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NEWS, VIEWS, & REVIEWS

Shining a Light on Vitiligo and Associated Comorbidities: What Is the Evidence?

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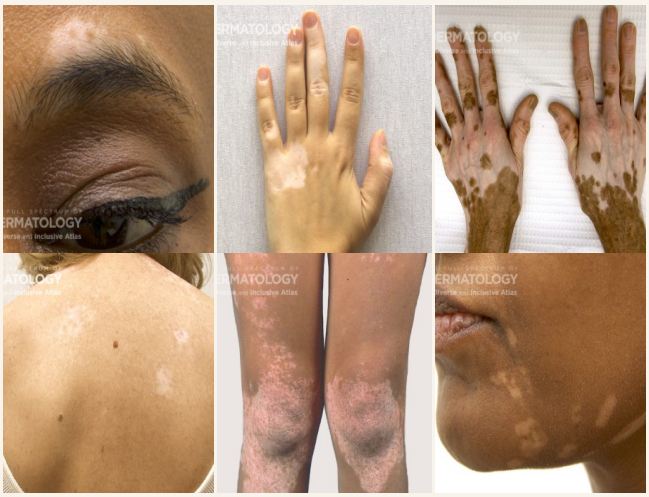
Introduction

Often dismissed as a cosmetic concern, vitiligo is anything but given its pathophysiology and tremendous impact on quality of life (QoL). Simply put- vitiligo is a medical disease,[1] exhibiting an estimated worldwide prevalence of 0.5 to 2%; irrespective of racial predilection and equally affecting adults and children of both genders.[2,5]

The pathophysiology of vitiligo is a complex interplay of genetics, reactive oxidative stress (ROS), and innate and adaptive immunity, culminating in injury and selective destruction of melanocytes.[3,18] While oxidative damage steers vitiligo onset by triggering redox homeostasis imbalance and amplified expression of proinflammatory cytokines and antigen presentation, signaling of IFN-γ through the Janus-kinase signal transducer and activator of transcription (JAK-STAT) pathway with subsequent transcription of IFN-γ-induced chemokines, namely CXCL9 and CXCL10, are pivotal in driving depigmentation, and mediate targeted melanocyte destruction by autoreactive cytotoxic CD8+ T lymphocytes.[2,4,5,24] Furthermore, increased prevalence of autoantibodies against melanocytes amongst individuals and recurrent presence of concomitant autoimmune comorbidities in 10 to 15% of vitiligo patients compared to 1 to 2% of the general population are some of the most apparent correlations between vitiligo and autoimmunity.[3,18,19]

Figure 1. Images of vitiligo.[17]



Over the decades, advances in knowledge and growing attention to vitiligo have improved understanding of the disease's implications, including the possibility of concurrent autoimmune and systemic diagnoses (Figures 2A and 2B) with plausible parallel pathogenetic pathways, many of which lead to increased morbidity. A recent prospective cross-sectional survey found that those with vitiligo were 2.6 times more likely to have at least one autoinflammatory/autoimmune comorbidity when compared to non-vitiligo groups.[25] Physicians must be aware of, identify, and treat additional complications in vitiligo patients to improve patient QoL. Herein, we review evidence and insight for the most frequent comorbidities associated with vitiligo.

Thyroid Disease

Autoimmune Thyroid Disease (AITD) including Hashimoto thyroiditis and Grave's disease, have strong links with vitiligo. A recent meta-analysis demonstrated the AITD prevalence in vitiligo patients is 14.3%, while positivity to thyroid-specific antibodies (ie, anti-thyroglobulin (Tg), anti-thyroid peroxidase (anti-TPO), and anti-thyrotropin receptor (TSHR)) is appreciated in 20.8% individuals.[6] Moreover, the presence of anti-thyroid hormone antibodies were detected in 77 of the 79 vitiligo patients analyzed, suggesting a probable pathogenetic role.[6,7]

More notably, there exists a 2.5-fold higher risk for development of AITD in older, non-segmental vitiligo (NSV) patients, and another study disclosed the risk of AITD also increases with vitiligo duration and distribution, with the risk doubling every five years and with greater than 10% body surface area involvement.[2]

The reported association of vitiligo with AITD additionally suggests the presence of shared heritable susceptibility genes. Among 27 genes mapping Autoimmune Susceptibility 1 (AIS1) locus on chromosome 1, mutations of FOXD3 exhibit the greatest connections for concurrent occurrence of vitiligo and AITD in both adult and pediatric patients.[6,7,8]

Alopecia Areata

Vitiligo and alopecia areata (AA) are autoimmune diseases that occur more commonly together than by chance, with a reported 3 to 8% prevalence of vitiligo in AA patients, and share striking similarities in pathogenesis that may better explain

Figure 2A. Frequencies reported are from literature review and provided for comparison purposes.

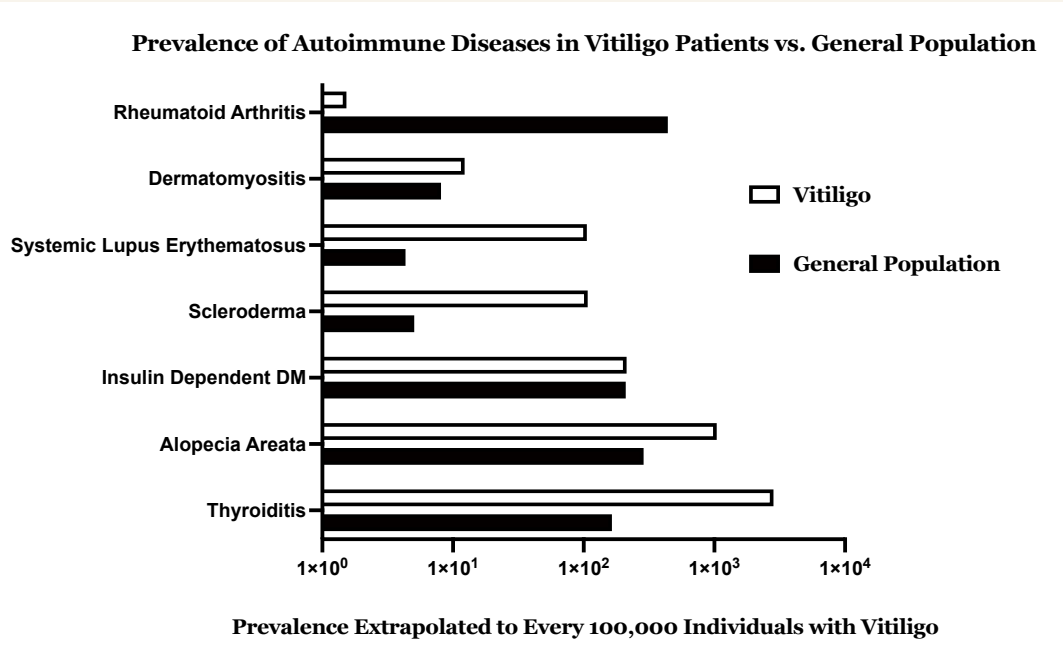
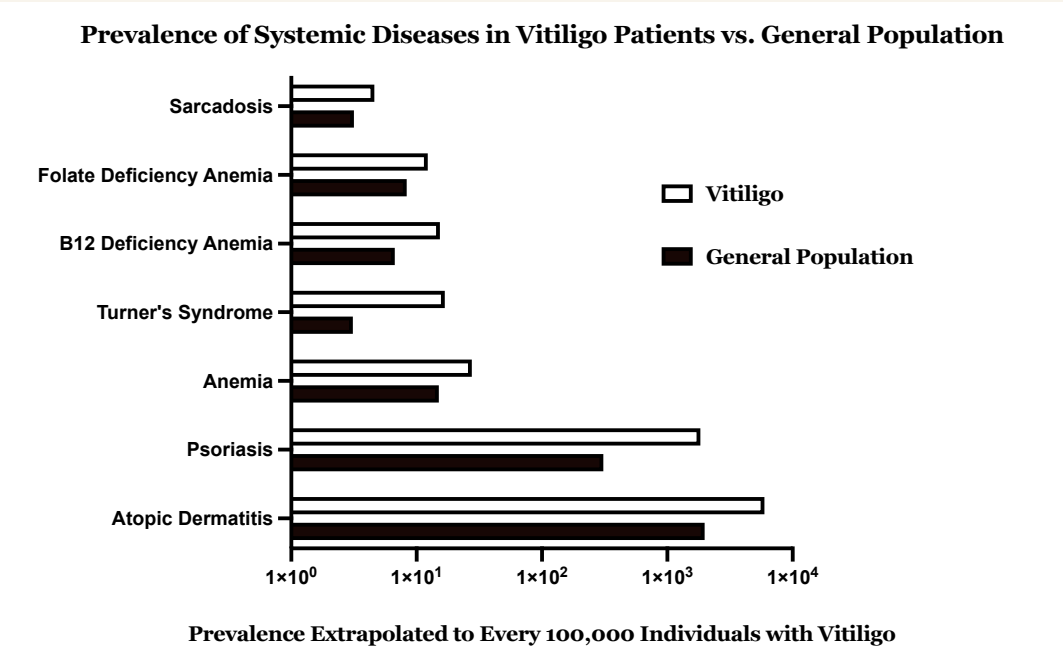


Figure 2B. Frequencies reported are from literature review and provided for comparison purposes.



their coexistence.[2,11] Increased ROS is an anticipated trigger of the innate immune system in both diagnoses. Genome-wide association studies have demonstrated both innate and adaptive immunity, and mechanistic studies in mouse models have implicated an IFN-γ driven immune response and cytotoxic CD8+T cells as chief pathogenic factors.[9]

Furthermore, statistics show IFN-γ, IL-1B, and IL-6 serum levels are significantly elevated in AA and NSV patients when compared to healthy controls.[10] Upregulation of several JAK-STAT pathway components downstream of gamma chain containing cytokines in the shared etiopathogenetic pathways. IFN-γ and γ_c cytokines, including IL-2, IL-7, and IL-15 are notorious for augmenting AA disease with studies highlighting that IFN-γ signals primary through JAK1/2 and IL-15 mostly via JAK1/3.[22,23]

Diabetes Mellitus

Many studies have explored potential ties between vitiligo and diabetes mellitus (DM) identifying 1 to 7% of vitiligo patients have concomitant DM.[2,20,21] T1DM is an autoimmune disease characterized by destruction of insulin-producing pancreatic beta cells, and coexistence of the two diagnoses provides further insight that vitiligo, too, is a T-cell mediated disease. A meta-analysis comparing 14 studies reported that the prevalence of vitiligo among T1DM patients ranged from 0.5 to 23.3%, with a mean incidence of 2.4% vs 0.4% in the general population. In other studies, estimated prevalence of vitiligo in T1DM patients was higher, 4.3% vs 1.4%, compared to studies that failed to perform active vitiligo screening.[11] Similarly, vitiligo was observed in 12% of cases, and 6% in the age and sex-matched controls amidst one study examining 600 T2DM patients.[2,12,13] Recent studies likewise determined a 4.9% prevalence of vitiligo in T2DM individuals contrasting with 0.6% in the general population.[14]

Metabolic Syndrome

Metabolic syndrome is defined as the co-occurrence of metabolic risk factors for cardiovascular disease and T2DM. Surprisingly, proinflammatory cytokines IL-6, IL-1, and TNF-a associated with insulin resistance and atherosclerosis, have also been recognized as influential cytokines affecting vitiligo pathogenesis, thus accentuating a likely correlation between the two as well as parallels between the syndrome and activity and duration of vitiligo.[15,16] One prospective cross-sectional study showed a significantly higher incidence of metabolic syndrome in vitiligo patients, especially those with a higher Vitiligo Area Severity Index (VASI). In all vitiligo individuals evaluated, fasting glucose, LDL cholesterol, and blood pressure levels were appreciably higher than controls after the exclusion of those affected by comorbidities including obesity, diabetes, and AITD; criteria for metabolic syndrome were met amidst 37.4% of studied vitiligo patients.[15]

Conclusion

Every case of vitiligo is unique, and the evidence to date supports an alignment of a multitude of comorbidities with vitiligo. Of importance, it is critical that healthcare professionals be aware of the possible autoimmune and systemic diseases that may concurringly ensue with vitiligo to provide optimal management and treatment; its chronicity and ease of relapsing warrants a necessary call to action to establish cornerstone screening assessment guidelines for early recognition and intervention.

Disclosure

The authors declare no conflicts of interest.

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