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Changes in the immune system during menopause and aging

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1. ABSTRACT

The fact that gender influences the immune system has long been recognised. The higther risk of women developing autoimmune diseases suggests that these are somehow mediated by sex steroids, with estrogens as enhancers at least of the humoral immunity and androgens and progesterone as natural immune-supressors. The concept of immunosenescence reflects changes in both cellular and humoral immune responses. This may be related with the higher incidence of infectious and chronic diseases. Besides age, in postmenopausal women, changes of the immune system have been attributed to estrogen deprivation. There is an increase in pro-inflammatory serum markers, an increasing response of the body's cells to cytokines, a decrease in CD4 T and B lymphocytes and in the cytotoxic activity of NK cells. In fact IL-6 is a key factor in bone reabsortion by osteoclast activation and also seems to be associated with diseases that occur more in menopause such as diabetes, atherosclerosis and cardiovascular diseases. Recent studies indicate several changes in immune response, either with suspension of hormone therapy or with its replacement at menopause.

2. INTRODUCTION

Menopause is the moment when permanent cessation of menses occurs after loss of ovarian function. Symptoms vary greatly across countries, with North American and European people reporting higher rates of symptoms than Asian women (1). Vasomotor symptoms, atrophic vaginitis, and breast tenderness are symptoms that appear to be directly related to the hormonal changes (2). Osteoporosis can also occur after a few years.

The fact that gender influences the immune system has long been recognised. The difference between the sexes has many explanations, such as an influence of sex hormones and influence of an endocrine pathway (3). The higher risk of women developing autoimmune diseases suggests that these diseases are somehow mediated by sex steroids.

The concept of immunosenescence reflects changes in the cellular and humoral immune response throughout the process of generating specific response to foreign antigens (4). The natural immune defences of the organism are also reduced because skin's fragility and the decrease of antibody's production. The dysfunction of the

immune system associated with age may be reflected in a higher incidence of infectious and chronic diseases (5).

The decline of sex steroids also occur in non-reproductive tissues. Thus, low levels of estrogen, observed in castrated animals or in postmenopausal women, have been shown to mitigate the immune response and predispose to disease and infection (6, 7).

3. THE IMMUNE AND THE ENDOCRINE SYSTEM

Immunis, meaning "free", gives rise to the word immunity that reflects a state of protection against an infectious disease. It provides the defense against infections caused by pathogens such as bacteria, viruses, fungi and parasites. It takes control of internal homeostasis and guarantees the recognition of self or non self, developing mechanisms and strategies of their own protection.

Innate immunity is the mechanism of resistance to disease which is not specific for any pathogen. It includes: anatomical, physiological, phagocytic and inflammatory barriers. Natural Killer`s (NK) are cells of the innate immunity system that represent an important line of defense against tumor and infected cells.

The adaptive immunity is a mechanism of resistance with a highly specific and great memory capacity. It includes the humoral system, in which the contact of an antigen with the lymphoid system stimulates B lymphocytes. These undergo differentiation, resulting in plasma cells and memory cells that produce antibodies specific for each antigen. The adaptive immune system includes also the cellular response, where T lymphocytes play an important role.

Cytokines are regulatory proteins, produced by different cell types acting in an autocrine, endocrine and paracrine way in response to many stimuli. Immune memory is a secondary antibody response that is typically faster and more intense. It is the imbalance between stimulating and inhibiting immunity factors that may lead to disease such as autoimmune`s diseases and immunodeficiency.

The existence of interaction between the endocrine and immune system is based on the observation that: 1) cells of both systems have receptors to cytokines, neuropeptides and neurotransmitters, 2) immune-neuroendocrine products are found in both tissues, 3) endocrine mediators modulate the immune system, 4) mediators immune structures may affect the endocrine system (8). Moreover, immune cells via receptors, may bind to steroids, growth hormone, estradiol and testosterone. The hypothalamic-pituitary-thyroid axis can be inhibited by IL-1, tumor necrosis factor (TNF) and IL6 and the hypothalamic-pituitary-adrenal axis may influence immune function with glucocorticoids suppressing the maturation, differentiation and proliferation of immune cells (9). Steroid hormones may affect the immune response by influence gene expression in cells that have receptors for these hormones (10). The hypothalamic-pituitary ovarian can also modulate the immune function. Gonadotropin-releasing hormone (GnRH) is also involved in the process of developing and modulating the immune system (11).

3.1. The women and the immune system

Females are prone to autoimmune diseases, although the reasons for this susceptibility are not fully understood. Immunization studies in both mice and humans suggest that females produce higher titter of antibodies, tend to mount more vigorous immune response (10) and have higher levels of CD4+T cells (10,11) and serum IgM.

Sex hormones appear to be partly responsible for the observed differences between the sexes, with estrogens as enhancers at least of the humoral immunity and androgens and progesterone as natural immunesupressors (10, 11, 12). Several physiological, pathological, and therapeutic conditions may change the serum estrogens levels including the menstrual cycle, pregnancy, menopause, aging, the use of corticosteroids, oral contraceptives (OC) and hormonal replacement treatment (HRT) and thus induce changes in immunity.

Both of the immune response, celular or humoral can be modified according to the different phase of the menstrual cycle (13).The menstrual period is associated with suppression of NK cells (14). In the follicular phase there is a domain of the cellular immune response. During the pre-ovulatory time, there is a decrease in cytolytic activity of NK cells (15) and in the luteal period there is a change in the cellular immune response towards humoral.

In humans it appears that estrogens on its own do not play a significant role in the etiology of either Rheumatoid Arthritis (RA) or Multiple Sclerosis (MS), but there are some indications that it may be important in Systemic Lupus Erythematosus (SLE). Additionally, androgens play an important role in some autoimmune diseases. Testosterone may be protective against some several autoimmune diseases such as MS, diabetes, SLE and Sjogren's syndrome (10). The suppressive role of progesterone seems to be supported by the knowledge that many autoimmune diseases as RA and MS, may improve during pregnancy and worsen after delivery. By the other hand, LES which has a strong humoral component tends to get worse.

Hormonal effects on immune system may not be limited to steroidal sex hormones. Prolactin, which is found in higher levels in women, is another hormone that seems to be implicated in regulation of the immune response. The presence of prolactin receptors on peripheral T and B lymphocytes may reflect the importance of this hormone. (10).

4. AGING AND THE IMMUNOLOGIC RESPONSE

Among body's systems, nervous, endocrine and the immune are the ones that suffers more changes with aging. The immune system undergoes changes in lymphocyte subsets, in cytokines, in immunological tolerance, among other functions. (16)

The concept of immunosenescence reflects changes in cellular and humoral immune response specific to foreigner antigens (4). The natural immune defences of the organism are also reduced because skin's fragility and the decrease of antibody's production.

The immune system dysfunction associated with age seems to be related with a higher incidence of infectious and chronic diseases such as hypertension, diabetes mellitus, autoimmune diseases, heart disease and atherosclerosis (16). These changes are probably associated with several immune alterations that occur as one grows older: changes in immune tolerance, an increase of autoantibodies; decline in function of NK cells, B lymphocytes and especially the T lymphocytes (17).

Another feature associated with immunosenescence is a chronic state of basal inflammatory activity that may result from increased production of proinflammatory cytokines such as IL6, TNF-alpha and free radicals (17, 16). Moreover important molecules like cytokine IL2 and INF-gama related to activation and proliferation of T lymphocytes are also decreased contributing to a greater number of neoplastic and infectious diseases (16). The inflammatory process induces oxidative stress and reduces cellular antioxidant capacity. The increased of free radicals can thus lead to DNA mutation or other serious cell changes (18).

5. MENOPAUSE, ESTROGEN DEPRIVATION AND THE IMMUNE SYSTEM

Besides age, in postmenopausal women changes of the immune system have been attributed to estrogen deprivation. In these stage of women's life there is an increase in pro-inflammatory serum markers (IL1, IL6, TNF-alpha), an increasing response of the body's cells to these cytokines, a decrease in CD4 T and B lymphocytes and in the cytotoxic activity of NK cells (9,19).

Low levels of estrogen and DHEA sulfate in postmenopausal women result in decreased number of cells secreting ITF-G contributing to the decline of immunologic reactivity. A significant increase of cytokines IL-1 and IL-6 were also detected after menopause. Several studies have also shown an increase in circulating levels of IL-6 and TNF-alpha after natural and surgical menopause (20, 21, 22).

Thus attenuated immune response and higher susceptibility to microbial invasion and infection are characteristic of postmenopausal women (6, 7). This dysfunction of the immune system associated with the hormonal changes that occur in menopause also seems to be related to a higher incidence of chronic degenerative diseases.

Cytokines are also involved in the mechanisms of ovarian follicular atresia, whether it occurs at a normal or accelerated rate. If the immune processes proceed continuously rather than cyclically, premature ovarian failure occurs (23). Women with premature ovarian failure have decreased NK cells and increased T and B lymphocytes (22).

There are studies relating the increase of proinflammatory cytokines and bone loss that arises in postmenopausal women. In fact IL6 is a key factor in bone reabsorption by osteoclast activation and also seems to be associated with other diseases that occur more in menopause such as diabetes, atherosclerosis and cardiovascular diseases (16, 24, 25, 26). IL1 and TNF-alpha have also been shown to increase bone reabsorption through indirect or direct modulation of osteoclasts (27). IL7 is another cytokine that appears to be associated with the increased IL-6 and bone metabolism but more studies are needed to prove it (25).

Hormone therapy in postmenopausal women is effective in alleviating vasomotor symptoms, genital atrophy, and contributes for the inhibition of bone loss. Potentially beneficial effects of hormone therapy on other systems need further investigation. However, recent studies indicate several changes in immune response, either with the suspension of hormone therapy or with its replacement (28, 29, 30). Epidemiological and clinical studies indicate the normalization of the cellular immune response after hormonal replacement, thus being a potential factor influencing development and course of autoimmune disorders and neoplasic diseases (9, 31). The effects of this therapy on humoral immunity are still inconsistent. Its also seems that soymilk and suplemtal isoflavones modulate B cells populations and appear to be protective against DNA damage in postmenopausal women (32).

6. CONCLUSION AND PERSPECTIVE

Gender and its particular hormones influence the immune system, with estrogens as enhancers of the humoral immunity and androgens and progesterone as natural immunesupressors. Thus the effect of steroid hormones should be viewed in a two-way interaction between the immune and endocrine system.

The function of the immune system undergoes changes associated with age such as in the subsets of lymphocytes, in the patterns secretion of cytokines, in immunological tolerance, among other functions. This seems to be associated with a higher incidence of infectious and chronic degenerative diseases.

Besides age, in postmenopausal women changes in the immune system have been attributed to estrogen deprivation. There is an increase in pro-inflammatory serum markers (IL1, IL6, TNF-alpha), an increasing response of the body's cells to these cytokines, a decrease in CD4 T and B lymphocytes and in the cytotoxic activity of NK cells. Thus attenuated immune response and higher susceptibility to microbial invasion and infection are characteristic in postmenopausal women. In fact IL-6 is important in bone reabsorption by osteoclast activation and also seems to be associated with other diseases that occur more often in menopause such as diabetes, atherosclerosis and cardiovascular diseases. IL7 is another cytokine that appears to be associated with the increased IL-6 and bone

metabolism but more studies are needed for this molecule. Epidemiological and clinical studies indicate the normalization of the cellular immune response after hormonal replacement, thus being a potential factor influencing the development and course of autoimmune disorders and neoplasic diseases. The effects of this therapy on humoral immunity need more studies. However, the effectiveness of hormonal therapy improving these diseases needs further clinical and epidemiological data.

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Abbreviations: IL1, Interleukin 1, IL6, Interleukin 6, IL2, Interleukin 2, IL7, Interleukin 7, IgM, Imumnoglobulin M, TNF-alpha, Tumor necrosis factor- alpha, INF-gama, Interferon gama, DHEA Sulfate, Dehydroepiandrosterone Sulfate

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