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Title:

Effect of Estrogen in Autoimmune Diseases

A graduation research project

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

(يَرْفَعِ ٱللَّهُ ٱلَّذِينَ ءَامَنُواْ مِنكُمْ وَٱلَّذِينَ أُوتُواْ ٱلْعِلْمَ دَرَجَـٰتٍ)

الآيه (١١) المجادلة

صـدق الله العلي العظيـم

Dedication

To those who, after God, were the reason for my arrival to this day, to my mother and father, thank you for your sacrifices and support.

Thanks and gratitude

To all the professors at the College of Dentistry / University of Maysan, especially the one who supervised our research, this respected **Dr. Khaled Jabbar** We thank you all because you Nere sincere, dedicated, and generous with your giving. You have embodied the spirit of the virtuous teacher and have become an example to follow to all those who stood by us and supported us, we will remain grateful to you as long as we live, because you were quick to do good, and we find no reward for your benevolence except reciprocation with benevolence.

List of Content

Introduction

Autoimmune diseases are a diverse group of conditions characterized by immune disturbances that cause aberrant B cell and T cell reactivity to normal constituents of the host. These diseases can involve essentially any organ system and affect individuals of any age, with a much greater prevalence among women (Piestsky, 2023)

Studies have found increased frequencies of autoimmunity and autoimmune diseases over recent decades (Batch, 2003).

The precise mechanisms for the development of autoimmunity and autoimmune diseases remain unclear, however, a growing consensus has developed that they evolve from still-to-be-defined gene-environment interactions (Leo et al, 2010).

With the advent of personalized medicine with growing utilization of gene-based diagnostic technologies and biological drugs, it is imperative for the astute clinician to be informed of new developments in our understanding of the pathogenesis of autoimmune (Liu and Peri, 2020)

The Aim of Study

To find out influence of estrogen on autoimmune disease

Review

An immune system is a complex network of special cells and organs that defend the body from pathogens, such as viruses, bacteria, and parasites, and keeps us in a healthy state. The immune system has a unique ability to differentiate between self and non-self, i.e., it destroys the non-self-proteins without attacking body's own (self) proteins. However, autoimmunity occurs to some degree in all individuals. When the immune system fails to differentiate between 'self' and 'non self', it can attack body's own proteins, thereby causing autoimmune disorders. (Shubha, 2015)

Disorder of immune system

Immune system disorder, any of various failures in the body's defense mechanisms against infectious organisms. Disorders of immunity include immune deficiency diseases, such as AIDS, that arise because of a diminution of some aspect of the immune response. Other types of immune disorders, such as allergies and autoimmune disorders, are caused when the body develops an inappropriate response to a substance—either to a normally harmless foreign substance found in the environment, in the case of allergies, or to a component of the body, in the case of autoimmune diseases. Lymphocytes (white blood cells of the immune system) can become cancerous and give rise to tumours called leukemias, lymphomas, and myelomas.(John and Samuel, 2016)

Immune deficiencies

Immune deficiency disorders result from defects that occur in immune mechanisms. The defects arise in the components of the immune system, such as the white blood cells involved in immune responses (T and B lymphocytes and scavenger cells) and the complement proteins, for a number of reasons. Some deficiencies are hereditary and result from genetic mutations that are passed from parent to child. Others are caused by developmental defects that occur in the womb. In some cases immune deficiencies result from damage inflicted by infectious agents. In others drugs used to treat certain conditions, or even the diseases themselves, can depress the immune system. Poor nutrition also can undermine the immune system. Limited contact with natural environmental factors, particularly with microorganisms found in biodiverse settings, also has been associated with increased risk of allergies, autoimmune disorders, and chronic inflammatory diseases. (John and Samuel, 2016)

What can go wrong with your immune system?

When your immune system doesn't work the way it should, it is called an immune system disorder. You may:

• Be born with a weak immune system. This is called primary immune deficiency.

• Get a disease that weakens your immune system. This is called acquired immune deficiency.

• Have an immune system that is too active. This may happen with an allergic reaction.

• Have an immune system that turns against you. This is called autoimmune disease. (Dr. Joel, 2024)

Autoimmune Disease

Autoimmune diseases are a diverse group of conditions characterized by aberrant B cell and T cell reactivity to normal constituents of the host. These diseases occur widely and affect individuals of all ages, especially women. Among these diseases, the most prominent immunological manifestation is the production of autoantibodies, which provide valuable biomarkers for diagnosis, classification and disease activity. Although T cells have a key role in pathogenesis, they are technically more difficult to assay. (David, 2023)

Etiology

In most autoimmune diseases the cause of antibody formation is unknown Genetics and environmental factors such as toxins are among the possible triggers.

Genetic factors: There are genetic variants that predispose humans to multiple autoimmune diseases and secondly, multiple genes predispose humans to each disease. The major histocompatibility complex (MHC) is central in mediating inflammatory responses to pathogens. The unique coding or noncoding genetic variations of HLA alleles determine the antigenic responses to self- or non-self-antigens. One of the most common genetic associations with autoimmune disorders is the protein tyrosine phosphatase gene PTPN22 expressed in lymphocytes. The tryptophan allele within PTPN22 has been found in patients with many autoimmune disorders, including type 1 diabetes mellitus, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune thyroiditis.

Environmental factors: There are a host of environmental factors that trigger autoimmune disorders, including chemical toxicants, heavy metals, viruses, bacteria, emotional stress, and drugs, Smoking is a known risk for RA and recent studies have demonstrated that cigarette smoking may induce citrullination of proteins in pulmonary alveolar cells. This is an important finding because antibodies to citrullinated peptides are highly specific for RA as are the HLA associations that are related to the development of these autoantibodies. Infectious agents, including bacteria, viruses, fungi, and parasites, are also known to trigger autoimmune disorders through several mechanisms: molecular mimicry, epitope spreading, standard activation, viral persistence, polyclonal activation, dysregulation of immune homeostasis, and auto inflammatory activation of innate immunity. It

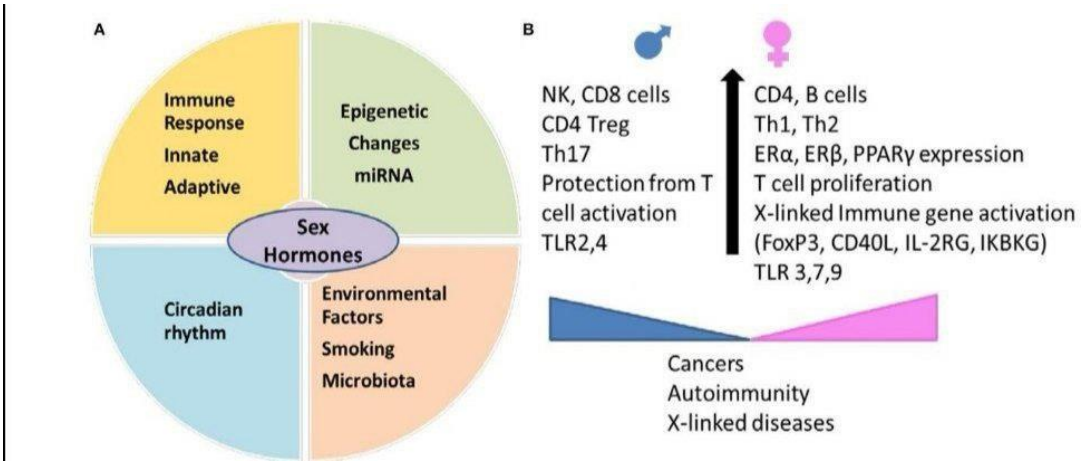
is important to note that an infection may not necessarily be the inducer but rather the total burden of infections from childhood on that trigger autoimmunity.

In general, autoimmune disease results from an interplay between a genetic predisposition and environmental factors. (Andrew, 2014)

The role of Hormones in pathogenesis of autoimmune diseases

Females and males differ in the energy consumption and nutritional requirements which are based on the interactions between environmental factors and sex hormones. The studies in early 1940s ascertained that females have enhanced capability of producing antibodies. This enhanced immune reactivity in females helps mount an effective resistance to infection and therefore females are less susceptible to viral infections, but can develop immune- pathogenic effects and predisposition to autoimmunity due to hyper immune responses. Sex hormones can also control the immune response via circadian rhythm. Many hormones like cortisol, known to regulate T cell mediated inflammation, have a circadian rhythm with a maximum peak at 8:00 a.m. and progressively lower levels as the day progresses. Interaction between sex hormones and environmental factors like cigarette smoke and infections lead to variable responses in both genders. There is emerging evidence that sex hormones impact microbial composition and the resulting immune response via secondary metabolites binding with receptors like estrogen receptors (ERs), peroxisome proliferator-activated receptors (PPARs) etc. These differences in immune response can lead to variability in disease phenotypes with autoimmunity occurring more often in females and cancers occurring more in males. (Veena, 2018)

Figure 1| Sex hormones interact with genetic and environmental factors and determine immunity



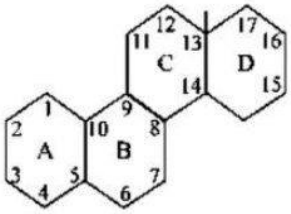
In an individual. (A) Environmental factors like smoking and gut microbiome generate sex-hormones dependent immunity leading to differences in circadian rhythm, innate and adaptive immune response and epigenetic changes between males and females. Sexual dimorphism between miRNA expressions contributes to sex-specific regulation of function in various tissues. (B) Sex determines expression of cell markers involved in innate and adaptive immunity. Females have higher expression of genes on X chromosome which include immune markers like regulatory marker FoxP3, CD40L. Females produce higher Th2 response and antibodies and better protection from infections but the hyperimmune response makes them susceptible to autoimmune diseases. Males generate more of Th17 response and are less likely to develop autoimmunity but have higher percent of non-reproductive cancers. miRNA, microRNA; TLR, Toll like receptor; ER, estrogen receptor; PPAR, peroxisome proliferator-activated receptor; IKBKG, inhibitor of nuclear factor kappa B kinase; IL2RG, interleukin receptor subunit gamma.

Estrogen

Is a steroid hormone associated with the female reproductive organs and is responsible for developing female sexual characteristics, and it's involved in numerous biological systems including the neuroendocrine, vascular, skeletal, and immune systems. Therefore, it is also implicated in many different diseases and conditions such as infertility, obesity, osteoporosis, endometriosis, and a variety of cancers. There are three major endogenous estrogens that have estrogenic hormonal activity: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Estradiol (E2) is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity during menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen in terms of serum levels while estetrol is produced only during pregnancy. Estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sexual characteristics, such as breasts, darkening and enlargement of nipples, and thickening of the endometrium and other aspects of regulating the menstrual cycle. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm and may be necessary for a healthy libido. Estradiol (E2) is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity. During menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen in terms of serum levels while estetrol is produced only during pregnancy. Estrogen works through its two distinct nuclear receptors, Estrogen Receptor alpha (ERα) and Estrogen Receptor beta (ERβ). (Lobo RA et al, 2016)

Structure of estrogen

Chemically, the estrogens are derivatives of a C18 hydrocarbon, estrange (figure 2)



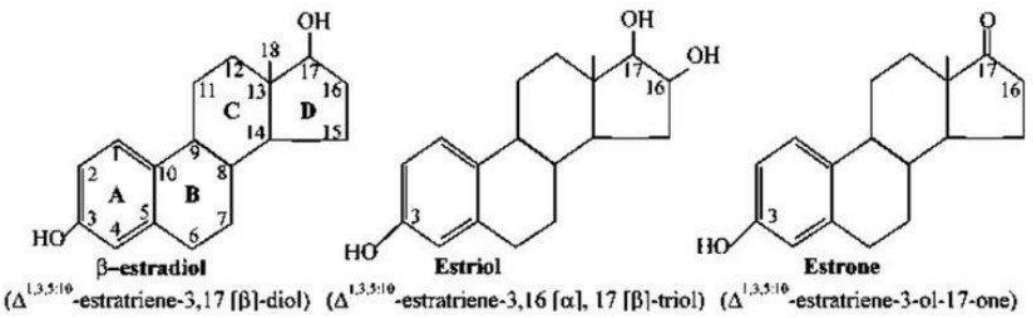
The three compounds of this group (figure 3) with hormonal activity are:

1. ß - estradiol (= dihydrotheelin), $C_{18}H_{24}O_2$

2. Estriol (theelol), C18H24O3,

3. Estrone (theelin), C18H22O2

Estrone is the first known member of the sex hormones and was Isolated by Adolf Butenandt and Doisy independently in 1929 from The urine of pregnant women. A year later, the estriol was isolated From human pregnancy urine by Marrian. Later, the estradiol was also isolated.



All these are characterized by the absence of a CH3 group at carbon 10 and by the aromatic nature of ring a making the OH group phenolic in character. Of all these, b - estradiol is most potent physiologically, estrone less potent and estriol is least active. Their relative potencies are 50: 5: 1 respectively. Although ovary is the chief source of esrognes, they are in smaller amounts also produced by the testis and the adrenal cortex. Estrogen production is highest when a woman is young and slows down with age, giving rise to menopausal symptoms. The symptoms vary with each women . By 40's, women enter perimenopause, when menstruation becomes less regular, skin becomes dryer, hair turn brittle and sparser; women may feel a loss of libido and may suffer fluctuations in mood. Menopause follows, on an average between 45 and 50 years of age. Heavy women have an advantage over the slim ones. Their fat cells manufacture a form of estrogen called estrone, even after estrogen from ovaries shuts off.(Satyanarayana and Chakra, 2013)(Jain, 2004)

Functions of estrogen in Women and Men

Estrogen has 400 functions in a woman's body, among which are that it:

• Stimulates the production of choline acetyltransferase, an enzyme that prevents Alzheimer's disease

• Increases metabolic rate

• Improves insulin sensitivity

• Regulates of body temperature

• Prevents of muscle damage

• Helps to maintain muscle

• Improves sleep

• Reduces the risk of cataracts

• Helping to maintain the elasticity of arteries

• Dilates small arteries

• Improves blood flow

• Inhibits platelet stickiness.

• Decreases accumulation of plaque on the arteries

• Enhances magnesium uptake and utilization

• Maintains the amount of collagen and the elasticity of the skin

• Decreases blood pressure.

• Decreases LDL cholesterol and prevents its oxidation.

• Helps maintain memory

• Increases reasoning and new ideas

• Helps with fine motor skills

• Increases the water content of the skin, and is responsible for its thickness and softness

• Enhances the production of nerve-growth factor

• Increases HDL by 10% to 15%

• Reduces the overall risk of heart disease by 40% to 50%

• Decreases lipoprotein (a)

• Acts as a natural calcium channel blocker to keep arteries open

• Enhances energy

• Improves mood and increases concentration

• Helps to maintain bone density

• Increases sexual interest

• Reduces homocysteine

• Decreases wrinkling

• Prevents macular degeneration

• Decreases the risk of colon cancer

• Helps prevent tooth loss

• Aids in the formation of neurotransmitters in the brain, for example serotonin, which decreases depression, irritability, anxiety, and pain sensitivity.(Gerabek, 2005)(Silbernagl et al, 2012)

In Men

The presence of estrogen in a man's body is extremely important, since they perform several important functions at once, including:

• ensuring that muscle mass gain is processed in the correct way

• Preservation of bone strength

• maintaining a stable nervous system and emotional state

• maintaining the correct metabolism.

• Prevention of the development of muscle and organ hypoxia even with strong physical exertion.

• Prevention of the development of diseases of the cardiovascular system.

• maintaining the normal appearance of the skin.

In men, estrogen in the form of estrone and estradiol is produced by the conversion of testosterone into the enzyme aromatase. Estradiol has a stronger affinity for estrogen receptors and is an isoform used in clinical practice.

The effects of estrogens on cognition and mood have been well documented. Indeed, estrogen receptors are densely concentrated in the structures of the brain that control cognitive and emotional functions. These include subcortical regions such as the hippocampus (memory) and amygdala (emotion), as well as several cortical regions involved in higher-order functioning.

Estrogens modulate neurotransmitters responsible for cognitive and emotional processes. For example, estrogens decrease sensitivity to dopamine receptors and increase the density of D2 receptors in the striatum of ovariectomized rats, and significantly increase serotonergic neurotransmission.

Estrogens appear to have a protective effect on neurodegenerative disorders characterized by major cognitive dysfunctions, including Parkinson's disease and Alzheimer's disease

The normal estrogen level that a man should have depends on his age and medical history. A fully grown male usually has an estradiol level of 10-40 picograms per milliliter (pg/ml) and an estrone level of 10-50 pg/ml.

Although the male body needs estrogen to function properly, high estrogen levels can cause health problems such as gynecomastia, or infertility.(Roth and Ivey, 2001)(Handa et al, 2012)

The role of estrogen in autoimmune diseases

Epidemiological evidence indicates that during the fertile period women are more often affected by rheumatic diseases than men, particularly autoimmune diseases. As a matter of fact, rheumatic disorders with autoimmune involve- ment such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) result from the combination of several predisposing factors, which include the relationships between epitopes of the trigger agent (i.e., virus) and histo- compatibility epitopes (i.e., human leukocyte antigen [HLA]), latitude effects, the status of the stress response system including the hypothalamic-pituitary- adrenocortical axis (HPA) and the sympathetic nervous system (SNS), and mainly the effects of the gonadal hormones (hypothalamic-pituitary-gonadal axis—HPG).

The pre- or postmenopausal serum sex hormonal status is a further factor influencing the rate of rheumatic diseases. It is therefore important, whenever possible, to evaluate epidemiologic data broken down into age (e.g., 10-year age band) and sex-specific group before making inferences. Obviously, sex hormones seem to play an important role as modulators of both disease onset and perpetuation and they show circadian rhythms together with cortisol. Sex hormones are implicated in the immune response, with estrogens as enhancers at least of humoral immunity and androgens and progesterone (and glucocorticoids) as natural immune-suppressors4, 5. Low concen- trations of gonadal and adrenal androgen [testosterone (T)/dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), respectively] levels, as well as reduced androgen/estrogen ratio, have been detected in serum and body fluids (i.e., blood, synovial fluid [SF], smears, saliva) of male and female RA patients, as well as in SLE, supporting the possible pathogenic role for the decreased levels of the immune-suppressive androgens.6 However, with respect to serum levels of estrogens, interestingly they are not significantly changed, which is in complete

contrast to androgen levels in RA patients (re- duced). Several physiological, pathological, and therapeutic conditions may change the serum estrogen milieu and/or peripheral conversion rate, including the men- strual cycle, pregnancy, postpartum period, menopause, being elderly, chronic stress, altered circadian rhythms (i.e., cortisol/melatonin), inflammatory cy- tokines, and use of corticosteroids, oral contraceptives, and steroid hormonal replacements, inducing altered androgen/estrogen ratios and related effects. Recently, it was shown that at physiological concentrations, 17-beta estradiol and a combination of downstream estrogens stabilized or increased immune stimuli–induced tumor necrosis factor (TNF) secretion.8 These effects are de- pendent on the presence of physiological concentrations of cortisol and are therefore related to its circadian rhythms.(Bijlsma and Janele, 2006)(Cutolo, 2005)

Women who have primary Sjogren's syndrome also have decreased lifetime exposure to estrogen, a new study has determined. In research published in a recent Arthritis Care & Research issue, investigators determined women who have lower estrogen levels and who have fewer years menstruating have a higher likelihood of developing primary Sjogren's.

Our findings suggest cumulative estrogen exposure may have a modulating effect on factors that predispose women to autoimmune disease," said study author Sara McCoy, M.D., a rheumatologist with the University of Wisconsin School of Medicine and Public Health. "In the case of primary Sjogren's Syndrome, lower cumulative estrogen exposure appears to augment the clinical expression of disease."

To analyze the role that sex hormone exposure plays with the development of primary Sjogren's, researchers examined reproductive

and menstrual factors in 1,320 women with primary Sjogren's syndrome and 1,360 women who only experience the dryness associated with this condition but no other symptoms. Researchers included the age of first period and the age of menopause, as well as the number of full-term pregnancies and miscarriages. They also included any use of female hormones and hysterectomy history.

According to results, women with primary Sjogren's Syndrome had a significantly reduced cumulative estrogen exposure when compared with women who only experienced dryness (Whitney, 2019).

One study from Stanford University shows that a molecule called Xist (pronounced 'exist'), which turns off one copy of the X-chromosome in every cell in the female body, can trigger a rogue immune response. Another study from France, not yet peer-reviewed, shows that when certain genes on the silenced X-chromosome become active again, it can cause lupus-like symptoms in older mice.(Bruce, 2024)

There are more than 100 autoimmune diseases.

• 50 million Americans have one or more autoimmune diseases.

• Approximately 75 percent of those affected are women.

• Autoimmune diseases are among the top 10 leading causes of death among American women.

American Autoimmune Related Disease Association.

Conclusion

When the estrogen hormone is outside the normal level, it will contribute to the occurrence of autoimmune diseases through its significant effect on the immune and inflammatory response, and this is more common in women than in men, this is due to many reasons that are still being studied, including sex hormones, as well as chromosomes and antibodies.

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