effects on healthy prostatic tissue. And due to the astute and detailed work of Dr. Abraham Morganthaler, the controversy has largely been put to bed.[252]

Testosterone Replacement Therapy Options

Creams, Gels, Oral

A common route of delivery for TRT is a transdermal route such as a cream or gel. The advantage of this is its ability to avoid first-pass liver metabolism and affect the androgen receptor immediately. However, a transdermal delivery can be extremely variant in its hormone delivery, providing variant results for the patient.

Oral routes consist of both typical gastrointestinal absorption and the more novel sublingual delivery. GI routes do not pass through the hydrochloric acid state of the stomach without being chemically linked to a transport such as methyltestosterone or testosterone undeconate. Methyltestosterone has issues with liver toxicity and makes it an unfavorable route. Sublingual testosterone has rapid absorption but also has rapid clearance, creating a large peak and trough effect within a few hours, making this route inconsistent and highly variable.

Testosterone Ester Injections: Intramuscular vs Subcutaneous Injections

Testosterone can be esterified and placed in a suspension oil. It is then injected most typically intramuscularly. Testosterone esters include the typically prescribed, at least in the US, testosterone cypionate. Other esters include testosterone proprionate and enanthate. In the UK, the typically prescribed testosterone ester is Sustanon, a combination of several esters. The half-life on each ester is variable, but in general, it is only about 3-5 days. The generalized reports that they have a 30 day half-life is simply clinically incorrect. Serum levels will never stay consistent and optimized with an injection frequency of 4 weeks, which is often administered by physicians in this fashion.

At the very least, a testosterone esters should be injected intramuscularly once weekly. This is the clinical minimum observed by this author. But even with this frequency, there is still a substantial peak and trough of levels throughout the week.

One strategy to maintain optimal hormone levels in a more consistent fashion is to inject twice weekly in divided doses. This keeps the levels more consistent but increases the risk for scar tissue build-up at the injection sites.

Another strategy would be to inject testosterone esters twice weekly, but do so subcutaneously. This strategy still allows for the consistency created by frequent dosing, but avoids the potential of scar tissue build up. Additionally, the subcutaneous fat acts as a depot for the testosterone and promotes a slower and steadier distribution of the testosterone.

Bioidentical Subcutaneous Pellet Implants

One of the most profound ways to create consistent hormone levels with consistent clinical outcomes is to use subcutaneous pellet implants. This therapy has been used since 1937 and in the US at the University of Georgia Medical School since 1939. Hormone pellets are placed subcutaneously in a simple minor surgery procedure, and through a slow and steady dissolution rate, the hormone is delivered constantly. When appropriate, this is one of the most effective ways to deliver hormone, keeping the levels consistent for up to six months. The other advantage of pellets is they are nothing but crystalline testosterone and their chemical structure has not been altered in any way.

Testosterone Ranges: A Functional Therapeutic Target

Testosterone range often comes into question for the physician utilizing testosterone replacement therapy. The functionally minded physician typically desires to optimize the patient versus simply keeping them in a designated population-based normal laboratory range. A recent study was published establishing a new normal range in a healthy non-obese population of European and American men, 19 to 39 years, of 264 to 916 ng/dL.[253] This range is similar to population ranges provided by most available laboratories. Functional medicine seeks, in many cases, to achieve optimal function by targeting the upper half (or lower half, depending) of a given range. This author uses a therapeutic functional total testosterone range of 600 to 1100 ng/dl. This is also a proposed therapeutic testosterone range by others who practice Functional Medicine.[254]

Therapeutically Influencing the Androgen Receptor

An often overlooked therapeutic target for clinicians focusing on TRT is Androgen Receptor (AR) sensitivity and number. However, it is considered in Prostate Cancer management because L-Dopa decarboxylase (DDC), a catecholamine synthesis enzyme and androgen receptor AR co-regulator protein, was identified as a neuroendocrine marker of prostate cancer.

Many patients do not benefit from TRT, despite optimal serum levels. The reason for this lack of effect be can be multifactorial. One possible reason is the insensitivity of

testosterone to the AR and lack of actual density of the AR. If the goal of therapy is to be optimization and androgenicity, it is logical to consider the influence of the AR in clinical outcomes.

Some Factors Influencing the AR:

Resistance exercise increases the AR [255] [256]
Short term fasting increases AR expression [257]
L-Carnitine L-Tartrate supplementation [258] [259]
Abstinence from ejaculation [260] [261]

Of these, resistance exercise is the most well documented and one of the easiest lifestyles to incorporate.

This author believes the therapeutic focus on the AR will be an important aspect of TRT and clinicians and researchers should continue to consider this in order to enhance the current body of work.

[1] Nettleship JE, Jones RD, Channer KS, Jones TH. Testosterone and coronary artery disease. Front Horm Res.2009;37:91-107. doi: 10.1159/000176047. Review. PubMed PMID: 19011291.

[2] Campion JM, Maricic MJ. Osteoporosis in men. Am Fam Physician. 2003;67:1521–6.

[3] Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004;62:188–93.

[4] Barrett-Connor E. Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. Ann Intern Med. 1992;117:807–11.

[5] Celec P, Ostatníková D, Hodosy J. On the effects of testosterone on brain behavioral functions. *Frontiers in Neuroscience*. 2015;9:12. doi:10.3389/fnins.2015.00012.

[6] Eisenegger C, Haushofer J, Fehr E. The role of testosterone in social interaction. Trends Cogn Sci 2011;15:263–71.

[7] Travison TG, Araujo AB, O'Donnell AB, et al. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab. 2007;92:196-202.

[8] Andersson A, Jensen T, Juul A, Petersen J, Jorgensen T, et al. (2007) Secular decline in male testosterone and sex hormone binding globulin serum levels in Danish population surveys. J Clin Endoc & Metab 92: 4696–4705

[9] Perheentupa A, Mäkinen J, Laatikainen T, Vierula M, Skakkebaek NE, Andersson AM, Toppari J. A cohort effect on serum testosterone levels in Finnish men. Eur J Endocrinol. 2013 Jan 17;168(2):227-33. doi: 10.1530/EJE-12-0288. Print 2013 Feb. PubMed PMID: 23161753.

[10] Bhasin S (2007) Secular decline in male reproductive function: Is manliness threatened? J Clin Endocrin & Metab 92: 44–45. doi: 10.1210/jc.2006-2438

[11] Travison, TG, AB Araujo, AB O'Donnell, V Kupelian, JB McKinlay. 2007. A population-level decline in serum testosterone levels in American men. Journal of Clinical Endocrinology and Metabolism 92:196–202.

[12] Swan, SH, EP Elkin and L Fenster. 2000. The Question of Declining Sperm Density Revisited: An Analysis of 101 Studies Published 1934-1996. Environmental Health Perspectives 108:961-966.

[13] Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ. 1992 Sep 12;305(6854):609-13. Review. PubMed PMID: 1393072

[14] Rolland M, Le Moal J, Wagner V, Royère D, De Mouzon J. Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in France. Hum Reprod. 2013 Feb;28(2):462-70. doi: 10.1093/humrep/des415. Epub 2012 Dec 4. PubMed PMID: 23213178

[15] Fain E, Weatherford C. Comparative study of millennials' (age 20-34 years) grip and lateral pinch with the norms. J Hand Ther. 2016 Jan 11. PubMed PMID: 26869476.

[16] Camacho E, Huhtaniemi I, O'Neil T, Finn J, Pye S, et al. (2013) Age-associated changes in hypothalamic–pituitary–testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur J Endocrinol 168: 445–455. doi: 10.1530/eje-12-0890

[17] Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. The global burden of mental disorders: An update from the WHO World Mental Health (WMH) Surveys. *Epidemiologia e psichiatria sociale*. 2009;18(1):23-33.

[18] Ellison P, Bribiescas R, Bentley G, Campbell B, Lipson S, et al. (2002) Population variation in age-related decline in male salivary testosterone. Human Reproduction 17: 3251–3253. doi: 10.1093/humrep/17.12.3251

[19] Campbell B, Leslie P, Campbell K (2006) Age-related changes in testosterone and SHBG among Turkana males. American Journal of Human Biology 18: 71–82. doi: 10.1002/ajhb.20468

[20] Vitzthum V, Worthman C, Beall C, Thornburg J, Vargas E, et al. (2009) Seasonal and circadian variation in salivary testosterone in rural Bolivan men. Amer J Human Biology 21: 762–768. doi: 10.1002/ajhb.20927

[21] Vallombrosa Consensus Statement on Environmental contaminants and human fertility compromise. October 2005. Convened by Women's Health at Stanford. Stanford University School of Medicine. <http://www.ourstolenfuture.org/Consensus/2005/2005-1030vallombrosa.htm>

[22] University of Edinburgh. "Male health linked to testosterone exposure in womb, study finds." ScienceDaily. ScienceDaily, 22 April 2014. <www.sciencedaily.com/releases/2014/04/140422113439.htm>.

[23] Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. J Androl. 2012 Jul-Aug;33(4):515-28. doi: 10.2164/jandrol.110.011874.

[24] Mazur A, Westerman R, Mueller U. Is rising obesity causing a secular (age-independent) decline in testosterone among American men? PLoS One. 2013 Oct 16;8(10):e76178. doi: 10.1371/journal.pone.0076178. eCollection 2013

[25] Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. Eur J Endocrinol. 2006 Sep;155(3):443-52.

[26] Meeker JD, Ferguson KK. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. J Clin Endocrinol Metab. 2014 Nov;99(11):4346-52. doi: 10.1210/jc.2014-2555. Epub 2014 Aug 14. PubMed PMID: 25121464

[27] Klinefelter GR, Laskey JW, Amann RP. Statin drugs markedly inhibit testosterone production by rat Leydig cells in vitro: implications for men. Reprod Toxicol. 2014 Jun;45:52-8.

[28] Cook PS, Notelovitz M, Kalra PS, Kalra SP. Effect of diazepam on serum testosterone and the ventral prostate gland in male rats. Arch Androl. 1979;3(1):31-5.

[29] Eisenegger, C. et al. (2010) Prejudice and truth about the effect of testosterone on human bargaining behaviour. Nature 463, 356–359

[30] Stanton, S.J. et al. (2009) Endogenous testosterone levels are associated with amygdala and ventromedial prefrontal cortex responses to anger faces in men but not women. Biol. Psychol. 81, 118–122

[31] Pletzer B, Petasis O, Ortner TM, Cahill L. Interactive effects of culture and sex hormones on the sex role self-concept. *Frontiers in Neuroscience*. 2015;9:240. doi:10.3389/fnins.2015.00240.

[32] Hämäläinen EK, Adlercreutz H, Puska P, Pietinen P. Decrease of serum total and free testosterone during a low-fat high-fibre diet. J Steroid Biochem. 1983 Mar;18(3):369-70. PubMed PMID: 6298507.

[33] Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, Clevidence BA, Campbell WS, Nair PP, Franz C, Kahle L, Taylor PR. Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. Am J Clin Nutr. 1996 Dec;64(6):850-5. PubMed PMID: 8942407.

[34] Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, Wehr E, Zittermann A. Effect of vitamin D supplementation on testosterone levels in men. Horm Metab Res. 2011 Mar;43(3):223-5. doi: 10.1055 s-0030-1269854. Epub 2010 Dec 10. PubMed PMID: 21154195.

[35] Reed MJ, Cheng RW, Simmonds M, Richmond W, James VH. Dietary lipids: an additional regulator of plasma levels of sex hormone binding globulin. J Clin Endocrinol Metab. 1987 May;64(5):1083-5. PubMed PMID: 3558725.

[36] Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4): 339-61. Review. PubMed PMID:15831061.

[37] Roaiah MF, El Khayat YI, GamalEl Din SF, Abd El Salam MA. Pilot Study on the Effect of Botanical Medicine (Tribulus terrestris) on Serum Testosterone Level and Erectile Function in Aging Males With Partial Androgen Deficiency (PADAM). J Sex Marital Ther. 2016 May 18;42(4):297-301. doi: 10.1080/0092623X.2015.1033579.
Epub 2015 Apr 7. PubMed PMID: 25849625.

[38] Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? Andrologia. 2012 May;44 Suppl 1:226-30. doi:10.1111/j.1439-0272.2011.01168.x. Epub 2011 Jun 15. PubMed PMID: 21671978.

[39] Gunnels and Bloomer. Increasing Circulating Testosterone: Impact of Herbal Dietary SupplementsJ Plant Biochem Physiol 2014, 2:2 http://dx.doi.org/10.4172/2329-9029.1000130

[40] Holtorf, Kent. Journal Postgraduate Medicine Volume 121, 2009 - Issue 1. Page 73-85. Published online: 13 Mar 2015. The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy? http://dx.doi.org/10.3810/pgm.2009.01.1949

[41] Marsden, Tracy. Natural Medicine Journal. Mar 2010. Vol 2. Issue 3. Bioidentical Hormone Replacement: Guiding Principles for Practice. <http://www.naturalmedicinejournal.com/journal/2010-03/bioidentical-hormone-replacement-guiding-principles-practice>

[42] Celec, P., Ostatníková, D., & Hodosy, J. (2015). On the effects of testosterone on brain behavioral functions. *Frontiers in Neuroscience*, *9*, 12. http://doi.org/10.3389/fnins.2015.00012

[43] Cooke B, Hegstrom CD, Villeneuve LS, Breedlove SM (October 1998). "Sexual differentiation of the vertebrate brain: principles and mechanisms". *Frontiers in Neuroendocrinology*. **19** (4): 323–62. doi:10.1006/frne.1998.0171. PMID 9799588.

[44] Zuloaga DG, Puts DA, Jordan CL, Breedlove SM (May 2008). "The role of androgen receptors in the masculinization of brain and behavior: what we've learned from the testicular feminization mutation". *Hormones and Behavior*. **53** (5): 613–26. doi:10.1016/j.yhbeh.2008.01.013. PMC 2706155. PMID 18374335.

[45] Hamson DK, Wainwright SR, Taylor JR, Jones BA, Watson NV, Galea LA (2013). "Androgens increase survival of adult-born neurons in the dentate gyrus by an androgen receptor-dependent mechanism in male rats". *Endocrinology*. **154** (9): 3294–304. doi: 10.1210/en.2013-1129. PMID 23782943.

[46] Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, della Monica PL, Bonfigli B, Volpe M, Chierchia SL Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation. 1999 Apr 6; 99(13):1666-70.

[47] Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart. 2010 Nov; 96(22):1821-5.

[48] Njølstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation. 1996 Feb 1; 93(3):450-6.

[49] Brand JS, et.al.Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PLoS One. 2014 Jul 14;9(7):e100409. doi: 10.1371/journal.pone.0100409. eCollection 2014. PubMed PMID: 25019163; PubMed Central PMCID: PMC4096400.

[50] Traish, A. M. (2014). Testosterone and weight loss: the evidence. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *21*(5), 313–322. http://doi.org/10.1097/MED.0000000000000086

[51] Saad F, Yassin A, Doros G, Haider A. Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data from two registry studies. Int J Obes (Lond). 2016 Jan;40(1):162-70. doi: 10.1038/ijo.2015.139. Epub 2015 Jul 29. PubMed PMID: 26219417; PubMed Central PMCID: PMC4722240.

[52] Saad F, Aversa A, Isidori AM, Gooren LJ. Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: a review. Curr Diabetes Rev. 2012 Mar;8(2):131-43. Review. PubMed PMID: 22268394; PubMed Central PMCID: PMC3296126.

[53] Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M, Chavarro JE, Koloszar S, Twigt JM, Ramlau-Hansen CH, Borges E Jr, Lotti F, Steegers-Theunissen RP, Zorn B, Polotsky AJ, La Vignera S, Eskenazi B, Tremellen K, Magnusdottir EV, Fejes I, Hercberg S, Lévy R, Czernichow S. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. Hum Reprod Update. 2013 May-Jun;19(3):221-31. doi: 10.1093/humupd/dms050. Epub 2012 Dec 12. Review. PubMed PMID:23242914; PubMed Central PMCID: PMC3621293.

[54] Cunningham GR. Testosterone and metabolic syndrome. Asian J Androl. 2015 Mar-Apr;17(2):192-6. doi: 10.4103/1008-682X.148068. Review. PubMed PMID: 25652634; PubMed Central PMCID: PMC4650473.

[55] Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010 Jul 8;363(2):123-35. doi:10.1056/NEJMoa0911101. Epub 2010 Jun 16. PubMed PMID: 20554979.

[56] World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organization Technical Report Series*. 1994;843:1–129.

[57] Melton LJ, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Bone density and fracture risk in men. J Bone Miner Res. 1998;13(12):1915–1923.

[58] Melton JL. Perspectives: how many women have osteoporosis now? J Bone Miner Res. 1995;10(2):175–177.

[59] Mohamad, N.-V., Soelaiman, I.-N., & Chin, K.-Y. (2016). A concise review of testosterone and bone health. *Clinical Interventions in Aging*, *11*, 1317–1324. http://doi.org/10.2147/CIA.S115472

[60] Verdile G., Laws S.M., Henley D., et al. Associations between gonadotropins, testosterone and beta amyloid in men at risk of Alzheimer's disease. Mol. Psychiatry. 2014;19(1):69–75.

[61] Bassil N., Alkaade S., Morley J.E. The benefits and risks of testosterone replacement therapy: a review. Ther. Clin. Risk Manag. 2009;5(3):427–448.

[62] Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. Arch Gen Psychiatry. 2004;61:162–167.

[63] Giltay E.J., Tishova Y.A., Mskhalaya G.J., Gooren L.J., Saad F., Kalinchenko S.Y. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J. Sex. Med. 2010;7(7):2572–2582.

[64] Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002 Feb;87(2):589-98. PubMed PMID: 11836290.

[65] Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab. 2007 Jan;92(1):196-202. Epub 2006 Oct 24. PubMed PMID: 17062768.

[66] Clifton S, Macdowall W, Copas AJ, Tanton C, Keevil BG, Lee DM, Mitchell KR, Field N, Sonnenberg P, Bancroft J, Mercer CH, Wallace AM, Johnson AM, Wellings K, Wu FC. Salivary Testosterone Levels and Health Status in Men and Women in the British General Population: Findings from the Third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). J Clin Endocrinol Metab. 2016 Nov;101(11):3939-3951. Epub 2016 Aug 23. PubMed PMID: 27552539; PubMed Central PMCID: PMC5095233.

[67] Clifton S, Macdowall W, Copas AJ, Tanton C, Keevil BG, Lee DM, Mitchell KR, Field N, Sonnenberg P, Bancroft J, Mercer CH, Wallace AM, Johnson AM, Wellings K, Wu FC. Salivary Testosterone Levels and Health Status in Men and Women in the British General Population: Findings from the Third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). J Clin Endocrinol Metab. 2016 Nov;101(11):3939-3951. Epub 2016 Aug 23. PubMed PMID: 27552539; PubMed Central PMCID: PMC5095233.

[68] Perheentupa A, Mäkinen J, Laatikainen T, Vierula M, Skakkebaek NE, Andersson AM, Toppari J. A cohort effect on serum testosterone levels in Finnish men. Eur J Endocrinol. 2013 Jan 17;168(2):227-33. doi: 10.1530/EJE-12-0288. Print 2013 Feb. PubMed PMID: 23161753.

[69] Andersson AM, Jensen TK, Juul A, Petersen JH, Jørgensen T, Skakkebaek NE. Secular decline in male testosterone and sex hormone binding globulin serum levels in Danish population surveys. J Clin Endocrinol Metab. 2007 Dec;92(12):4696-705. Epub 2007 Sep 25. PubMed PMID: 17895324.

[70] Orwoll ES, Nielson CM, Labrie F, Barrett-Connor E, Cauley JA, Cummings SR, Ensrud K, Karlsson M, Lau E, Leung PC, Lunggren O, Mellström D, Patrick AL, Stefanick ML, Nakamura K, Yoshimura N, Zmuda J, Vandenput L, Ohlsson C; Osteoporotic Fractures in Men (MrOS) Research Group.. Evidence for geographical and racial variation in serum sex steroid levels in older men. J Clin Endocrinol Metab. 2010 Oct;95(10):E151-60. doi: 10.1210/jc.2009-2435. Epub 2010 Jul 28. PubMed PMID: 20668046; PubMed Central PMCID: PMC3050097.

[71] Rajan TV, Kerstetter J, Feinn R, Kenny A. Evidence for low androgenicity among Indian (South Asian) men. Aging Male. 2014 Mar;17(1):30-4. doi: 10.3109/13685538.2013.832192. Epub 2013 Nov 11. PubMed PMID: 24206051.

[72] Kumar TCA. Fertility and *in-vitro* fertilization in India. Curr Sci. 2004;86:254–6.

[73] Jørgensen N, Asklund C, Carlsen E, Skakkebaek, NE. Coordinated European investigations of semen quality: results from studies of Scandinavian young men is a matter of concern. Int J Androl. 2006 Feb; 29(1):54-61; discussion 105-8.

[74] Andersson AM, Jørgensen N, Main KM, Toppari J, Rajpert-De Meyts E, Leffers H, Juul A, Jensen TK, Skakkebaek NE. Adverse trends in male reproductive health: we may have reached a crucial 'tipping point'. Int J Androl. 2008 Apr; 31(2):74-80.

[75] Calverton, Maryland, USA: ORC Macro and the World Health Organization; 2004. World Health Organization. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No 9.

[76] Bonde JP, Ernst E, Jensen TK, Hjollund NH, Kolstad H, Henriksen TB, Scheike T, Giwercman A, Olsen J, Skakkebaek NE. Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. Lancet. 1998 Oct 10; 352(9135):1172-7.

[77] Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ. 1992 Sep 12;305(6854):609-13. Review. PubMed PMID: 1393072; PubMed Central PMCID: PMC1883354.

[78] Swan SH, Elkin EP. Declining semen quality: can the past inform the present? Bioessays. 1999 Jul;21(7):614-21. Review. PubMed PMID: 10472188.

[79] Rolland M, Le Moal J, Wagner V, Royère D, De Mouzon J. Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in France. Hum Reprod. 2013 Feb;28(2):462-70. doi: 10.1093/humrep/des415. Epub 2012 Dec 4. PubMed PMID: 23213178; PubMed Central PMCID: PMC4042534.

[80] R.J. Sherins and G. Delbès "Is there a decline in sperm counts in men?" American Society of Andrology. Handbook of Andrology. Available: Accessed on May 27, 2017: http://andrologysociety.org/getattachment/2d3132da-b376-43e0-80e5-1ba52c158936/Chapter-26.aspx

[81] Jouannet P, Wang C, Eustache F, Kold-Jensen T, Auger J. Semen quality and male reproductive health: the controversy about human sperm concentration decline. APMIS. 2001;109:333–344.

[82] Merzenich H, Zeeb H, Blettner M. Decreasing sperm quality: a global problem? BMC Public Health. 2010;10:24–24

[83] Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ. 1992;305:609–613.

[84] Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A reanalysis of global trend data. Environ Health Perspect. 1997;105:1228–1232.

[85] Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. Environ Health Perspect. 2000;108:961–966.

[86] Rolland M, Le Moal J, Wagner V, Royère D, De Mouzon J. Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in France. Hum Reprod. 2013 Feb;28(2):462-70. doi: 10.1093/humrep/des415. Epub 2012 Dec 4. PubMed PMID: 23213178; PubMedCentral PMCID: PMC4042534.

[87] Bilotta P, Guglielmo R, Steffè M. [Analysis of decline in seminal fluid in the Italian population during the past 15 years]. Minerva Ginecol. 1999 Jun;51(6):223-31. Review. Italian. PubMed PMID: 10479874.

[88] Irvine S, Cawood E, Richardson D, MacDonald E, Aitken J. Evidence of deteriorating semen quality in the United Kingdom: birth cohort study in 577 men in Scotland over 11 years. *BMJ : British Medical Journal*. 1996;312(7029):467-471.

[89] Sripada S, Fonseca S, Lee A, Harrild K, Giannaris D, Mathers E, Bhattacharya S. Trends in semen parameters in the northeast of Scotland. J Androl. 2007 Mar-Apr;28(2):313-9. Epub 2006 Nov 1. PubMed PMID: 17079743.

[90] Fernandez MF, Duran I, Olea N, et al. Semen quality and reproductive hormone levels in men from Southern Spain. *International Journal of Andrology*. 2012;35(1):1-10. doi:10.1111/j.1365-2605.2010.01131.x.

[91] Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Møller H. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer. 2006 Jun 15; 118(12):3099-111.

[92] Manning, John T. (2002). *Digit Ratio: A Pointer to Fertility, Behavior, and Health.* Rutgers University Press. New Brunswick, New Jersey. USA.

[93] Wu, X., Yang, D., Chai, W., Jin, M., Zhou, X., Peng, L., & Zhao, Y. (2013). The Ratio of Second to Fourth Digit Length (2D:4D) and Coronary Artery Disease in a Han Chinese Population. *International Journal of Medical Sciences*, *10*(11), 1584–1588. http://doi.org/10.7150/ijms.6360

[94] Zhao JL, Liu L, Liu W, Li FH, Yuan YY, Jing WH, Li CY. [Digit length ratio and male fertility among infertile patients in Ningxia]. Zhonghua Nan Ke Xue. 2012 Oct;18(10):881-5. Chinese. PubMed PMID: 23297494.

[95] Manning JT, Barley L, Walton J, Lewis-Jones DI, Trivers RL, Singh D, Thornhill R, Rohde P, Bereczkei T, Henzi P, Soler M, Szwed A. The 2nd:4th digit ratio, sexual dimorphism, population differences, and reproductive success. evidence for sexually antagonistic genes? Evol Hum Behav. 2000 May 1;21(3):163-183. PubMed PMID: 10828555.

[96] Kim, T. B., & Kim, K. H. (2016). Why is digit ratio correlated to sports performance? *Journal of Exercise Rehabilitation*, *12*(6), 515–519. http://doi.org/10.12965/jer.1632862.431

[97] Muller DC, Giles GG, Bassett J, Morris HA, Manning JT, Hopper JL, English DR, Severi G. Second to fourth digit ratio (2D:4D) and concentrations of circulating sex hormones in adulthood. Reprod Biol Endocrinol. 2011 Apr 27;9:57. doi: 10.1186/1477-7827-9-57. PubMed PMID: 21521531; PubMed Central PMCID: PMC3107785.

[98] Manning, J. T. (2011). Resolving the role of prenatal sex steroids in the development of digit ratio. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(39), 16143–16144. http://doi.org/10.1073/pnas.1113312108

[99] Manning, J., Kilduff, L., Cook, C., Crewther, B., & Fink, B. (2014). Digit Ratio (2D:4D): A Biomarker for Prenatal Sex Steroids and Adult Sex Steroids in Challenge Situations. *Frontiers in Endocrinology*, *5*, 9. http://doi.org/10.3389/fendo.2014.00009

[100] Manning JT, Bundred PE. The ratio of 2nd to 4th digit length: a new predictor of disease predisposition? Med Hypotheses. 2000 May;54(5):855-7. PubMed PMID:10859702.

[101] Butovskaya ML, Vasilyev VA, Lazebny OE, Burkova VN, Kulikov AM, Mabulla A, Shibalev DV, Ryskov AP. Aggression, digit ratio, and variation in the androgen receptor, serotonin transporter, and dopamine D4 receptor genes in African foragers: the Hadza. Behav Genet. 2012 Jul;42(4):647-62. doi:10.1007/s10519-012-9533-2. Epub 2012 Mar 6. PubMed PMID: 22392544.

[102] 1: Hurd PL, Vaillancourt KL, Dinsdale NL. Aggression, digit ratio and variation in androgen receptor and monoamine oxidase a genes in men. Behav Genet. 2011 Jul;41(4):543-56. doi: 10.1007/s10519-010-9404-7. Epub 2010 Oct 22. PubMed PMID: 20967566.

[103] Muller DC, Giles GG, Bassett J, Morris HA, Manning JT, Hopper JL, English DR, Severi G. Second to fourth digit ratio (2D:4D) and concentrations of circulating sex hormones in adulthood. Reprod Biol Endocrinol. 2011 Apr 27;9:57. doi: 10.1186/1477-7827-9-57. PubMed PMID: 21521531; PubMed Central PMCID: PMC3107785.

[104] Schug TT, Janesick A, Blumberg B, Heindel JJ. Endocrine disrupting chemicals and disease susceptibility. J Steroid Biochem Mol Biol. 2011 Nov;127(3-5):204-15. doi: 10.1016/j.jsbmb.2011.08.007. Epub 2011 Aug 27. Review. PubMed PMID: 21899826; PubMed Central PMCID: PMC3220783.

[105] United States Government Accountability Office. Testimony before the Committee on Environment and Public Works, U.S. Senate. CHEMICAL REGULATION
"Actions Are Needed to Improve the Effectiveness of EPA's Chemical Review Program." For Release on Delivery Expected at 9:30 am EDT Wednesday, August 2, 2006. Available: http://www.gao.gov/assets/120/114641.pdf Accessed March 7, 2017.

[106] Mocarelli P, Gerthoux PM, Needham LL, Patterson DG Jr, Limonta G, Falbo R, Signorini S, Bertona M, Crespi C, Sarto C et al. Perinatal exposure to low doses of dioxin can permanently impair human semen quality. Environ Health Perspect 2011;119:713–718.

[107] Vested A, Ramlau-Hansen CH, Olsen SF, Bonde JP, Kristensen SL, Halldorsson TI, Becher G, Haug LS, Ernst EH, Toft G. Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men. Environ Health Perspect 2013;121:453–458.

[108] Vested A, Ramlau-Hansen CH, Olsen SF, Bonde JP, Stovring H, Kristensen SL, Halldorsson TI, Rantakokko P, Kiviranta H, Ernst EH et al. In utero exposure to persistent organochlorine pollutants and reproductive health in the human male. Reproduction 2014;148:635–646.

[109] Axelsson J, Rylander L, Rignell-Hydbom A, Lindh CH, Jonsson BA, Giwercman A. Prenatal phthalate exposure and reproductive function in young men. Environ Res 2015;138:264–270.

[110] Bonde, J. P., Flachs, E. M., Rimborg, S., Glazer, C. H., Giwercman, A., Ramlau-Hansen, C. H., … Bräuner, E. V. (2017). The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. *Human Reproduction Update*, *23*(1), 104–125. http://doi.org/10.1093/humupd/dmw036

[111] Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. J Clin Endocrinol Metab. 2015 Apr;100(4):1245-55. doi: 10.1210/jc.2014-4324. Epub 2015 Mar 5. PubMed PMID: 25742516; PubMed Central PMCID: PMC4399291.

[112] Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015 Dec;36(6):E1-E150. doi: 10.1210/er.2015-1010. Epub 2015 Nov 6. Review. PubMed PMID: 26544531; PubMed Central PMCID: PMC4702494.

[113] del Mazo, J., Brieño-Enrìquez, M. A., Garc'a-López, J., López-Fernández, L. A., and De Felici, M. (2013). Endocrine disruptors, gene deregulation and male germ cell tumors. *Int. J. Dev. Biol.* 57, 225–239. doi: 10.1387/ijdb.130042jd

[114] Zhang, L., Dong, L., Ding, S., Qiao, P., Wang, C., Zhang, M., et al. (2014). Effects of *n*-butylparaben on steroidogenesis and spermatogenesis through changed E2 levels in male rat offspring. *Environ. Toxicol. Pharmacol.* 37, 705–717. doi: 10.1016/j.etap.2014.01.016

[115] Lange, A., Paull, G. C., Coe, T. S., Katsu, Y., Urushitani, H., Iguchi, T., et al. (2009). Sexual reprogramming and estrogenic sensitization in wild fish exposed to ethinylestradiol. *Environ. Sci. Technol.* 43, 1219–1225. doi: 10.1021/es802661p

[116] Zhao, Y., and Hu, J. (2012). Development of a molecular biomarker for detecting inter-sex after exposure of male medaka fish to synthetic estrogen. *Environ. Toxicol. Chem.* 31, 1765–1773. doi: 10.1002/etc.1892

[117] Edwards, T. M., and Myers, J. P. (2007). Environmental exposures and gene regulation in disease etiology. *Environ. Health Perspect.* 115, 1264–1270. doi: 10.1289/ehp.9951

[118] Moral, R., Wang, R., Russo, I. H., Lamartiniere, C. A., Pereira, J., and Russo, J. (2008). Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. *J. Endocrinol.* 196, 101–112. doi: 10.1677/JOE-07-0056

[119] Anway, M. D., and Skinner, M. K. (2008). Epigenetic programming of the germ line: effects of endocrine disruptors on the development of transgenerational disease. *Reprod. Biomed. Online* 16, 23–25. doi: 10.1016/S1472-6483(10)60553-6

[120] Skinner, M. K. (2011). Role of epigenetics in developmental biology and transgenerational inheritance. *Birth Defects Res. C Embryo Today* 93, 51–55. doi: 10.1002/bdrc.20199

[121] Balabanic, D., Rupnik, M., and Klemencic, A. K. (2011). Negative impact of endocrine-disrupting compounds on human reproductive health. *Reprod. Fertil. Dev.* 23, 403–416. doi: 10.1071/RD09300

[122] Marques-Pinto, A., and Carvalho, D. (2013). Human infertility: are endocrine disruptors to blame? *Endocr. Connect.* 2, R15–R29. doi: 10.1530/EC-13-0036

[123] The Endocrine Disruptor Exchange. Critical Windows of Development. Accessed March 8, 2017. Available: http://endocrinedisruption.org/prenatal-origins-of-endocrine-disruption/critical-windows-of-development/overview

[124] Widespread Pollutants with Endocrine-disrupting Effects. Available: http://www.ourstolenfuture.org/basics/chemlist.htm Accessed: April 7, 2017.

[125] Meeker JD, Ferguson KK. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. J Clin Endocrinol Metab. 2014 Nov;99(11):4346-52. doi: 10.1210/jc.2014-2555. Epub 2014 Aug 14. PubMed PMID: 25121464; PubMed Central PMCID: PMC4223430.

[126] Aly HA, Domenech O, Abdel-Naim AB. Aroclor 1254 impairs spermatogenesis and induces oxidative stress in rat testicular mitochondria. Food Chem Toxicol (2009) 47:1733–810.1016/j.fct.2009.03.019

[127] Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002 Feb;87(2):589-98. PubMed PMID: 11836290.

[128] La Vignera S, Condorelli RA, Balercia G, Vicari E, Calogero AE. Does alcohol have any effect on male reproductive function? A review of literature. Asian J Androl. 2013 Mar;15(2):221-5. doi: 10.1038/aja.2012.118. Epub 2012 Dec 31. Review. PubMed PMID: 23274392; PubMed Central PMCID: PMC3739141.

[129] Barnett G, Chiang CW, Licko V. Effects of marijuana on testosterone in male subjects. J Theor Biol. 1983 Oct 21;104(4):685-92. PubMed PMID: 6316036.

[130] Cone EJ, Johnson RE, Moore JD, Roache JD. Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol Biochem Behav. 1986 Jun;24(6):1749-54. PubMed PMID: 3016764.

[131] Krajewska-Kulak, E., & Sengupta, P. (2013). Thyroid Function in Male Infertility. *Frontiers in Endocrinology*, *4*, 174. http://doi.org/10.3389/fendo.2013.00174

[132] Mínguez-Alarcón, L., Chavarro, J. E., Mendiola, J., Roca, M., Tanrikut, C., Vioque, J., Torres-Cantero, A. M. (2017). Fatty acid intake in relation to reproductive hormones and testicular volume among young healthy men. *Asian Journal of Andrology*, *19*(2), 184–190. http://doi.org/10.4103/1008-682X.190323

[133] Fain E, Weatherford C. Comparative study of millennials' (age 20-34 years) grip and lateral pinch with the norms. J Hand Ther. 2016 Oct - Dec;29(4):483-488. doi: 10.1016/j.jht.2015.12.006. Epub 2016 Jan 11. PubMed PMID: 26869476.

[134] Eriksson J, et al. Causal relationship between obesity and serum testosterone status in men: A bi-directional mendelian randomization analysis. PLoS One. 2017 Apr 27;12(4):e0176277. doi: 10.1371/journal.pone.0176277. eCollection 2017. PubMed PMID: 28448539; PubMed Central PMCID: PMC5407807.

[135] Ricciuti A, Travison TG, Di Dalmazi G, Talor MV, DeVincentiis L, Manley RW, Bhasin S, Caturegli P, Basaria S. A Subset of Men With Age-Related Decline in Testosterone Have Gonadotroph Autoantibodies. J Clin Endocrinol Metab. 2016 Apr;101(4):1535-41. doi: 10.1210/jc.2016-1016. Epub 2016 Mar 10. PubMed PMID: 26963952; PubMed Central PMCID: PMC4880156.

[136] Thompson IM, et.al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003 Jul 17;349(3):215-24. Epub 2003 Jun 24. PubMed PMID: 12824459.

[137] Howell SJ, Radford JA, Adams JE, Smets EM, Warburton R, Shalet SM. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Clin Endocrinol (Oxf). 2001 Sep;55(3):315-24. PubMed PMID: 11589674.

[138] Morrison D, Capewell S, Reynolds SP, Thomas J, Ali NJ, Read GF, Henley R, Riad-Fahmy D. Testosterone levels during systemic and inhaled corticosteroid therapy. Respir Med. 1994 Oct;88(9):659-63. PubMed PMID: 7809437.

[139] Jarow JP, Lipshultz LI. Anabolic steroid-induced hypogonadotropic hypogonadism. Am J Sports Med. 1990 Jul-Aug;18(4):429-31. PubMed PMID: 2403193.

[140] Coward RM, Rajanahally S, Kovac JR, Smith RP, Pastuszak AW, Lipshultz LI. Anabolic steroid induced hypogonadism in young men. J Urol. 2013 Dec; 190(6):2200-5.

[141] Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009 Feb; 25(2):170-5.

[142] Schooling CM, Au Yeung SL, Freeman G, Cowling. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. BJ BMC Med. 2013 Feb 28; 11():57.

[143] Escasa MJ, Casey JF, Gray PB. Salivary testosterone levels in men at a U.S. sex club. Arch Sex Behav. 2011 Oct;40(5):921-6. doi: 10.1007/s10508-010-9711-3. Epub 2010 Dec 17. PubMed PMID: 21165688.

[144] Dabbs JM Jr, Mohammed S. Male and female salivary testosterone concentrations before and after sexual activity. Physiol Behav. 1992 Jul;52(1):195-7. PubMed PMID: 1529008.

[145] Stahl SM. The psychopharmacology of sex, Part 1: Neurotransmitters and the 3 phases of the human sexual response. J Clin Psychiatry. 2001 Feb;62(2):80-1. PubMed PMID: 11247105.

[146] Motofei IG, Rowland DL. Neurophysiology of the ejaculatory process: developing perspectives. BJU Int. 2005 Dec;96(9):1333-8. Review. PubMed PMID: 16287455.

[147] Twenge JM, Sherman RA, Wells BE. Declines in Sexual Frequency among American Adults, 1989-2014. Arch Sex Behav. 2017 Mar 6. doi: 10.1007/s10508-017-0953-1. [Epub ahead of print] PubMed PMID: 28265779.

[148] Sapolsky, Robert M. The Trouble with Testosterone and other Essays on the Biology of the Human Predicament. Touchstone Publishing. New York, NY. 1998. *Will Boys Just Be Boys? pages 147-159.*

[149] Mehta PH, Josephs RA. Testosterone and cortisol jointly regulate dominance: evidence for a dual-hormone hypothesis. Horm Behav. 2010 Nov;58(5):898-906. doi: 10.1016/j.yhbeh.2010.08.020. Epub 2010 Sep 15. PubMed PMID: 20816841.

[150] Winter DG. The power motive. Free Press; New York: 1973.

[151] Stanton, S. J., & Schultheiss, O. C. (2009). The hormonal correlates of implicit power motivation. *Journal of Research in Personality*, *43*(5), 942. http://doi.org/10.1016/j.jrp.2009.04.001

[152] Eisenegger C, Naef M, Snozzi R, Heinrichs M, Fehr E. Prejudice and truth about the effect of testosterone on human bargaining behaviour. Nature. 2010 Jan 21;463(7279):356-9. doi: 10.1038/nature08711. PubMed PMID: 19997098.

[153] Wibral M, Dohmen T, Klingmüller D, Weber B, Falk A. Testosterone administration reduces lying in men. PLoS One. 2012;7(10):e46774. doi: 10.1371/journal.pone.0046774. Epub 2012 Oct 10. PubMed PMID: 23071635; PubMed Central PMCID: PMC3468628.

[154] Is sociopolitical egalitarianism related to bodily and facial formidability in men? Price, Michael E. et al. Evolution and Human Behavior , Volume 0 , Issue 0. DOI: http://dx.doi.org/10.1016/j.evolhumbehav.2017.04.001

[155] Petersen MB, Sznycer D, Sell A, Cosmides L, Tooby J. The ancestral logic of politics: upper-body strength regulates men's assertion of self-interest over economic redistribution. Psychol Sci. 2013 Jul 1;24(7):1098-103. doi: 10.1177/0956797612466415. Epub 2013 May 13. PubMed PMID: 23670886.

[156] Carney DR, Cuddy AJ, Yap AJ. Power posing: brief nonverbal displays affect neuroendocrine levels and risk tolerance. Psychol Sci. 2010 Oct;21(10):1363-8. doi:10.1177/0956797610383437. Epub 2010 Sep 20. PubMed PMID: 20855902.

[157] D. B. Lubahn, D. R. Joseph, P. M. Sullivan, H. F. Willard, F. S. French, and E. M. Wilson, “Cloning of human androgen receptor complementary DNA and localization to the X chromomose,” *Science*, vol. 240, no. 4850, pp. 327–330, 1988.

[158] Francomano D, Greco EA, Lenzi A, Aversa A. CAG repeat testing of androgen receptor polymorphism: is this necessary for the best clinical management of hypogonadism? J Sex Med. 2013 Oct;10(10):2373-81. doi: 10.1111/jsm.12268. Epub 2013 Jul 11. Review. PubMed PMID: 23844628.

[159] Rana K, Davey RA, Zajac JD. Human androgen deficiency: insights gained from androgen receptor knockout mouse models. Asian J Androl. 2014 Mar-Apr;16(2):169-77. doi:10.4103/1008-682X.122590. Review. PubMed PMID: 24480924; PubMed Central PMCID: PMC3955325.

[160] Mooradian AD, Morley JE, Korenman SG. Biological actions of androgens. Endocr Rev. 1987 Feb;8(1):1-28. Review. PubMed PMID: 3549275.

[161] A. Ferlin, L. Bartoloni, G. Rizzo, A. Roverato, A. Garolla, and C. Foresta, “Androgen receptor gene CAG and GGC repeat lengths in idiopathic male infertility,” *Molecular Human Reproduction*, vol. 10, no. 6, pp. 417–421, 2004.

[162] Buchanan G, Yang M, Cheong A, Harris JM, Irvine RA, Lambert PF, et al. Structural and functional consequences of glutamine tract variation in the androgen receptor. Hum Mol Genet (2004) 13:1677–9210.1093/hmg/ddh181

[163] M. Katsuno, H. Adachi, F. Tanaka, and G. Sobue, “Spinal and bulbar muscular atrophy: ligand-dependent pathogenesis and therapeutic perspectives,” *Journal of Molecular Medicine*, vol. 82, no. 5, pp. 298–307, 2004.

[164] Giovannucci, E., Stampfer, M. J., Krithivas, K., Brown, M., Brufsky, A., Talcott, J., … Kantoff, P. W. (1997). The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(7), 3320–3323.

[165] Giovannucci E, Platz EA, Stampfer MJ, Chan A, Krithivas K, Kawachi I, Willett WC, Kantoff PW. The CAG repeat within the androgen receptor gene and benign prostatic hyperplasia. Urology. 1999 Jan;53(1):121-5. PubMed PMID: 9886600.

[166] Rajpert-De Meyts E, Skakkebaek NE. The possible role of sex hormones in the development of testicular cancer. Eur Urol. 1993;23(1):54-9; discussion 60-1. Review. PubMed PMID: 8477778.

[167] Tirabassi, G., Cignarelli, A., Perrini, S., delli Muti, N., Furlani, G., Gallo, M., … Balercia, G. (2015). Influence of CAG Repeat Polymorphism on the Targets of Testosterone Action. *International Journal of Endocrinology*, *2015*, 298107. http://doi.org/10.1155/2015/298107

[168] Francomano D, Greco EA, Lenzi A, Aversa A. CAG repeat testing of androgen receptor polymorphism: is this necessary for the best clinical management of hypogonadism? J Sex Med. 2013 Oct;10(10):2373-81. doi: 10.1111/jsm.12268. Epub 2013 Jul 11. Review. PubMed PMID: 23844628.

[169] Woodhouse LJ, Reisz-Porszasz S, Javanbakht M, Storer TW, Lee M, Zerounian H, Bhasin S. Development of models to predict anabolic response to testosterone administration in healthy young men. Am J Physiol Endocrinol Metab. 2003 May; 284(5):E1009-17. Epub 2003 Jan 7. PubMed PMID: 12517741.

[170] R. Haring, F. Ernst, C. Schurmann et al., "The androgen receptor CAG repeat polymorphism as a risk factor of low serum testosterone and its cardiometabolic effects in men," *International Journal of Andrology*, vol. 35, no. 4, pp. 511–520, 2012.

[171] Tirabassi G, Delli Muti N, Corona G, Maggi M, Balercia G. Androgen Receptor Gene CAG Repeat Polymorphism Regulates the Metabolic Effects of Testosterone Replacement Therapy in Male Postsurgical Hypogonadotropic Hypogonadism. Int J Endocrinol. 2013;2013:816740. doi: 10.1155/2013/816740. Epub 2013 Dec 12. PubMed PMID: 24454369; PubMed Central PMCID: PMC3876679.

[172] Ueda T, Mawji NR, Bruchovsky N, Sadar MD. Ligand-independent activation of the androgen receptor by interleukin-6 and the role of steroid receptor coactivator-1 in prostate cancer cells. J Biol Chem. 2002 Oct 11;277(41):38087-94. PubMed PMID: 12163482.

[173] Hämäläinen E, Adlercreutz H, Puska P, Pietinen P. Diet and serum sex hormones in healthy men. J Steroid Biochem. 1984 Jan; 20(1):459-64. PubMed PMID: 6538617.

[174] MInguez-Alarcón L, Chavarro JE, Mendiola J, Roca M, Tanrikut C, Vioque J, Jørgensen N, Torres-Cantero AM. Fatty acid intake in relation to reproductive hormones and testicular volume among young healthy men. Asian J Androl. 2017 Mar-Apr;19(2):184-190. doi: 10.4103/1008-682X.190323. PubMed PMID: 27834316; PubMed Central PMCID: PMC5312216.

[175] Nagata C, Takatsuka N, Kawakami N, Shimizu H. Relationships between types of fat consumed and serum estrogen and androgen concentrations in Japanese men. Nutr Cancer. 2000;38:163–7.

[176] Giltay EJ, Geleijnse JM, Heijboer AC, de Goede J, Oude Griep LM, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. Int J Androl. 2012;35:680–7.

[177] Safarinejad MR. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile and enzymatic anti-oxidant capacity of seminal plasma in infertile men with idiopathic oligoasthenoteratospermia: a double-blind, placebo-controlled, randomised study. Andrologia. 2011;43:38–47.

[178] Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, et al. Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod. 2012;27:1466–74.

[179] Jensen TK, Heitmann BL, Jensen MB, Halldorsson TI, Andersson AM, et al. High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. Am J Clin Nutr. 2013;97:411–8.

[180] Veganism booms by 350%. Accessed on June 16, 2017: http://www.veganlifemag.com/veganism-booms/

[181] Armstrong BK, Brown JB, Clarke HT, Crooke DK, Hahnel R, Masarei JR, Ratajczak T. 1981 Diet and reproductive hormones: a study of vegetarian and nonvegetarian postmenopausal women. *J Natl Cancer Inst* . 67:761–767.

[182] Key TJA, Roe L, Thorogood M, Moore JW, Clark GMG, Wang DY. 1990 Testosterone, sex hormone-binding globulin, calculated free testosterone, and oestradiol in male vegans and omnivores. *Br J Nutr* . 64:111–119.

[183] Anderson KE, Rosner W, Khan MS, New MI, Pang SY, Wissel PS, Kappas A. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. Life Sci. 1987 May 4;40(18):1761-8. PubMed PMID: 3573976.

[184] Habito RC, Montalto J, Leslie E, Ball MJ. Effects of replacing meat with soyabean in the diet on sex hormone concentrations in healthy adult males. Br J Nutr. 2000 Oct;84(4):557-63. PubMed PMID: 11103227.

[185] Dietary Guidelines JANUARY 1, 2000 BY JILL NEINHISER. Available: https://www.westonaprice.org/health-topics/abcs-of-nutrition/dietary-guidelines/. Accessed on June 29, 2017

[186] United States Department of Labor Bureau of Labor Statistics: Sports and exercise among Americans. August 04, 2016. Accessed May 26, 2017: https://www.bls.gov/opub/ted/2016/sports-and-exercise-among-americans.htm

[187] Ibañez, J et al. 12-Week Exercise Program Significantly Improved Testosterone Levels In Overweight, Obese Men. Diabetes Care 2005; 28(3): 662-667

[188] MacKelvie, K et al. Bone mineral density and serum testosterone in chronically trained, high mileage 40–55 year old male runners. Br J Sports Med. 2000; 34(4): 273–278

[189] Carla, SC et al. Divergent responses of serum testosterone and cortisol in athlete men after a marathon race. Arq Bras Endocrinol Metab. 2006; 50(6)

[190] Hackney AC. Effects of endurance exercise on the reproductive system of men: the "exercise-hypogonadal male condition". J Endocrinol Invest. 2008 Oct;31(10):932-8. Review. PubMed PMID: 19092301.

[191] Hackney AC, Lane AR, Register-Mihalik J, O'Leary CB. Endurance Exercise Training and Male Sexual Libido. Med Sci Sports Exerc. 2017 Feb 13. doi:10.1249/MSS.0000000000001235. [Epub ahead of print] PubMed PMID: 28195945.

[192] Hackney AC, Hosick KP, Myer A, Rubin DA, Battaglini CL. Testosterone responses to intensive interval versus steady-state endurance exercise. J Endocrinol Invest. 2012 Dec;35(11):947-50. PubMed PMID: 23310924.

[193] Villanueva, M., Villanueva, M., Lane, C., & Schroeder, E. (2012). Influence of Rest Interval Length on Acute Testosterone and Cortisol Responses to Volume-Load Equated Total Body Hypertrophic and Strength Protocols. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *26*(10), 2755–2764. http://doi.org/10.1519/JSC.0b013e3182651fbe

[194] Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4): 339-61. Review. PubMed PMID:15831061.

[195] Hollander AB, Pastuszak AW, Hsieh TC, Johnson WG, Scovell JM, Mai CK,Lipshultz LI. Cabergoline in the Treatment of Male Orgasmic Disorder-A Retrospective Pilot Analysis. Sex Med. 2016 Mar;4(1):e28-33. doi:10.1016/j.esxm.2015.09.001. PubMed PMID: 26944776; PubMed Central PMCID:PMC4822480.

[196] The Neurochemisty of Sex and Addiction. Life Change Institute: Available. Accessed May 27, 2017: http://www.lifechangehealthinstitute.ie/the-neurochemistry-sex-addiction/

[197] Komisurak Barry R., Carlos Beyer-Flores, Beverly Whipple. The Science of Orgasm. The Johns Hopkins University Press. p. 165-66

[198] Exton MS, Krüger TH, Bursch N, Haake P, Knapp W, Schedlowski M, Hartmann U. Endocrine response to masturbation-induced orgasm in healthy men following a 3-week sexual abstinence. World J Urol. 2001 Nov;19(5):377-82. PubMed PMID: 11760788.

[199] Jiang M, Xin J, Zou Q, Shen JW. A research on the relationship between ejaculation and serum testosterone level in men. J Zhejiang Univ Sci. 2003 Mar-Apr;4(2):236-40. PubMed PMID: 12659241.

[200] Shahid M, Riaz M, Talpur MM, Pirzada T. Phytopharmacology of Tribulus terrestris. J Biol Regul Homeost Agents. 2016 Jul-Sep; 30(3):785-788. Review. PubMed PMID: 27655498.

[201] Chhatre, S., Nesari, T., Somani, G., Kanchan, D., & Sathaye, S. (2014). Phytopharmacological overview of *Tribulus terrestris*. *Pharmacognosy Reviews*, *8*(15), 45–51. http://doi.org/10.4103/0973-7847.125530

[202] Qureshi A, Naughton DP, Petroczi A. A systematic review on the herbal extract Tribulus terrestris and the roots of its putative aphrodisiac and performance enhancing effect. J Diet Suppl. 2014 Mar;11(1):64-79. doi:10.3109/19390211.2014.887602. Review. PubMed PMID: 24559105.

[203] Neychev V, Mitev V. Pro-sexual and androgen enhancing effects of Tribulus terrestris L.: Fact or Fiction. J Ethnopharmacol. 2016 Feb 17;179:345-55. doi: 10.1016/j.jep.2015.12.055. Review. PubMed PMID: 26727646.

[204] Roaiah MF, El Khayat YI, GamalEl Din SF, Abd El Salam MA. Pilot Study on the Effect of Botanical Medicine (Tribulus terrestris) on Serum Testosterone Level and Erectile Function in Aging Males With Partial Androgen Deficiency (PADAM). J Sex Marital Ther. 2016 May 18;42(4):297-301. doi: 10.1080/0092623X.2015.1033579. Epub 2015 Apr 7. PubMed PMID: 25849625.

[205] Gauthaman K, Adaikan PG, Prasad RN. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci. 2002;71:1385–96. doi: 10.1016/S0024-3205(02)01858-1.

[206] Ghosian Moghaddam MH, Khalili M, Maleki M, Ahmad Abadi ME. The Effect of oral feeding of Tribulus terrestris L. on sex hormone and gonadotropin levels in addicted male rats. Int J Fertil Steril. 2013;7:57–62.

[207] Yin L, Wang Q, Wang X, Song LN. Effects of Tribulus terrestris saponins on exercise performance in overtraining rats and the underlying mechanisms. Can J Physiol Pharmacol. 2016 Jun 22:1-9. [Epub ahead of print] PubMed PMID: 27482746.

[208] Gauthaman K, Adaikan PG. Effect of Tribulus terrestris on nicotinamide adenine dinucleotide phosphate-diaphorase activity and androgen receptors in rat brain. J Ethnopharmacol. 2005 Jan 4;96(1-2):127-32. PubMed PMID: 15588660.

[209] de Souza KZ, Vale FB, Geber S. Efficacy of Tribulus terrestris for the treatment of hypoactive sexual desire disorder in postmenopausal women: a randomized, double-blinded, placebo-controlled trial. Menopause. 2016 Nov;23(11):1252-1256. PubMed PMID: 27760089.

[210] Gama CR, Lasmar R, Gama GF, Abreu CS, Nunes CP, Geller M, Oliveira L, Santos A. Clinical Assessment of Tribulus terrestris Extract in the Treatment of Female Sexual Dysfunction. Clin Med Insights Womens Health. 2014 Dec 22;7:45-50. doi:10.4137/CMWH.S17853. eCollection 2014. PubMed PMID: 25574150; PubMed CentralPMCID: PMC4275110.

[211] Khaleghi S, Bakhtiari M, Asadmobini A, Esmaeili F. Tribulus terrestris Extract Improves Human Sperm Parameters In Vitro. J Evid Based Complementary Altern Med. 2016 Sep 30. pii: 2156587216668110. [Epub ahead of print] PubMed PMID: 27694560.

[212] Frydrychová S, Opletal L, Macáková K, Lustyková A, Rozkot M, Lipenský J. Effects of herbal preparation on libido and semen quality in boars. Reprod DomestAnim. 2011 Aug;46(4):573-8. doi: 10.1111/j.1439-0531.2010.01703.x. Epub 2010 Nov 23. PubMed PMID: 21092065.

[213] Singh S, Nair V, Gupta YK. Evaluation of the aphrodisiac activity of tribulus terrestris linn. in sexually sluggish male albino rats. J Pharmacol Pharmacother. 2012;3:43–7. doi: 10.4103/0976-500X.92512.

[214] Salgado RM, Marques-Silva MH, Gonçalves E, Mathias AC, Aguiar JG, Wolff P. Effect of oral administration of Tribulus terrestris extract on semen quality and body fat index of infertile men. Andrologia. 2017 Jun;49(5). doi: 10.1111/and.12655. Epub 2016 Jul 12. PubMed PMID: 27401787.

[215] Asadmobini A, Bakhtiari M, Khaleghi S, Esmaeili F, Mostafaei A. The effect of Tribulus terrestris extract on motility and viability of human sperms after cryopreservation. Cryobiology. 2017 Apr;75:154-159. doi:10.1016/j.cryobiol.2017.02.005. Epub 2017 Feb 17. PubMed PMID: 28216339.

[216] Tremellen K. Oxidative stress and male infertility--a clinical perspective. Hum Reprod Update. 2008 May-Jun;14(3):243-58. doi: 10.1093/humupd/dmn004. Epub 2008 Feb 14. Review. PubMed PMID: 18281241.

[217] Ebisch IM, Thomas CM, Peters WH, Braat DD, Steegers-Theunissen RP. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Hum Reprod Update. 2007 Mar-Apr;13(2):163-74. Epub 2006 Nov 11.Review. PubMed PMID: 17099205.

[218] Tee TT, Cheah YH, Hawariah LP. F16, a fraction from Eurycoma longifolia jack extract, induces apoptosis via a caspase-9-independent manner in MCF-7 cells. Anticancer Res. 2007;27:3425–30.

[219] Farouk AE, Benafri A. Antibacterial activity of Eurycoma longifolia Jack. A Malaysian medicinal plant. Saudi Med J. 2007;28:1422–4.

[220] Kuo PC, Damu AG, Lee KH, Wu TS. Cytotoxic and antimalarial constituents from the roots of Eurycoma longifolia. Bioorg Med Chem. 2004;12:537–44.

[221] Ang HH, Lee KL, Kiyoshi M. Sexual arousal in sexually sluggish old male rats after oral administration of Eurycoma longifolia Jack. J Basic Clin Physiol Pharmacol. 2004;15:303–9.

[222] Chan KL, Choo CY, Abdullah NR, Ismail Z. Antiplasmodial studies of Eurycoma longifolia Jack using the lactate dehydrogenase assay of Plasmodium falciparum. J Ethnopharmacol. 2004;92:223–7.

[223] Thu HE, Mohamed IN, Hussain Z, Jayusman PA, Shuid AN. Eurycoma Longifolia as a potential adoptogen of male sexual health: a systematic review on clinical studies. Chin J Nat Med. 2017 Jan;15(1):71-80. doi:10.1016/S1875-5364(17)30010-9. Review. PubMed PMID: 28259255.

[224] Kotirum S, Ismail SB, Chaiyakunapruk N. Efficacy of Tongkat Ali (Eurycoma longifolia) on erectile function improvement: systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2015 Oct;23(5):693-8. doi: 10.1016/j.ctim.2015.07.009. Epub 2015 Jul 31. Review. PubMed PMID: 26365449.

[225] Ulbricht C, Conquer J, Flanagan K, Isaac R, Rusie E, Windsor RC. An evidence-based systematic review of tongkat ali (Eurycoma longifolia) by the Natural Standard Research Collaboration. J Diet Suppl. 2013 Mar;10(1):54-83. doi: 10.3109/19390211.2012.761467. Review. PubMed PMID: 23419023.

[226] Rehman SU, Choe K, Yoo HH. Review on a Traditional Herbal Medicine, Eurycoma longifolia Jack (Tongkat Ali): Its Traditional Uses, Chemistry, Evidence-Based Pharmacology and Toxicology. Molecules. 2016 Mar 10;21(3):331. doi: 10.3390/molecules21030331. Review. PubMed PMID: 26978330.

[227] Talbott SM, Talbott JA, George A, Pugh M. Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. J Int Soc Sports Nutr. 2013 May 26;10(1):28. doi: 10.1186/1550-2783-10-28. PubMed PMID:23705671; PubMed Central PMCID: PMC3669033.

[228] Shuid AN, Abu Bakar MF, Abdul Shukor TA, Muhammad N, Mohamed N, Soelaiman IN. The anti-osteoporotic effect of *Eurycoma Longifolia* in aged orchidectomised rat model. Aging Male. 2011;14:150–4.

[229] Chaing HS, Merino-chavez G, Yang LL, Wang FN, Hafez ES. Medicinal plants: conception / contraception. Adv Contracept Deliv Syst. 1994;10(3-4):355-63. PubMed PMID: 12287843.

[230] Talbott S, Talbott J, Christopulos AM, Ekberg C, Larsen W, Jackson V. Ancient wisdom meets modern ailment – traditional Asian medicine improves psychological vigor in stressed subjects. Progress in Nutrition. 2010;12(1):3–8.

[231] Wahab, N. A., Mokhtar, N. M., Halim, W. N. H. A., & Das, S. (2010). The Effect of *Eurycoma Longifolia* Jack on Spermatogenesis in Estrogen-Treated Rats. *Clinics*, *65*(1), 93–98. http://doi.org/10.1590/S1807-59322010000100014

[232] Solomon MC, Erasmus N, Henkel RR. In vivo effects of Eurycoma longifolia Jack (Tongkat Ali) extract on reproductive functions in the rat. Andrologia. 2014 May;46(4):339-48. doi: 10.1111/and.12082. Epub 2013 Mar 6. PubMed PMID: 23464350.

[233] Shuid AN, El-arabi E, Effendy NM, Razak HS, Muhammad N, Mohamed N, Soelaiman IN. Eurycoma longifolia upregulates osteoprotegerin gene expression in androgen-deficient osteoporosis rat model. BMC Complement Altern Med. 2012 Sep 12;12:152. doi: 10.1186/1472-6882-12-152. PubMed PMID: 22967165; PubMed Central PMCID:PMC3493384.

[234] Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism Andrologia. 2012 May;44 Suppl 1:226-30. doi: 10.1111/j.1439-0272.2011.01168.x. Epub 2011 Jun 15. PubMed PMID: 21671978.

[235] Low BS, Das PK, Chan KL. Standardized quassinoid-rich Eurycoma longifolia extract improved spermatogenesis and fertility in male rats via the hypothalamic-pituitary-gonadal axis. J Ethnopharmacol. 2013 Feb 13;145(3):706-14. doi: 10.1016/j.jep.2012.11.013. Epub 2012 Dec 20. PubMed PMID: 23261482.

[236] Jin-Chul Ahn, Young-Hoon Kim, Chung-Ku Rhee. The effects of low level laser therapy (LLLT) on the testis in elevating serum testosterone levels in rats. Biomedical Research 2013; 24 (1): 28-32

[237] Taha MF, Valojerdi MR. Quantitative and qualitative changes of the seminiferous epithelium induced by Ga. Al. As. (830 nm) laser radiation. Lasers Surg Med. 2004;34(4):352-9. PubMed PMID: 15083497.

[238] Salman Yazdi R, Bakhshi S, Jannat Alipoor F, Akhoond MR, Borhani S, Farrahi F, Lotfi Panah M, Sadighi Gilani MA. Effect of 830-nm diode laser irradiation on human sperm motility. Lasers Med Sci. 2014 Jan;29(1):97-104. doi: 10.1007/s10103-013-1276-7. Epub 2013 Feb 14. PubMed PMID: 23407899.

[239] Firestone RS, Esfandiari N, Moskovtsev SI, Burstein E, Videna GT, Librach C, Bentov Y, Casper RF. The effects of low-level laser light exposure on sperm motion characteristics and DNA damage. J Androl. 2012 May-Jun;33(3):469-73. doi: 10.2164/jandrol.111.013458. Epub 2011 Jul 14. PubMed PMID: 21757512.

[240] Iurshin VV, Sergienko NF, Illarionov VE. [Etiopathogenetic basis for using magnetolaser therapy in the complex treatment of male infertility]. Urologiia. 2003 Mar-Apr;(2):23-5. Russian. PubMed PMID: 12811920.

[241] Bossini L, Fagiolini A, Valdagno M, Roggi M, Tallis V, Trovarelli S, Ponchietti R, Castrogiovanni P. Light therapy as a treatment for sexual dysfunctions. Psychother Psychosom. 2009;78(2):127-8. doi: 10.1159/000203119. Epub 2009 Feb 18. PubMed PMID: 19223689.

[242] Mooventhan, A., & Nivethitha, L. (2014). Scientific Evidence-Based Effects of Hydrotherapy on Various Systems of the Body. *North American Journal of Medical Sciences*, *6*(5), 199–209. http://doi.org/10.4103/1947-2714.132935

[243] Lue YH, Sinha Hikim AP, Swerdloff RS, Im P, Khay ST, Bui T, Leung A, Wang C 1999 Single exposure to heat induces stage-specific germ cell apoptosis in rats: role of intratesticular testosterone on stage specificity. *Endocrinology* 140:1709–1717

[244] Levitas E, Lunenfeld E, Weisz N, Friger M, Har-Vardi I. Seasonal variations of human sperm cells among 6455 semen samples: a plausible explanation of a seasonal birth pattern. Am J Obstet Gynecol. 2013 May;208(5):406.e1-6. doi:10.1016/j.ajog.2013.02.010. Epub 2013 Feb 8. PubMed PMID: 23395928.

[245] Bassil, N., Alkaade, S., & Morley, J. E. (2009). The benefits and risks of testosterone replacement therapy: a review. *Therapeutics and Clinical Risk Management*, *5*, 427–448.

[246] Traish, A. (2016). Testosterone therapy in men with testosterone deficiency: Are we beyond the point of no return? *Investigative and Clinical Urology*, *57*(6), 384–400. http://doi.org/10.4111/icu.2016.57.6.384

[247] Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab. 1997;82:682–5.

[248] Zgliczynski S, Ossowski M, Slowinska-Srzednicka J, Brzezinska A, Zgliczynski W, et al. Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. Atherosclerosis. 1996;121:35–43.

[249] Mårin P, Holmäng S, Gustafsson C, Jönsson L, Kvist H, et al. Androgen treatment of abdominally obese men. Obes Res. 1993;1:245–51.

[250] Zitzmann M, Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. J Clin Endocrinol Metab. 2007;92:3844–53.

[251] Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22:232–240.

[252] Morgentaler A. Testosterone therapy can be given to men with no concern that it will promote prostate cancer development or progression: pro. J Urol. 2016;196:985–988.

[253] Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, Lapauw B, Fiers T, Matsumoto AM, Bhasin S. Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. J Clin Endocrinol Metab. 2017 Apr 1;102(4):1161-1173. doi: 10.1210/jc.2016-2935. PubMed PMID: 28324103; PubMed Central PMCID: PMC5460736.

[254] Hertoghe, Thierry. The Hormone Handbook, 2nd ed. 2014.

[255] Willoughby DS, Taylor L. Effects of sequential bouts of resistance exercise on androgen receptor expression. Med Sci Sports Exerc. 2004 Sep;36(9):1499-506. PubMed PMID: 15354030.

[256] Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, McLafferty CL Jr, Urban RJ. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab. 2001 Mar;280(3):E383-90. PubMed PMID: 11171591.

[257] Röjdmark S, Asplund A, Rössner S. Pituitary-testicular axis in obese men during short-term fasting. Acta Endocrinol (Copenh). 1989 Nov;121(5):727-32. PubMed PMID: 2686332.

[258] Kraemer WJ, Spiering BA, Volek JS, Ratamess NA, Sharman MJ, Rubin MR, French DN, Silvestre R, Hatfield DL, Van Heest JL, Vingren JL, Judelson DA, Deschenes MR, Maresh CM. Androgenic responses to resistance exercise: effects of feeding and L-carnitine. Med Sci Sports Exerc. 2006 Jul;38(7):1288-96. Erratum in: Med Sci Sports Exerc. 2006 Oct;38(10):1861. PubMed PMID: 16826026.

[259] Volek JS, Kraemer WJ, Rubin MR, Gómez AL, Ratamess NA, Gaynor P. L-Carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. Am J Physiol Endocrinol Metab. 2002 Feb;282(2):E474-82. PubMed PMID:11788381.

[260] Exton MS, Krüger TH, Bursch N, Haake P, Knapp W, Schedlowski M, Hartmann U. Endocrine response to masturbation-induced orgasm in healthy men following a 3-week sexual abstinence. World J Urol. 2001 Nov;19(5):377-82. PubMed PMID: 11760788.

[261] Jiang M, Xin J, Zou Q, Shen JW. A research on the relationship between ejaculation and serum testosterone level in men. J Zhejiang Univ Sci. 2003 Mar-Apr;4(2):236-40. PubMed PMID: 12659241.