

Does Thyroid Function Decline with Aging Contribute to Immunosenescence?

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One of the most significant social transformations of the 21st century is the aging of the population. The growing proportion of people over 65 is a phenomenon that is observed in virtually every country in the world [1]. Aging is a universal, unavoidable and irreversible process, in which changes in body composition and organ function occur. As we age, our bodies adapt with several natural changes in the functioning of all body systems. The endocrine system is not an exception and suffers profound hormonal changes with aging [2]. The endocrine system in humans is a driver of the aging process since many of the signs and symptoms that accompany this process can be reversed or compensated with hormone replacement therapy [2]. Not only blood levels of some hormones are altered, but also target tissues become less sensitive in response to hormones controlling them (including feedback mechanisms). Additionally, several endocrine changes are able to trigger processes associated with aging, such as menopause in women or andropause in men [2]. In fact, menopause is associated with decreased amount of ovary production of estrogen and progesterone, and with increased levels of pituitary follicle stimulating hormone (FSH) production. On the other hand, andropause is accompanied by a significant decline in testosterone production.

During aging, the two most relevant changes with clinical implications that could be associated with pathological conditions are those related to glucose tolerance and thyroid function [3]. Thyroid dysfunction and, especially, hypothyroidism is one of the most common disorders in the elderly [3]. The prevalence of thyroid disorders in people 65 years of age or older can reach up to 20%, however the diagnosis is often difficult, since thyroid dysfunction can go unnoticed due to absence of clinical symptoms or may be confused with the aging process. This makes it difficult to know if it is a pathology that needs treatment [4].

As mentioned, the decrease in thyroid function is very common in the elderly. This decline is mild and is accompanied by normal or slightly low levels of free T4, decreased levels of T3 and a gradual increase in circulating TSH. However, this decline in thyroid function would be "normal" in the healthy old people and they are not associated with important outcomes such as impaired quality of life, cognition, cardiovascular events and mortality. Moreover, a negative correlation between thyroid hormone levels and longevity was shown by several studies both in animals and in humans [5]. Therefore, the use of age-specific reference ranges has been suggested in order to diagnose and decide treatment of thyroid disease with aging [4-6].

The age-related decline of the immune system is known as immunosenescence. This state affects both functioning and development of the immune system resulting in a negative impact on the immune response of the elderly. This predisposes them to suffer from infectious diseases, cancer, autoimmunity and development of poor responses after vaccination. In fact, autoimmune thyroid disorders are one of the most common conditions in elder females. Both lymphopoiesis and the two branches of immunity, innate and adaptive, are affected,

being the functional capacity and the development of T cells the most influenced. Related to this, the thymus atrophy, the bias towards an increased production of myeloid instead of lymphoid cells in bone marrow, and the burden of persistent infections, are involved in the decline of immunity [7-9].

The immune system is also influenced by the changes associated with the age that occurs in the endocrine system. In fact, both growth hormone (GH) and IGF-1 were demonstrated to stimulate thymopoiesis. Since the production of both hormones decreases with age, it has been suggested that these changes would be related to the decrease in lymphopoiesis. This supports clinical trials proposing the use of GH to improve these immune parameters [10].

Despite, thyroid axis was demonstrated to regulate immunity [11,12], few studies have addressed how aging affects these interactions. So, would it be possible that thyroid decline with ageing would be somehow related to immune decline with ageing?

Decreased levels of circulating thyroid hormones, as those found in hypothyroidism, lead to immunosuppression. Hypothyroid conditions lead to a depression of humoral and cell-mediated immune responses, effects that were reversed by restoration of the euthyroid state [13,14]. A decreased activation of intracellular signals upon antigen or polyclonal activation of lymphocyte leading to cell proliferation is one of the mechanisms involved in immune cell dysfunction during hypothyroid conditions [13,14].

Since circulating thyroid hormones levels are relatively constant it is difficult to assess the relationship between thyroid hormones and immune function in healthy individuals. A study by Hodkinson., *et al.* [15] analyzes these interrelations in healthy elderly individuals devoid of thyroid illness. They found that serum levels of thyroid hormones were positively associated with markers of inflammation, natural killer-like T cells, expression of IL-6 by activated monocytes, percentage of memory T-lymphocytes, and higher IL-2 receptor density in T-cells. Conversely, thyroid hormone concentration was inversely associated with early lymphocyte apoptosis and the ratio of naïve- to memory T-cytotoxic lymphocytes. This current study suggests a role of T3 and T4, within physiological ranges, in the inflammatory response and in the maintenance of lymphocyte subpopulations. Similar findings were described by El-Shaikh., *et al.* [16] showing that T4 treatment restored the decreased immune responsiveness in aged mice.

Moreover, in addition to the effects of GH and IGF-1 on thymopoiesis, other extrathyroidic factors such as zinc [17] and thyroid hormone [16] were shown to be important in maintaining thymus cellularity and function. Recently, it was demonstrated that T-cell suppression was related to zinc deficiency in hypothyroid mice, and that zinc restoration to physiological levels was able to restore T-cell function [18].

Chronic stress is the biological response to emotional pressure suffered for a prolonged period of time, resulting from a state of continuous physiological arousal. Immune system and thyroid axis are both affected by chronic stress. In fact, alteration of several immune parameters have been described in chronic stressed old people [19], such as decreased humoral responses or cytokine production to vaccination in elderly caregivers. Chronic stress is associated with the accelerated aging of the immune system and is involved in the development and progression of autoimmune diseases among others. Moreover, a reduction in the serum levels of thyroid hormones that correlates with lower humoral responses and reduced lymphocyte activation was found in chronic stressed mice. Restoration of euthyroid conditions by T4 treatment reversed the stress-mediated effect on immunity as well, showing that chronic stress induces an alteration of thyroid axis function, which in turn alters the immune response [20]. These findings on the modulation of the immune system during stress would participate in the etiology of many diseases, including cancer. Chronic stress was demonstrated to disrupt T-cell and to promote tumor progression in mice [21]. Moreover, decreased circulating levels of T3 and of the antitumor immunity were demonstrated to be induced by stress in mice bearing syngeneic tumors. These effects were accompanied with an increase in tumor growth. Treatment with T4 restoring euthyroidism abolished all these effects [22].

So, the answer to the question whether thyroid decline with ageing would be related to immunosenescence seems to be yes. However, the exact mechanisms connecting the changes in thyroid function and immunity with ageing deserves more investigation.

Bibliography

1. United Nations, Department of Economic and Social Affairs, Population Division. "World Population Prospects 2019: Highlights" (2019).
2. van den Beld AW, *et al.* "The physiology of endocrine systems with ageing". *Lancet Diabetes and Endocrinology* 6.8 (2018): 647-658.
3. Taylor PN, *et al.* "Global epidemiology of hyperthyroidism and hypothyroidism". *Nature Reviews Endocrinology* 14.5 (2018): 301-316.
4. Chaker L, *et al.* "Clinical aspects of thyroid function during ageing". *Lancet Diabetes and Endocrinology* 6.9 (2018): 733-742.
5. Bowers J, *et al.* "Thyroid hormone signaling and homeostasis during aging". *Endocrine Reviews* 34.4 (2013): 556-589.
6. Duntas LH and Yen PM. "Diagnosis and treatment of hypothyroidism in the elderly". *Endocrine* (2019).
7. Fukushima Y, *et al.* "The impact of senescence-associated T cells on immunosenescence and age-related disorders". *Inflammation and Regeneration* 38 (2018): 24.
8. Müller L, *et al.* "The immune system and its dysregulation with aging". *Subcellular Biochemistry* 91 (2019): 21-43.
9. Xu W and Larbi A. "Markers of T Cell Senescence in Humans". *International Journal of Molecular Sciences* 18.8 (2017): 1742.
10. Montecino-Rodriguez E, *et al.* "Causes, consequences, and reversal of immune system aging". *Journal of Clinical Investigation* 123.3 (2013): 958-965.
11. Barreiro Arcos ML, *et al.* "Immune system modulation by thyroid axis includes direct genomic and nongenomic actions of thyroid hormones on immune cells". *Immunology, Endocrine and Metabolic Agents in Medicinal Chemistry* 10.1 (2010): 1-10.
12. Montesinos MDM and Pellizas CG. "Thyroid Hormone Action on Innate Immunity". *Frontiers in Endocrinology* 10 (2019): 350.
13. Klecha A, *et al.* "Experimental evidence pointing to the bidirectional interaction between the immune system and the thyroid axis". *International Journal of Immunopharmacology* 22.7 (2000): 491-500.
14. Klecha A, *et al.* "Integrative study of hypothalamus-pituitary-thyroid-immune system interaction: thyroid hormone-mediated modulation of lymphocyte activity through the protein kinase C signaling pathway". *Journal of Endocrinology* 189.1 (2006): 45-55.
15. Hodkinson CF, *et al.* "Preliminary evidence of immune function modulation by thyroid hormones in healthy men and women aged 55-70 years". *Journal of Endocrinology* 202.1 (2009): 55-63.
16. El-Shaikh KA, *et al.* "Recovery of age-dependent immunological deterioration in old mice by thyroxine treatment". *Journal of Animal Physiology and Animal Nutrition* 90.5-6 (2006): 244-254.
17. Majumdar S and Nandi D. "Thymic Atrophy: Experimental Studies and Therapeutic Interventions". *Scandinavian Journal of Immunology* 87.1 (2018): 4-14.
18. Paulazo MA, *et al.* "Hypothyroidism-related zinc deficiency leads to suppression of T lymphocyte activity". *Endocrine* (2019).
19. Punder K, *et al.* "Stress and immunosenescence: The role of telomerase". *Psychoneuroendocrinology* 101 (2019): 87-100.
20. Cremaschi GA, *et al.* "Chronic stress influences the immune system to through the thyroid axis". *Life Science* 67.26 (2000): 3171-3179.

21. Frick LR, *et al.* "Chronic restriction stress disrupts the immunity of T cells and promotes tumor progression in mice". *Stress* 12.2 (2009): 134-143.
22. Frick LR, *et al.* "Implication of thyroid hormones in alterations of T cell immunity and tumor progression induced by chronic stress". *Biological Psychiatry* 65.11 (2009): 935-942.

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