

# Thyroid Disorders in Vitiligo Patients

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## ABSTRACT

Vitiligo is an acquired chronic dermatological disease characterized by well-delineated, depigmented macules. Its pathogenesis is mostly considered autoimmune and this pigmentary disorder is strongly associated with autoimmune thyroid disorders. Such close association seems to be the result of a complex pathogenesis sustained by shared genetic, autoimmune, inflammatory and pro-oxidative factors. Hence, according to recent clinical, epidemiological and experimental findings, a regular thyroid screening is recommended in individuals affected by vitiligo.

Vitiligo is an acquired, chronic pigmentary dermatological disease characterized by well-delineated, depigmented macules that are the result of a loss of functional melanocytes in the epidermis [1,2]. This disorder affects 0.1-2% of the world population, with no sexual or racial preference [3], and it can appear at any age. In nearly 50% of patients however it presents in the first two decades.

Three major forms of vitiligo have been recently classified: non segmental vitiligo, segmental vitiligo, and undetermined/unclassified vitiligo [4].

Various theories have been proposed to explain vitiligo pathogenesis but the autoimmune and the auto-cytotoxic theories are at present the most accredited. The autoimmune one is confirmed by the frequent association with organ- and non-organ-specific antibodies and autoimmune diseases [5]. In particular, vitiligo is strongly associated with autoimmune thyroid disorders, a group of diseases defined by the presence of serum thyroid autoantibodies directed against thyroglobulin, thyroperoxidase or thyroid-stimulating hormone receptor, which are pivotal thyroid-specific molecules for the production of thyroid hormones. Autoimmune thyroid disorders can be associated or not with thyroid dysfunction [6]. Several researches have demonstrated that both clinical and subclinical thyroid diseases are more common in patients with vitiligo compared to healthy subjects [7,8], and in particular non-segmental vitiligo is associated with an excess of thyroperoxidase antibodies and shows a high prevalence of autoimmune thyroid diseases [9].

A recent systematic review pointed out that the risk for vitiligo patients to develop ATD diseases is even higher (2.5 fold) compared to non-vitiligo patients, while the risk to develop elevated thyroid antibodies is more than 5 fold higher in vitiligo patients than in non-vitiligo patients [6]. Accordingly, a screening of ATD is recommended in vitiligo patients [6].

It was also shown that the presence of anti-thyroid antibodies is predictive of thyroid disease clinically manifested within 7 years [6]. Therefore the presence of elevated thyroid antibodies may be used as a clinical tool in vitiligo patients to identify patients at risk for thyroid disease. The British guidelines for the diagnosis and management of vitiligo invite clinicians to consider a blood test to check thyroid function [10], and the Dutch guideline for vitiligo recommends as well to check thyroid function, although only when there are clinical symptoms of thyroid disease [11]. The European Dermatology Forum consensus in 2013 pointed out that thyroid antibodies are a recommended diagnostic procedures in patient with vitiligo [12].

The clinical characteristics of vitiligo in patients with both vitiligo and autoimmune thyroid disease have been investigated by many authors. They underlined that these patients are more likely to display an advanced age [13], a family history of thyroid disease [13], a post puberal onset of vitiligo (> 12 years) [14], female sex, long duration of disease, greater extension of vitiligo [15] and stress at disease onset [16]. All these works encourage to carry out a regular thyroid screening in patients with vitiligo who exhibit these clinical features.

Vitiligo and thyroid have notable similarities and share common genetic background like NALP1 genes, AIRE, PTPN22, CTLA-4 and other susceptibility loci. All of these are genes coding for regulatory proteins of the mechanisms involved in maintaining immune tolerance processes [17].

Besides a shared genetic background, the association between vitiligo and thyroid diseases might also be sustained by a common shared inflammatory pathway.

Several interesting evidences indeed highlights the importance of the (C-X-C motif) receptor 3 (CXCR3) and cognate chemokines (C-X-C motif) ligand (CXCL)9, CXCL10 and CXCL11, which are expression of a T helper 1 immune response, in inflammatory diseases such as thyroid autoimmune disorders [18]. CXCL10, 9 and 11, which are induced by IFN gamma in different cells (T lymphocytes, monocytes, fibroblasts, thyrocytes, preadipocytes, and others), bind to the CXCR3 chemokine receptor expressed not only by immune cells but also by endothelial cells, mesangial cells, thyrocytes and other epithelial cells [18]. Such interaction regulates inflammation by generating directional migration of multiple immune cell types (activated T cells, monocytes, and natural killer cells) and by inducing other cytokines, such as IL-8 and CXCL5 [18]. Interestingly, Th1 chemokines CXCL9, CXCL10 and CXCL11 have been recently reported to be highly induced in vitiligo [19,20,21]. In serum of vitiligo patients CXCL10 level indeed has been reported to be elevated and melanocyte-specific CD8+ T cells expressed CXCR3 (the common receptor for CXCL9, CXCL10 and CXCL11), unlike healthy controls [19,20,21].

In this scenario we can assume the existence of a close interaction between genetics, autoimmunity, inflammation and possibly oxidative stress able to determine the association between vitiligo and thyroid diseases.

With regards to the most recent clinical associations, a study has investigated the presence of another group of thyroid autoantibodies directed against thyroid hormones (triiodothyronine and/or tiroxine) (**THAb**) in patients with vitiligo [22]. These autoantibodies, which are considered to be a subset of Thyroglobulin autoantibodies, are the less frequently detected class of thyroid antibodies in human serum and are rare in general population [23]. Their pathogenetic role is still unknown, but they have been found to be increased in individuals with autoimmune thyroid diseases and extrathyroid autoimmune diseases such as Hashimoto's thyroiditis, Graves' disease, primary Sjögren's syndrome, and rheumatoid arthritis [24].

Colucci et al., found that these hormones have a surprisingly high prevalence in patients with vitiligo and that they significantly correlate with active vitiligo, leucotrichia, disease duration and thyroglobulin antibodies positivity [22].

As no other study regarding the presence of THAbs in vitiligo exists, and their pathogenetic role is still unknown, such study was not able to clarify the physiopathological mechanisms underlying this association, nor to identify a possible causal role.

However, authors postulated that possible connections between thyroid proteins and melanocytes might exist and could imply a potential cross-reactivity [22].

An autoimmune background shared by both vitiligo and autoimmune thyroid disorders might also create a persistent inflammatory milieu in which Reactive Oxygen Species (**ROS**) accumulate and exert a toxic effect on surrounding cells [25], able to trigger the development of melanocytic or thyroid neo-antigens. Such postulated continuous autoimmune and oxidative interaction between the melanocytic and thyroid systems could eventually create a vicious cycle in which thyroid autoimmune processes give rise to vitiligo lesions, and in turn the presence of vitiligo perpetuates the formation of thyroid autoantibodies.

Another recent study of the same group investigated the role of diet and self reported environmental exposure in vitiligo patients in eliciting THAb [26]. They highlighted that an important role in such process might be played by goitrogenic foods, heavy metals, pollutants, ionizing radiations and other chemical substances. Namely, authors found a positive association between specific types of THABs and Polychlorinated Biphenyls (**PBCs**) or assumption of food intake containing nitrate, thiocyanate, and soy isoflavones. Since it has been reported that such chemicals are able to induce ROS production and that the above mentioned foods are able to interfere with thyroid function and to trigger the development of immunoreactive thyroid fragments, authors postulated that such self reported exposure might induce thyroid diseases, which can in turn trigger vitiligo lesions, through a mechanism of ROS accumulation which is able to induce melanocyte-neo antigens [26].

The reported observational cross sectional study does not provide a causal role, thus more in depth evaluation are needed to assess whether in case of exposure to thyroid disruptors a thorough thyroid assessment in vitiligo patients should be performed, in order to early reveal possible associated autoimmune thyroid diseases.

## CONCLUSION

In conclusion, according to the evidences and theories discussed above, we can state that patients with vitiligo have a sort of 'thyroid autoimmune diathesis', which we could define as a strong predisposition of patients with vitiligo to develop ATD. Such close association seems to be the result of a complex pathogenesis sustained by common genetic, autoimmune, inflammatory and pro-oxidative factors.

A regular thyroid screening is therefore recommended in individuals affected by vitiligo.

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