Chapter

Role of Sex Hormones in Human Body

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Abstract

Gonadal Steroids hormones play an important role in the reproductive and non-reproductive systems. Estrogen has important rule in cardiovascular system as it has vasodilator effect and reduces or prevents platelet activation. In addition, it improves the profile of circulating lipoproteins. All of which may explain why women at premenopausal age are less likely to have heart disease than menopause women or men. E2 play a grate effect on the skeletal system as it is one of the strongest regulators of osteoblast and osteoclast function, and it is responsible for the reduction of adipose tissue and regulation of the body weight, and also has dermatological effect,hence it stimulates the proliferation of keratinocytes and prevents their apoptosis, in addition to the progesterone which increases collagen synthesis. Estrogen is necessary for the functioning and integrity of the tissues of the urinary system specially of the lower urinary tract. Sex steroid are crucial for nervous system, as progesterone is important for production of neurosteroid, and estrogen is currently used in Parkinson's and Alzheimer's disease because of its effects on mental health. The androgens also have a crucial biological effects on neural, muscle, bone, adipose tissue,prostate, cardiovascular, haemopoietic, and the reproductive systems. The gonadal steroid hormones play an important role in immune system and regulating the immune response against different viral or bacterial infections.

Keywords: sex hormones, cardiovascular, brain, bone, urinary tract, immunity

1. Introduction

Gonadal Steroid hormones (GSH) play an important role in reproductive and non-reproductive systems. As this effect occurs early in the fetus' life, gonads are initially present at the fifth weeks and developed on the medial surface of mesonephric ridges.

Therefore, sexual development and discrimination are depending on the type of hormones and gonads that present. GSH play an important role in determining sexual function and behavior. Structures of the central nervous system, such as the hypothalamus, midbrain, amygdala, cortex and anterior pituitary gland, contain androgens and estrogen receptors. The GSH must bind to specific receptors to produce cellular response. While binding of receptor antagonists generally lead to inactivation of these receptors [1].

This chapter explain the effect of sex hormones on the human body and the differences in their action in both genders.

2. Physiological effects of sex hormones

Sex hormones are chemical structures derived from cholesterol, and they are a group of steroidal hormones act as chemical messengers in the body. The activity of steroid hormones is carried out by receptors on extracellular proteins belonging to the family of nuclear substances. Through genomic and non-genomic action, these receptors intervene transduction of signals in a manner of specific context [2].

2.1 Estrogen receptor

2.1.1 Genomic activity

Estrogen binds to SHBG in the blood and in the interstitial fluid, where it penetrates the cell membrane and enters the cell nucleus and binds to receptors. These 2 genes are encoded for 2 estrogen isoforms α and β.

The hormone- receptors structures forms dimer (usually ERα-ERα, ERβ- ERβ or ERα- ERβ) that bind to a specific nucleotide sequence, namely, Estrogen-response elements (EREs) in regions that control different genes regulation of transcription [3] (see **Figure 1**).

Estrogen acts through several nuclear receptors. Estrogen affects the endometrium, the vagina and the breast [4]. And it interact with Calcitonin, parathyroid hormone, vitamin D and interleukin. Estrogen stimulates the division and growth of the skin cells, connective tissue and mucosal membrane [5].

2.1.2 Non genomic activities

The rapid effects of estrogen, such as the removal of Ca^{2+} granular cells and uterine blood-flow are mediated by non-genomic actions [3].

Non-genomic activity occur without bind to cellular receptors of estrogen. The beneficial effects of estrogen on blood vessels are an important non-genomic effect [5]. It affects not only blood vessels in the reproductive system, but also the cerebral, coronary and carotid arteries.

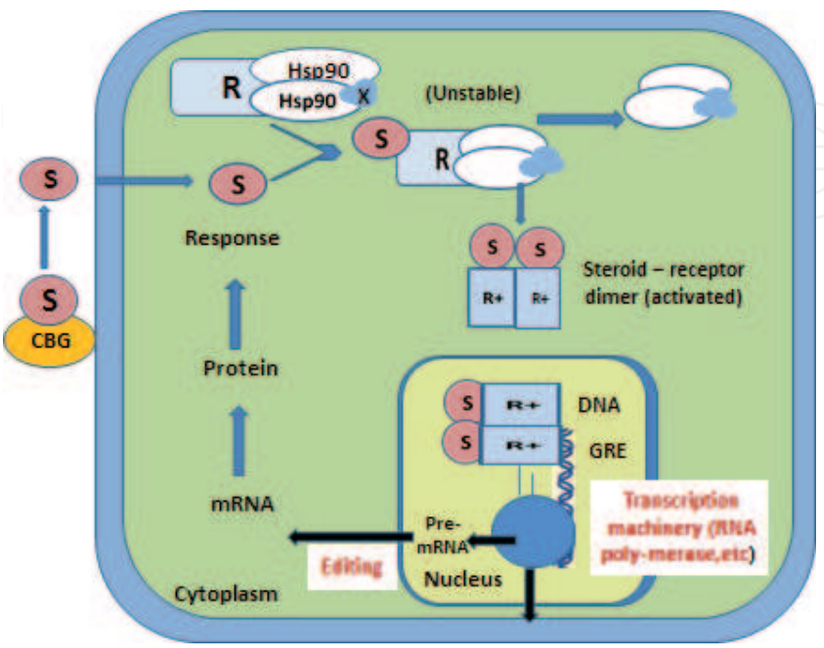

Figure 1.
Genomic action of steroid hormones (estrogen) in the cell.

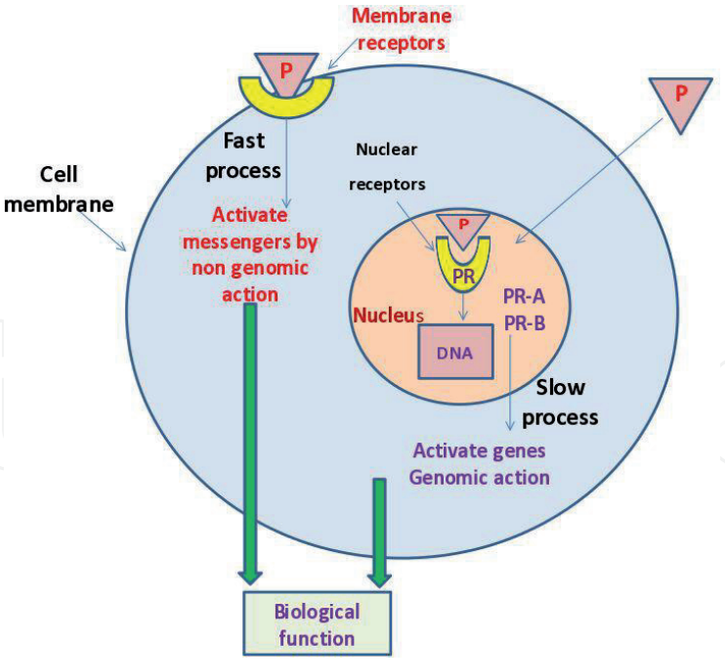

Figure 2.
Mode of progesterone action by genomic and non- genomic action.

Production of nitrous oxide, mediates vasodilation and endothelial protection. Estrogen also stimulates the production of prostacyclin vasodilating, prevents vasoconstriction and prevents platelet aggregation. Also Acetylcholine dilates blood vessels only in the presence of estrogen [6].

2.2 Progesterone receptors

Like estrogen, progesterone act through nuclear receptors, progesterone action is by 2 isoform of progesterone receptors (PR-A and PR-B). These 2 isoforms differ in fact that PR-B has an extra (164) amino acid at N-terminal region termed the B-upstream segment,and this is absent in PR-A.And any mutations of amino acids in B-upstream segment lead to loss of PRB specific gene regulation activity. Normally in human tissues, PR-A and PR-B are as a rule present at same levels but impairment of this ratio regulation lead to tissue abnormalities like that occur in breast cancers [7].

Like estrogen progesterone receptors has genomic and non -genomic activities as shown in **Figure 2**.

2.3 Androgen receptors

Androgen is one of steroid hormone nuclear receptor family. The location of androgen receptors is on the X chromosome. And these receptors composed of 3 functional domains: the ligand binding domain, the DNA binding domain, and N-terminal transcriptional regulation domain (**Figure 3**).

The DBD is the most highly protected part among the various types of the steroid hormone receptors in the nucleus,while the N-terminal domain in androgen receptor is the mostly changeable. And due to the highly protected quality of DNA binding domain among steroid hormone receptors (nuclear receptors), and having selective androgen response elements, this will result in particular activation of the androgen receptors.

Figure 3.
Functional domains of the androgen receptor (AR): N-terminal domain, DNA binding domain (DBD), ligand binding domain. AF-1 – Transcriptional activating function 1. AF-2 – Transcriptional activating function 2. H – Hinge region. NLS –nuclear localization signal. NES – Nuclear export signal.

The dihydrotestosterone bind to the androgen receptors with a twofold and more affinity with less dissociation of about fivefold in comparison with testosterone.

Like estrogen and progesterone there are 2 ways of ligand-dependent androgen receptors action, DNA dependent (genomic) and DNA independent (non-genomic) binding (**Figure 4**).

The androgens have a crucial biological effects on, muscle, bone, adipose tissue,prostate, neural, cardiovascular, haemopoietic,immune, and the reproductive systems [8].

The biological effects of the AR mutation lead to insensitivity of receptors to androgens in men, resulting feminization of external genitalia of the male (XY female) [9].

Studies in animals with AR deficiency have shown that androgenic signaling is associated with a greater number of women with premature ovarian senility, associated with follicular atresia. Subsequent analysis of AR-free mice showed defects in lutenization of the ovarian follicle [10–12].

As a result of the development of the reproductive system, androgens (especially testosterone and 5α-dehydrotestosterone), induces and maintain secondary sexual characteristics, stimulate male reproductive activity and assist in the production of the sperms. The prostate epithelium is also sensitive for androgen, and androgen signaling is necessary to maintain cell homeostasis in the adult prostate. As the apoptosis in epithelial cells affects the prostate, can be altered by the supplementation of androgens [13].

A predictive model of AR in the prostate showed that strategic paracrine signals control the proliferation of epithelial cells [14].

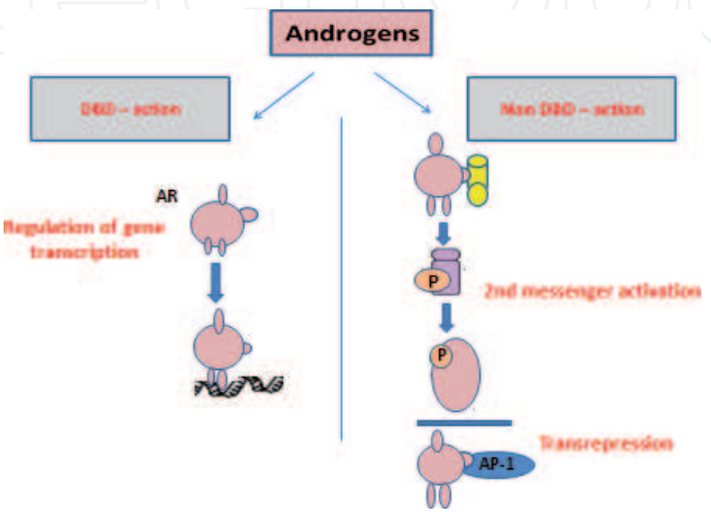

Figure 4.
Mechanisms of ligand-dependent androgen receptor (AR) action.

The effect of AR on the prostate pro-survival, plays a vital role in the pathogenesis of the prostatic cancers. It has been shown 75 years ago that prostate cancer regeneration occurs due to androgen deprivation after castration [15].

In many ways, this is due to the transport of androgens to the prostate, which are involved in metabolism, in the formation of the cell cycle and in the control of growth factors signaling [16].

In addition, the epithelial AR signal is correlated with an 'infection' in the prostate, which is independent of the parasitic AR signal in the stroma. AR increases VEGF-related angiogenesis and increases prostate growth, therefore, AR is an important treatment for prostate cancer. AR signaling has been shown to cause cancers in other organs, including breast, bladder, pancreas, ovary and endometrium [17, 18].

3. The biological effects of sex steroids

Although estradiol and progesterone levels vary during menstruation, estrogen and progesterone levels are always higher in women than in men [1] (**Table 1**).

Estradiol and progesterone have many effects depend on its relation to the venereal system. All steroid hormones have a great effect on the ovaries, fallopian tubes, uterus, external genitalia, hypothalamus and pituitary gland. Estrogen, progesterone and androgen, have significant effects on non-reproductive tissues [1].

3.1 Cardiovascular system

A significant lower risk of CVD has shown in premenopausal women than men and postmenopausal women. Estrogen support the vasodilation effect through relaxation of smooth muscle via increases the production of nitric oxide, which helps maintain low platelet activity, and the angiogenesis is stimulated by estrogen production.

Variation in the epidemiology, incidence and sequel of cardiovascular diseases in both sexes indicate changes in susceptibility to hereditary cardiovascular diseases that can result from several factors. In other cases, gender differences are important in expression of genes (especially X-chromosome genes), incidence of heart disease,as explained previously at the same age, cardiovascular disease is more common in men than in women [19].

Gonadal steroids	Normal range, conventional units
Estradiol	Women, basal 20–60 pg./mL Women, ovulatory surge >200 pg./mL Men <50 pg./mL
Progesterone	Women, luteal phase 2–20 ng/mL Women, follicular phase <2 ng/mL Men <2 ng/mL
Dihydrotestosterone	Women 0.05–0.3 ng/mL Men 0.25–0.75 ng/mL
Testosterone	Women <1 ng/mL Men 3–10 ng/mL

Table 1.
Normal ranges of sex steroid in male and female.

Therefore, it has been suggested that variation in sex steroid hormones have the key role on cardiovascular pathophysiology. Androgens and estrogens are mainly male and female sex hormones respectively, they are found in different levels and with different biological effects in the body in men and women.

Unlike androgens, which are dangerous due to the risk of heart disease and atherosclerosis, estrogens have a protective effect. In fact, a decrease in plasma Estrogen and elevated androgen is associated with an increase in cardiovascular disease in men and women during their menopause time (average age of menopause is between 51 and 52 years). This indicates an enhancing risk of getting cardiovascular disease in postmenopausal women and also in women who have developing hyperandrogenism [20, 21].

3.1.1 Characteristics of the action of sex hormones on the cardiovascular system, development of atherosclerosis and coagulation

Due to their metabolic and vasoactive properties, sex hormones directly or indirectly affect cardiac function through genomic and non-genomic mechanisms [22–24].

This effect is mainly depend on the receptors, such as estrogen/testosterone are found in different cardiac cells in humans and animals.

The contractions of the vascular walls was same in male rats (in normal and castrated), but it more evident in female with removed ovaries, indicating specific differences in vascular tone with estrogen in both sexes [25, 26].

3.1.1.1 Oestrogenic effects

Estrogen affects vascular function through genomic and non-genomic mechanisms [27–29].

In fact, administration of estrogen in vivo leads to vascular dilatation that occurs 5 to 20 minutes after ingestion and is not associated with any change in gene expression. The responses shown to be sex-related. In this regard, intracoronary, administration of estradiol increases coronary blood flow in women, but has not been demonstrated in male with coronary diseases [30].

Acute vasodilation effect of estrogen is endorsed by endothelial related and unrelated mechanism. The properties related to estrogen retention and transport of secondary ions (antagonist action of this hormone on ca^{2+}), while the endothelial related mechanism are highly dependent on the types of endothelial cells associated with the active estrogen receptor (EPs) by the activity of endothelial nitric oxide.

In addition, effect of 17β-estradiol on endothelial, NO synthesis and releases has been suggested to be happen through ER alpha activation [31, 32], while ER-β shows stronger role in the non-genomic effects of estrogen include changes in blood vessels. The expression of extracellular genes and proteins is initiated by two different nuclear ER (α and β) [27–29].

Both ERα and ER β have significant physiological effects on blood vessels. Animal studies have shown that ERα protects against vascular damage and atherosclerosis [33, 34].

ER- also controlled genes are involved in the regulation of blood volume and blood pressure [35, 36].

Since the expression of sex hormone receptors may vary with sex, and type of gonad, so the sex-related changes in vascular response may be related to specific receptor density in vascular tissue, why do women have more ER than in men [37]

in addition, although this activity is low in postmenopausal women, ER intensity decreases dramatically in women with cardiovascular and cerebrovascular disease.

These data may indicate a decrease in the protective effect of estrogen in women who have deprive from it for a long time. In fact, estrogen's effects on endothelial function depend on duration from starting menopause rather than chronological age of the menopause [38, 39].

In general, estrogen dilates the systemic arteries [24, 27], improves the coronary artery and peripheral endothelial function, prevents coronary artery spasm and reduces endothelial secretion in women with coronary heart disease [27, 28, 40–42].

Estrogen also affects blood vessels in men. Previous studies have shown that defective mutations in estrogen synthesis or receptor expression are associated with vascular endothelial dysfunction and atherosclerosis [43, 44].

Male estrogen levels are depend on androgen production. Almost 80% of plasma 17-estradiol in men formed from testosterone aromatization and androstendione into estrogen. In addition, estradiol is produced directly in male blood vessels, where it stimulates ERs of endothelial smooth muscle cells. It has been noted that aromatase deficiency and endothelial dysfunction in men with atherosclerosis, low dose of estrogen improves endothelial function [45, 46].

Furthermore, endothelial dysfunction occurs in normal men who receive aromatase inhibitors [23, 47, 48].

Sex hormones can affect the level of vasomotor tones, altering different responses to vascular factors, such as norepinephrine, angiotensin II (AII) or aldosterone. In fact, norepinephrine less likely to cause constriction of blood vessels in women, than men.

Endogenous estrogen helps in control of blood pressure in premenopausal women due to its vasodilation effect. High blood pressure in women occurs after about ten years and is higher in older women than in men at the same age [49–51].

Human and animal studies have shown that atherosclerosis affected by gender. Many animal models with atherosclerosis cause early and more severe symptoms, regardless of male or female fat and hypertension.

Estrogen and androgen motivate metabolic, hemodynamic and humeral effect which affect in turn the CV profile. In addition, these hormones can directly affect the development of atheromas through various blood stimuli. In women, the loss of estrogen (menopause or after surgery) is associated with hardening of the arteries. When estrogen/hormone therapy is started immediately after menopause, the severity of atherosclerosis decreases [52, 53].

HRT starts in younger women (50–59 years) lead to a low rate of cardiovascular event and lower mortality within 10 years after menopause [54, 55].

For this reason, there is sometimes a balance between the positive and negative effects of exogenous estrogen on blood vessels. The use of hormone replacement therapy prevents hardening of the arteries. Before the appearance of atherosclerosis, only when hormones are started before the advancing atherosclerosis over time after menopause. The current concept is that there is a 'window of opportunity' in the peri-menopausal or early postmenopausal years through which the taking of hormonal replacement therapy might reduce the diseases and fatality from cardiovascular diseases by preventing the formation of atheroma [20, 24, 56, 57].

The significant effects of estrogen can only be achieved with oral medicines that are caused by first liver passages of hormones, that stimulate enzyme activity in the organs. In some patients, antithrombin III decreases, factor VII and X are dose dependent increase [58].

3.1.1.2 Mediated Effects of testosterone

The function of the endothelium derived NO in testosterone induced vasodilation is unclear in many studies. Inhibitors of NO synthesis and endothelium-denuded tissue are used in some studies and have suggested a partial contribution, while other studies did not link the role of NO to vasodilation induced by testosterone [59, 60, 61]. Testosterone-induced, an endothelium independent relaxation,not related to gender, and not mediated by hormonal receptor but appear to include the opening of K + channels and L-type calcium channel block [62, 63].

There is a difference in the amount of estrogen in the expression of androgen receptors in the blood stream, which indicates the density of different types of receptors in men, proposing sex linked response to androgen [23, 24, 59, 64].

Although the effects of testosterone in men are not fully understood, the effects of androgens in women are less clear, but appear to be related to estrogen levels. In woman changing her sex rule to male (transsexual) who receive long-lasting testosterone, same plasma concentration is obtained. The diameter of brachial arteries is larger with impaired nitrate induced vasodilation, Nonetheless, the shape and pattern are similar to that in female at the same age. In postmenopausal women treated with estrogen, blood testosterone is about five times increase in concentration than normal levels with improved vasodilation [65, 66]. Testosterone has an estrogen-like effect in women [67] and, in place of estrogen levels, the estradiol/testosterone ratio plays an important role in the androgenic effects of women with atherosclerosis.

Negative correlations have been found between levels of free testosterone and coronary heart disease in men undergoing coronary angiography [68, 69]. In addition, low androgen levels have been reported in men who have larger intima media thickness.

Potential androgenic effects in women are assessed based on observations from women with serious medical conditions, such as PCOS. Women with PCOS suffer from heart disease and atherosclerosis due to high testosterone levels, and elevated risk of having myocardial infarction (MI), a risk factor was used on (33) females have PCOS, and (132) with same age normal females. The risk factor sample was determined from independent risk factors for MI in a prospective population study of (1462) females done in Göteborg, Sweden, the factors were age, diagnosed hypertension, and diabetes mellitus, increased waist/hip circumference ratio (central obesity), serum level of triglyceride. A frequently elevated risk (relative risk of 7.4) of having MI was seen for females with poly cystic ovary syndrome in compression to the normal females with same age [70].

3.2 Lipid metabolism and sex hormones

Sex hormones can directly or indirectly affecting the lipid profile, lipoprotein, HDL, LDL, and triglycerides, the last two are important in development of CVD. This is mainly due to the impaired production of estrogen [71, 72]. Estrogen stimulates lower triglyceride levels, synthesis of HDL and apoliporotein A-I in the liver. It also improve reversion of transport of cholesterol. As a result, these hormones reduce total cholesterol levels and LDLc levels too, levels of triglycerides and it increases the levels of HDL. Testosterone can affect fat metabolism due to its specific androgenic effects and the role as aromatization substrate to Estradiol (E2).

Elevated plasma testosterone levels are believed to influence the profile of lipoproteins, and cardiovascular disease is more common in both sexes. Male data show that plasma testosterone levels correlate positively with HDL-c serum levels

and negatively related to triglycerides, LDL, total cholesterol, fibrinogen and PAI-1 [59, 73–75].

Several studies show that the overall effect on fat metabolism is part of the unexplained effects on excess weight and insulin resistance but clinical studies have shown that testosterone treatment do not affect HDL cholesterol in older men. The positive effects of these properties have the necessary effect [76]. The effect of testosterone therapy on female lipid profile (mainly by lowering HDL cholesterol) depends on the level of estrogen and therefore estradiol/testosterone ratio. However, HDL-c deficiency is androgenic. The reduction in HDL-c should not be assumed as a direct pro-atherogenic risk factor because it can exhibit a reduction in sub fraction of HDL3 and therefore is not associated with a significant reduction in cholesterol transport [77].

3.3 Obesity

Gender differences in body fat distribution are related to sex hormones. Although androgens have been linked to the formation of abdominal fat,. Android's fat distribution is associated with androgen deficiency [78]. The distribution and amount of female fat is related to ovarian function. During menstruation, women gain weight, fat is distributed is gynoid, with peripheral obesity, while in menopause is in the middle (abdomen) [79–81].

In both genders, high abdominal circumference or waist/hip ratio are markers of android's fat distribution which are associated independently with insulin resistance, serum triglycerides, low-density lipoprotein cholesterol, hypertension and increase in sympathetic drive, in addition to participating in the negative metabolic changes mentioned above, also affect hormonal metabolism due to the lack of sex hormones [82, 83].

Male testosterone supplements are designed to reduce belly fat, stimulate lipolysis and thus reduce fat accumulation. Testosterone also has beneficial effects on metabolic parameters, such as glucose and lipid metabolism, therefore, hormone replacement therapy causes weight gain in women and prevents the spread of menopausal pattern body fat. The exact mechanism of this effect is not generally known [84–87].

3.4 The effect of sex hormones on bone regeneration and resorption

Deficiency of the hormone estrogen (E2) causes osteoporosis in postmenopausal women and helps to promote osteoporosis in older men. As E2 deficiency result in enhancement in the number of osteoclast cells (OC), and at the same time there is reduction in apoptosis of these cells and also increases their activity [88–90]. Sincethe formation of osteoblasts, including functional estrogen receptors (see **Figure 5**).

In 1988, the understanding of the molecular basis for estrogen activity has been rapid, but fragmented and incomplete. The importance of metabolism is centered on the specific role of cytokines: IL-1, IL6, TNF-A, granulocytes, macrophage stimulating factor (M-CSF) and prostaglandin E2 (PGE2) these substances Increase in OC volume and their activity in bone marrow [91].

An elegant study by Cenci et al [92], reported that production of TNF-α by T-cells increase bone resorption in overiectomized (OVX) mice.

The authors raised the hypothesis that in overiectomized animals bone loss can be inhibited by giving either E2, TNF-a binding protein, or by inhibiting the antibodies that is specific to the TNFa.

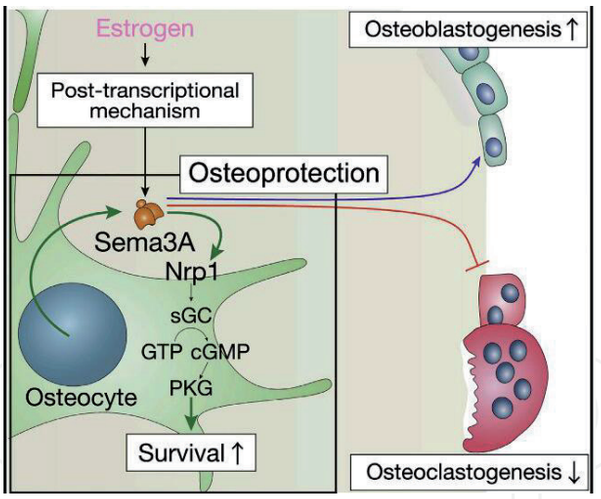

Figure 5.
Biological effect of estrogen on the bone.

T cell deficient OVX mice increase TNF-a production in T cells, which can increase the number of T cells instead of TNF. In this case, the tumor necrosis factor-α is not controlled by bone marrow monocytes. It increases the production of RANKL depending OC, augmenting M-CSF. TNF-a has a direct effect on OC precursors.

Estradiol B (E2) alters the bone protective effects of men and women, reducing the estrogen signal, especially in bone cells. ER A is needed to convert bone cells into bone marrow. However, the formation of osteocytes that require estrogen is difficult [93].

3.5 Sex hormones role in skin

Estrogen and progesterone, makes the skin healthy and soft and maintains the natural thickness of dermis and epidermis. Estrogen motivate, multiplies and prevent apoptotic keratinocytes. When estrogen increase collagen synthesis in the skin, progesterone inhibits matrix metalloproteases and together with estrogen decrease breaking down of collagen. Estrogen increases the production and accumulation of glycosaminoglucan in the dermis. Estrogen also promotes healing of wounds.

Several studies have shown that estrogen has an important protective function and is beneficial for skin physiology [94–96].

They have been shown to accelerate the healing of skin lesions [97]. Most women recover from inflammatory skin conditions, such as psoriasis, during pregnancy, also estrogen, shows some protective effect to photo aging of skin [98–105].

3.6 Effect of sex hormones on the uro-genital tract

The urogenital tract of females developed initially from the primitive urogenital sinuses at the 4th week of intrauterine life. The estrogen receptor is located in both systems, and their levels fluctuating in the circulation.

During the menstruation, the symptoms are vary, and mainly developed in pregnancy or after menopause, when there is genital atrophy, lower urinary tract and vaginal symptoms are frequently reported. Nonetheless, aging may affect these changes. Which result in difficulty to prove the causation [106].

3.6.1 Pathophysiology

Estrogen receptors are steadily presented in the squamous epithelia of vagina and urethra in addition to the bladder-trigone in areas with metaplasia [107, 108].

However, they are not found in the epithelium of the transitional dome of the bladder, which clearly reflects the germinating roots of this tissue. The pelvic floor is also under effect of estrogens [109, 110]. In woman lower urinary tract, Estrogen raise the activity of cell cycle [111], and there is increment in the number of superficial and intermediate cells, the changes are similar to vaginal changes in postmenopausal women [112–114].

During menstruating, changes in cytology of urinary tract are almost identical with that in vaginal cytology [115]. Changes also occur in sediment after estrogen therapy [116]. Frequent changes in urinary symptoms during menstruation can be detected by the urethral pressure profilometry (UPP) [117].

The functional, anatomical, and physiological length of the urethra increases with mid menstruation and earlier luteal phase, indicating changes in serum concentration of estrogen. Changes also occur during pregnancy [118, 119], which sanctifies a relative increase in urinary out-put and gravid uterus pressure.

A recent article by the University of London School of Medicine suggested possibility of influencing hormones on bladder that mediated by progesterone [120]. Progesterone receptors are expressed in the lower urinary tract and may be associated with estrogenic status in women. Androgen receptors are found in the bladder and urinary tract of women, but their function is currently unknown [108, 121].

3.6.1.1 Estrogen and urinary incontinence

In women, during menopause are usually complaining of frequent symptoms in the urinary system. The most common are frequent micturition, bed wetting, stress and urge incontinence, they may also experience urinary tract infection and vaginal symptoms, such as itching or dryness. The specific diagnosis of the underlying pathology is based on a comprehensive clinical study and the study of urodynamic. There are many causes for urinary incontinence; these include bladder dysfunction, instability with constipation, excessive urination, fistula (between vagina and the bladder, or between vagina and ureter or with urethra) or due to diverticulum or immobility.

The causes of transient enuresis in the elderly include urinary tract infections, estrogen deficiency, restricted mobility, medications, and depression. The two most common symptoms are stress and\ or urge incontinence.

Urinary tract and pelvic tissues are sensitive to estrogen, as it play an important role in the storage mechanism. For a woman to be on the continent, the pressure of the urethra must be greater than that of the bladder. The urethra consists of four functional layers sensitive to estrogen that are involved in maintaining positive pressure, by its effect on epithelium, blood vessels, muscles and connective tissues [122].

Extracellular changes in the urinary epithelial layer have been reported in response to estrogen. There is some evidence that estrogen affects the blood vessels in the system, and can treat urinary incontinence in women by hypersensitivity to the alpha-adrenergic receptors of the ureteral smooth muscles, stimulation of collagen production around the urinary tract, increased sensitivity of the bladder, increased pressure in the urethra [123, 124].

3.6.1.2 Estrogen to prevent and treatment of enuresis

Although less research is done, the role of estrogen in the treatment of enuresis is controversial. Some have shown reliable results, but this may be due to different estrogens, different doses, and instructions over the duration. This disease is more difficult to treat. There are now two methods of meta-analysis to clarify the situation. It was the first report by the Hormones and Urogenital Therapy (HUT) Committee.

The use of estrogen has been discussed to treat all causes of enuresis in postmenopausal women [125].

Of the 166 articles in English published between 1969 and 1992, only six were considered, but this was not the case. The results showed that real stress is a major psychological development for all patients with urinary incontinence. However, the analysis of the target parameters showed no change in urine volume. The maximum pressure to close the urethra increases, but only one test significantly affects the result. In the second meta-analysis [126], potentially controlled cases and 14 indirect studies related to estrogen therapy were considered. They also found that estrogen therapy does not relieve stress, but it can help with sudden and recurring symptoms. This method can be useful for women with low stress or who need surgery. Estrogen to prevent rapid urination, and has been used to treat menopause for many years, but several controlled studies have shown its benefits. A combination of estradiol (2 mg) and 1 mg estriol (Imagine Daily) reduced urinary retention in 7 of 11 women, compared with 1 in 10 in the placebo group [127, 128].

3.6.1.3 Estrogen for urinary tract infections

Changes in urine production in women after childbirth increase the risk of developing UTI in women, especially during intercourse. The pH of the vagina increases and the number of lactobacilli decreases, that is colonization induces Gram-negative bacteria that play a pathogenic role in urine. In response to these changes, estrogen can be used for treatment or prophylaxis, which can occur in adult women with recurrent steroid intake [129].

3.7 Effects of testosterone on erythropoietin (EPO) and on muscle

High levels of testosterone, important for hemoglobin and hematocrit and stimulate EPO and reduction of cellular exhaustion. Testosterone increases iron absorption by red blood cells, stimulates EPO and restores EPO-bound hemoglobin [130].

As a large amount of DNA accumulates in adult muscles after birth and is made up of dependent cells, satellite cells, which are an important area for controlling muscle growth, and protein regulation in muscle fibers. Testosterone is a blood transporter that binds directly to muscles and therefore increases protein [131].

3.8 Sex hormones and brain

Estrogen is involved in many processes throughout life. Minds of men and women. For example, neurological developmental and synaptic changes resulting in sexual behavioral differentiation [132, 133].

Progesterone is important for synthesis of neurosteroid, and estrogen regulates rapid and prolonged neuroplastic processes in the central nervous system, including synaptic-cyclical changes [134, 135].

Estrogen affects many neurological functions and behaviors, such as mood, cognitive function, blood pressure regulation, motor coordination, pain and sensitivity to opioids. Many of these characteristics have small gender differences that lead to uncertainties about hormones and genetic factors, including the mitochondrial genome [136].

Brain aging is often associated with many diseases of the nervous system resulting from disorders in the workplace. Recent evidence suggests that estrogen replacement therapy may reduce the risk of degenerative diseases such as Alzheimer's disease and cognitive decline in women [137–139].

Estrogen is the broadest group of drugs used to prevent Alzheimer's disease (AD). These steroids are powerful neurotransmitters in vitro and in vivo and have been shown to have similar effects in preventing attention deficit disorder. This includes suppression of the amyloid expression of the pro-amyloid protein (A), Epidemiological evidence supports the use of estrogen to lower the stress at the beginning of menopause and treatment of Alzheimer's disease [140].

Epidemiological studies have shown that women are 1.5 to 2 times Lower than men to develop Parkinson's disease (PD), indicating a protective effect of estrogen. Experimental data show that estradiol has a protective effect on neurons and dopaminergic proteins. Studies have shown that higher levels of estrogen are associated with fewer symptoms of Parkinson's disease and an increased risk of Parkinson's disease in postmenopausal women. These data indicate that estrogen may have a protective effect on dopaminergic neurons [141].

3.8.1 Neuromprotective effect of estrogen

Obviously, estrogen has other functions, such as stimulating nerve cells and protecting them from stimuli caused by other diseases, such as seizures, stroke and Alzheimer's [142, 143].

The exact role of cellular nuclear ERs detected on inhibitory effect between neurons is unclear, but one key is the function of E2 to enhance neuropeptide Y (NPY) expressing and releasing, because NPY has antiexcitatory actions [144, 145].

The second fact that E2 is neuroprotective its function is translocate ER-β to mitochondria, in addition its ability to sequestrate mitochondrial Ca^{2+} ion, including Bcl-2 translocation [146].

Studies on estrogen's ability to prevent stroke and fight Alzheimer's and Parkinson's disease have shown that the brain can produce estrogen and possibly cholesterol [147, 148]. Like E2, androgens have a protective effect on nerve cells, the pyramidal neurons are an important type of CA1 AR nucleus. In men, nuclear ARAS may play an important role in the development of spinal synapses, not in NMDA, but in cholinergic activity [149–151].

3.8.2 The behavioral effects of sex hormones

Genital steroids affect children's brains, especially the hypothalamus, and cause gender differences. The differences in behavior between men and women are related to the sexual ability of the three families of steroid hormones (estrogen, androgen and progesterone) in the nervous system. The classic family of receptors is associated with elements that act as transcription factors after the breakdown of layers, nuclear translation and hormonal effects of DNA [152]. Gender differences in the brain are usually anatomical, neurochemical or molecular.

The neurochemical change in sex occurs at the level of neurotransmitters, enzymes or local hormones. Molecular changes in sex, gene expression and

epigenetic changes in phase signaling occur with any gender difference in the hypothalamus regulated by the regulatory effects of estradiol.

Estrogen has long been known to have a psychoactive effect. Therefore, it is believed that the inappropriate metabolism of estradiol may play a role in the development of mental illness. Differences in brain area, size, cell number or radiation intensity (for example, differences in cell size, neural complexity or morphology, dendritic cell length and number of contacts) [153].

3.9 The effect of sex hormones on the immune system

The role of estrogen in the negotiations between the internal system and the immune system was described about 15 years ago [154, 155].

Estrogen effects: macrophages, CD8 + lymphocytes and ERF3 B lymphocyte rings are also expressed in lymphoid tissue and can be membranes linked to the receptor. Estrogen and anti-estrogen binding sites (AEBS) are also found in lymphocytes [156, 157].

Regarding cytokines: TNF levels in endotoxin coatings increase significantly with estrogen, while levels of IL-6 (due to ethylene 17 in the blood) decrease [158, 159]. Active ER stimulates nuclear transcription factors and maintains NF-IL6, NF-ICB and C/EBPf3 [160, 161].

Physiological levels of estradiol in cultured human cells significantly increase the activity of the IL-1 receptor antagonist (mRNA) but it suppressed by higher estradiol concentrations [162]. Estradiol 17F3 produces IL-5 mRNA in vitro [163]. Estradiol and glucocorticoids activate secretory substances that prevent leukemia, sagging and overuse in humans [164].

And in uterus the uterine epithelial cells stimulate antigen secretion and preserve uterine E2 cells [165].

In adults, the activity of natural killer cells increases after in vitro treatment with 17G3-estradiol [166]. Estradiol increases the sensitivity of natural human prostate killer cells in classic ER [167, 168]. Cytotoxic activity of estrogen-dependent CD4 + cells [169].

The chemotactic activity of human polymorphonuclear leukocytes is greatly reduced due to the physiological concentration of estradiol (10-IOM) [170].

In short, antiestrogens act on specific estrogen receptors and lymphocytes when they affect the nervous and endocrine systems and on target cells, or tissues in the transplant system.

As the nervous system and the immune system produce a regulatory response, immune changes cause changes in the nerves and vice versa. This is a phrase was made possible by for example, the thymus is an organ that produces the steroid hormone. In addition, the immune system can convert steroid precursors into active hormones [171].

Steroid hormones are the ones that most control the immune system, as they can control signaling at the level of nuclear transcription factors [172]. However, it is not clear whether estrogen is necessary for the normal functioning of the immune system or if its effect on primary levels of estrogen in the regulation of the vaccine varies. We are not aware of the potential differences between the different steroids and estrogen receptors in the immune system. Estrogen regulates immune function differently in men and women [170–176].

Estrogen is important for building the body's immune system against viral infections. Stabilization of the cytokine storm has been shown to control and mediate immunological changes against the influenza virus and pneumonia. Due to the effects of estrogen, SARS-CoV-2 is lower in women than in men. Some believe that SARS-CoV-2 cause stress in the endoplasmic reticulum (ER), which inturn aggreviate the infection.

This problem can controlled by estrogen as it cause degradation of phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol triphosphate (IP3). IP3 in-fluxing Ca + 2 ions and helps activate UPR (unfolded protein responce). Data from 392 patients were analyzed and found that 26% of females and 74% of men were affected by SARS-CoV-2. It indicated that women are less affected due to the possible effect of E2 hormone in females [177].

4. Summary

Sex steroids roles have not limited to their reproductive function, but their roles are also shown to be extend to a lot off effects on other body systems including cardiovascular, neural, musculoskeletal, adipose tissue, dermatological, immune, and haemopoietic systems, The sex hormones include the androgens, estrogens, and progestogens, their effects are exert by either slow (genomic process) via nuclear receptors, or by rapid non-genomic process through membrane related receptors and signal cascades.

Androgens and oestrogens impact biology of the blood vessels, predominantly in a sex specific way. And this effect is a cardioprotective, while oestrogens having benefit effect in both males and females, but the effect of androgens different in the two genders. As the effect of testosterone in females rely on the estrogen levels and thereby on estradiol to testosterone ratio. Estrogens and androgens exert potent influences on the post-natal building of muscles and bones and important for their sexual dimorphism, these 2 hormones also vital for the homeostasis of both tissue in addition to the skin, adipose tissues, and regulation of body weight through adulthood, as well as integrity and function of female genitourinary system (specially the estrogen).

The nervous system is a target for effect of sex hormones. Estrogens, progestins, and androgens, all effect the function and physiology of the brain,these steroids are powerful neurotransmitters in vitro and in vivo and have been shown to have similar effects in preventing attention deficit disorder. Experimental data show that estradiol has a protective effect on neurons and dopaminergic proteins. Sex hormones also play a vital role as modulators of the immune system, as the sex steroids and immunity are closely connected, and their mutual regulation is involved in the maintenance of immune balance.

5. Conclusion

The sex steroid are considers balance of the functions and protection of the body systems, and can use for prevention and treatment of many systemic disorders, and the possibility of applying of their effects on the incidence of many organic and infectious diseases.

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