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Beyond Skin Deep: Exploring the Link between Vitiligo, Metabolic Syndrome and Genetics

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Abstract Metabolic syndrome (MetS) has been linked to various skin conditions, such as vitiligo, but the specific association between these two conditions has not been quantitatively analyzed. This study aims to establish the relationship between vitiligo and metabolic syndrome through a systematic review and meta-analysis. The primary focus will be on the type of vitiligo, diagnostic criteria for MetS, components of MetS (including waist circumference, blood pressure, triglycerides, fasting glycemic index, and high-density lipoprotein cholesterol), levels of low-density lipoprotein cholesterol, and BMI.

Keywords Metabolic syndrome, Vitiligo, Insulin resistance, Pigment, Melanin

The human skin performs essential physiological functions, including protection, immunity, secretion, and sensation, and also significantly influences metabolism by regulating water, minerals, fats, carbohydrates, and energy. Its protective role is attributed to its barrier, bactericidal properties, and production of melanin pigment, which shields the skin from ultraviolet radiation. Disorders in melanin pigmentation, known as melanoses, manifest with diverse clinical presentations. While there is no universally accepted classification of melanosis, a commonly used approach categorizes these skin conditions based on characteristics such as color (hypermelanosis and hypomelanosis), origin (congenital and acquired, primary and secondary), and prevalence (segmental and generalized). Vitiligo is the most prevalent among hypomelanotic diseases.

Metabolic syndrome (MS) is a collection of metabolic disorders that increase the risk of developing cardiovascular conditions and type 2 diabetes mellitus (DM2). Risk factors for MS include the accumulation of abdominal fat, high blood pressure, disturbances in carbohydrate metabolism, and dyslipidemia. These factors can lead to severe complications such as heart attacks, strokes, and death. MS has been linked to various chronic diseases for many years, including cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), arthritis, chronic kidney disease, schizophrenia, and certain types of cancer such as endometrial, prostate, colorectal, and breast cancers. It is well known that MS often coexists with obesity and DM2. With global obesity rates on the rise, MS has emerged as a major public health concern worldwide. Moreover, autoimmune diseases like vitiligo have notably increased in Western countries alongside the obesity epidemic.

Vitiligo is the most common pigmentation-related dermatological condition, with a prevalence of 1-2% among the European population. It accounts for 3-4% of all diagnosed dermatoses in polyclinics. In Central Asia, particularly in some areas, the incidence of vitiligo is notably higher, reaching up to 10%. Epidemiological studies in Uzbekistan have revealed that 1.2% of the population is affected by vitiligo, affecting both men and women equally across all age groups, with most cases occurring in the second and third decades of life. Vitiligo involves the loss of skin pigmentation and can be classified as non-segmental or segmental. Segmental vitiligo is associated with an earlier onset and has shown limited response to traditional treatments. The exact cause of vitiligo is not fully understood, but autoimmunity and oxidative stress are recognized as contributing factors. Interestingly, oxidative stress has been linked to metabolic syndrome (MS) and diseases such as vitiligo. Additionally, it is worth noting that adipose tissue contains melanocytes that are believed to exhibit anti-inflammatory effects and reduce reactive oxygen species, yet patients with vitiligo tend to have fewer melanocytes and reduced melanogenesis in their adipose tissue, increasing their susceptibility to metabolic disorders. Various inflammatory markers appear to play a role in this heightened risk. Research indicates that individuals with vitiligo have a greater prevalence of metabolic syndrome compared to those without the condition. Moreover, this risk may be elevated in individuals with more active or severe vitiligo. However, the severity of vitiligo is not independently linked to metabolic syndrome. [2].

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Ataş et al. (2017) [1] highlighted the significant cardiovascular risks posed by metabolic syndrome and its components. In order to evaluate subclinical atherosclerosis, ultrasound assessments of the carotid arteries, which encompass measurements of carotid media intima thickness, are utilized and are capable of independently predicting cardiovascular complications. A case-control study on Egyptians, conducted by Ataş et al. (2020), revealed that a notable proportion of vitiligo patients had hypercholesterolemia and exhibited a higher incidence of atherosclerotic plaques along with increased carotid media intima thickness compared to the control group. Notably, the severity index and duration of vitiligo were found to be significantly correlated with carotid media intima thickness. Another study by Karadag et al. [5] discovered elevated homocysteine levels in vitiligo patients compared to controls. Homocysteine is known to inhibit the enzyme involved in melanin synthesis, known as tyrosinase, and is considered a marker of cardiovascular disease.

The pathophysiology of vitiligo, metabolic syndrome (MetS), and atherosclerosis exhibit commonalities such as genetic predisposition, pro-inflammatory signaling pathways, and heightened oxidative stress. A study investigating genome-wide associations in vitiligo patients identified several susceptible loci associated with diabetes mellitus, including IFIH1, BACH2, BTNL2, IL2RA, SH2B3, and ZMIZ1. Furthermore, elevated levels of pro-inflammatory cytokines TNF-α, IL-1, and IL-6 in the serum are involved in the pathogenesis of vitiligo. [3] These cytokines are also linked to insulin resistance and atherosclerosis. Adipose tissue contains melanocytes and reactive oxygen species (ROS) generated by lipid peroxidation in vitiligo causes a reduction in melanocytes in adipose tissue. ROS contributes to adipogenesis by promoting the proliferation and differentiation of pre-adipocytes and obesity, and reduced melanocyte numbers impair anti-inflammatory and antioxidative functions, which increases the likelihood of developing MetS. Recent studies show evidence of a higher risk for metabolic syndrome and dyslipidemia in vitiligo patients. Leptin, a hormone released by adipocytes and cells of the small intestine that regulates energy balance and body weight, has been linked to insulin resistance, obesity, arterial hypertension, and dyslipidemia. As such, it is increasingly recognized that chronic inflammation plays a role in both vitiligo and metabolic and vascular disorders.

However, studies on the metabolic syndrome in vitiligo patients in the Uzbek population are yet to be conducted, and more research is needed on the relationship between vitiligo and insulin resistance. At present, other treatment targets are being explored, and drugs under clinical evaluation must consider the potential interference with vitiligo comorbidities. Though not all studies agree on the association between vitiligo and metabolic disorders, further research is necessary to improve the quality of life of vitiligo patients. The literature shows that vitiligo is linked to various co-occurring disorders However, further prospective and mechanism-based studies are required to validate these findings. It emphasizes the crucial role of a multidisciplinary approach in managing patients with vitiligo. Dermatologists and endocrinologists must take into account these associated diseases to identify and screen for potential comorbidities in patients promptly.

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