Immune and Metabolic Alterations Associated with Postmenopausal Estrogen Deficiency

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INTRODUCTION

Estrogen sex hormone plays a role in reproductive, cardiovascular, skeletal and central nervous systems. In menopause, the rapid decline of estrogen secretion leads to immune and metabolic alterations. These changes can initiate the development of life-threatening diseases (osteoporosis, cardiovascular diseases, tumours, immune and haemopoietic disturbances). I think, only few doctors and patients are aware of these events, which may be improved with naringenin diet, sufficient vitamin D3 supply and exercise regularly.

Newest data reveal the more widespread actions of estrogen connecting to energy balance, glucose and haemopoietic homeostasis. In some cases, a sex difference could be demonstrated, such as in estrogen-related adiposity, immune responses and allergic inflammation.

Immune alterations

Estrogen acts on its receptors (ERα and ERβ), which are present on cells (macrophages, dendritic cells, eosinophils, mast cells, T and B lymphocytes) involved in innate and adaptive immunity. Estrogen deficiency resulted in T cell activation with the increase in proinflammatory cytokines (TNFα, IL-1, IL-6, IL-7) and T cell output from thymus, bone marrow or spleen [1]. In estrogen deficiency, the production, mobilization and recruitment of hematogenous thymocyte progenitors increase via thymic output in bone marrow T cell pool affecting systemic bone remodelling via osteoclastogenesis and the peripheral blood T cell populations.

The well-known life-threatening disease, osteoporosis develops due to estrogen deficiency and the immune alterations. The bone structure is in dynamic balance between osteoblast and osteoclast cell activities. In postmenopause, the bone resorptive osteoclast dominance is present. The postmenopausal bone loss is a complex interplay among the bone, estrogen deficiency and the immune system reflecting that besides the direct action of estrogen on bone cells, cytokine producing activated T cells with the bone marrow stromal cells are also involved in osteoclast formation. In our previous paper, the role of IL-17A cytokine and its mediating role in the elevation of soluble receptor activator NF-κB (RANK) ligand could be demonstrated in postmenopausal osteoporosis [2]. Our results highlighted that the increased IL-6 was associated with moderate increase in osteoprotegerin (OPG), but with relevant increase in sRANK ligand [3].

Macrophages are important cellular mediators of inflammation and tissue remodelling. M2-polarized macrophages possess reparative feature via their secreting chemokines, which are dominant in female, while inflammatory M1-polarized macrophages (iNOS and TNFα secretions) are dominant in males [4]. In postmenopause, the M2-polarization is missed. M1-polarized macrophages are involved in the development of different tumours.

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Metabolic alterations

The direct role of estrogen receptors in glucose and lipid homeostasis is very important newly revealed viewpoints. In menopause, the decreased estrogen level is associated with increased visceral fat mass and lipid accumulation with decreased lipid utilization, as well as with suppressed glucose transporter 4 (GLUT4) expression. Estrogen directly acts on skeletal muscle, adipose tissue and pancreas [5]. The direct action of estrogen on pancreatic islets and insulin secretion highlights its role in the development of insulin resistance or diabetes in postmenopause. After the glucose input, the postmenopausal women secreted smaller amount of insulin with reduced elimination.

Estrogen deficiency in postmenopause affects the vasculature and endothelium structures, which express estrogen receptors and produce cytokines [IL-8, monocyte chemoattractant protein-1 (MCP-1), RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) (CCL5) chemokine] [6]. In this case, estrogen deficiency decreases the nitrogen monoxide generation and increases vascular endothelial growth factor (VEGF) tissue level causing hypertrophy of vascular smooth muscle cells. Estrogen inhibits the renin-angiotensin system, therefore at early stage of postmenopause, the significantly higher plasma renin and angiotensin-converting enzyme activity lead to increased amount of angiotensin II. Angiotensin II is associated with atherogenesis and arterial subendothelial mononuclear leukocyte infiltration connecting to endothelial expression of P-selectin and VCAM-1 (vascular cell adhesion protein-1) [7].

In summary, the missing of the beneficial estrogen effect leads to low grade of inflammation, obesity, insulin resistance and vascular lesions and the consequences of these alterations will manifest in postmenopausal women. Their knowledge is very important for their prevention and judging of symptoms.

Preventing factors

The postmenopausal immune and metabolic alterations can made weakened by sufficient vitamin D3 supply, naringenin diet and exercise regularly.

Vitamin D receptor (VDR) are present on the cells of immune system (Treg cells, neutrophils, dendritic cells and macrophages). Vitamin D plays a role in the adaptive and innate immunity exhibiting inhibitory effect on T-cell activation and proliferation, cytokine productions, as well as on toll-like receptor (TLR) activation [8]. Our data demonstrated that the increased IL-17A serum levels could be decreased by sufficient vitamin D3 supply in postmenopause (unpublished data).

Flavonoid, naringenin improves the metabolic alterations. Naringenin is abundant in citrus fruits (orange and grapefruit juice) and tomatoes. The effect of naringenin demonstrated lower fasting glucose and insulin levels, as well as MCP-1 and IL-6 cytokine levels after ovariectomy in female mice with metabolic disturbances [9]. Naringenin increases hepatic fatty acid oxidation, reduces hyperinsulinemia in liver and skeletal muscle, decreases hepatic cholesterol and cholesterol ester synthesis, reduces VLDL, prevents muscle triglycerid accumulation, improves insulin sensitivity and glucose tolerance [10].

Exercise regularly results in higher insulin sensitivity and the muscles replenish their glycogen stores with glucose from the bloodstream. The regularity increases the physical adequacy improving memory and thinking skills.

BIBLIOGRAPHY

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