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Serum concentrations of Co Q10 and Interleukin-6 in patients with non-segmental Vitiligo

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Abstract
Background: Vitiligo is a condition where areas of skin lose their pigmentation; oxidative stress and immunological dysregulation have been linked to its development. The purpose of this research was to examine the relationship between Coenzyme Q10 (Co Q10) and Interleukin-6 (IL-6) in the blood of individuals diagnosed with non-segmental vitiligo. The purpose of this article is to provide readers a thorough introduction to vitiligo, including such topics as the disease's epidemiology, categorization, probable causes, underlying pathogenic processes, diagnostic approaches, and several treatment options. Our goal in compiling this summary is to be a useful tool for clinicians and researchers interested in vitiligo by providing an overview of the current state of knowledge. Conclusions: Because of its complex aetiology, vitiligo is difficult to diagnose and treat. Melanocyte dysfunction is fueled by a complex web of elements including genetic susceptibility, autoimmune processes, oxidative stress, and environmental influences. In order to choose the best course of therapy for vitiligo, the severity and duration of the condition must be evaluated. Treatment for this ailment includes a combination of medicinal, phototherapeutic, and psychosocial approaches. Additional research into the roles of coenzyme Q10 and interleukin-6 in the development of vitiligo is warranted.
Vitiligo, Coenzyme Q10, Interleukin-6, Oxidative Stress, Immune Dysregulation, Disease Activity, Biomarkers .

Keywords: that have been used to categorise this article.

1 Opening Remarks

Depigmented patches appear on people with vitiligo, a persistent skin condition caused by the death of melanocytes. The estimated global frequency of this illness is about 1% [1], and it affects people of various ages, races, and ethnicities.

The most prevalent kind of vitiligo, known as non-segmental vitiligo, is defined by the symmetrical distribution of depigmented patches on different areas of the body. The visible character of vitiligo and the potential for psychological discomfort mean that it may considerably damage the quality of life of those who suffer from it [2].

The specific cause of vitiligo is unknown, however research has shown that both hereditary and environmental factors have a role [3]. Recent years have seen a rise in support for the autoimmune hypothesis, which proposes that an abnormal immune response is responsible for the death of melanocytes. Supporting this theory are the higher levels of proinflammatory cytokines like Interleukin-6 (IL-6) seen in people with vitiligo [4].

Interleukin-6 is a multifunctional cytokine that controls inflammation and immunological response. Multiple autoimmune and inflammatory disorders have been linked to IL-6 dysregulation [5].

Lipophilic antioxidant coenzyme Q10 (Co Q10) is another chemical of importance while thinking about vitiligo. Coenzyme Q10 (Co Q10) has been linked to cellular energy generation and anti-inflammatory and antioxidant benefits. Some research has linked CoQ10 insufficiency to vitiligo and other skin diseases. With antioxidant and anti-inflammatory properties, Co Q10 may be involved in the development of non-segmental vitiligo [6, 7]. However, it is possible that Co Q10 levels are already abnormal in these patients.

Because they may provide insight into the underlying processes of non-segmental vitiligo, the blood concentrations of Co Q10 and IL-6 in individuals with this illness are of significant interest. Such knowledge may also help in the design of innovative therapeutic methods aimed at these molecules in an effort to alter the disease's progression or enhance the efficacy of existing treatments [8].

Therefore, the purpose of this research is to assess IL-6 and Co Q10 levels in the blood of people who have non-segmental vitiligo.

Vitiligo

Because of structural and functional damage to melanocytes, vitiligo is a persistent skin condition characterised by the depigmentation of localised regions. Vitiligo's origins are mostly mysterious. There may be a hereditary component, but other variables are likely in play as well. Vaccination, radiation therapy, and sun exposure all fall into this category, as

do melanoma and its treatment (bone marrow transplant, interferon, and other medications), as do psychological variables, endocrine disorders, and contact vitiligo [9].

Epidemiology

Vitiligo is a pigmentary condition that affects people of all ages, races, and sexes equally. It has a worldwide incidence of 0.2 percent. There is a 7- to 10-fold greater risk for first-degree relatives [10], and the familial pattern is non-Mendelian with an unusual autosomal dominant inheritance.

Although most cases emerge between the ages of 10 and 30, the prevalence gradually decreases with age. Patients sometimes attribute the onset of their vitiligo to a particular incident, although the evidence connecting such events to the illness is scant, with the exception of the Koebner phenomenon [11].

Vitiligo's Origins and Progression

Vitiligo is characterised by a gradual beginning and an uncertain course in which new depigmented macules may appear, or existing lesions may grow in size. The illness may advance slowly over time, or it may remain stable for long stretches. Although full and persistent spontaneous repigmentation is uncommon, some repigmentation might occur as a result of sun exposure or on its own. Patients with early onset (12 years or younger) often have halo nevi, Koebner phenomenon, a familial history of atopic illness, segmental disease, and atopy, whereas those with late onset typically have more acro-facial lesions and thyroid disease. The median age of onset is between 5 and 10 years old [12], with 11% happening before age 2, 28% between ages 2 and 5, 40% between ages 5 and 10, and 21% between ages 10 and 18 years old.

Vitiligo is categorised as follows:

Clinically, vitiligo may be classified as either segmental vitiligo (SV) or non-segmental vitiligo. In addition, there are four subtypes of generalised vitiligo: acrofacial vitiligo (which only affects the face, head, hands, and feet), mucosal vitiligo (which affects the oral and/or vaginal mucosa alongside other skin regions), and universal vitiligo (which affects all skin areas) (affects 80 percent -90 percent of body surface). A case of mixed vitiligo (MV) is defined as an initial SV followed by the spread of bilateral NSV patches (typically within six months). However, because to the unpredictability of vitiligo's development, NSV often changes over time, altering its extent and distribution. Focal vitiligo (isolated macules with no segmental distribution and no progression into NSV for at least 2 years) and mucosal vitiligo are two unclassified variants mentioned in the literature (Exclusive involvement of oral or genital areas). Unilateral (one or more macules), bilateral (two lesions), and multilateral (many lesions on one or both sides of the body) are all types of segmental vitiligo (SV).ly) [1].

Table (1)classification of vitiligo [2]:

Classification	Description
1. Segmental Vitiligo	Unilateral, segmental or band-shaped distribution; early onset; rapid stabilization; hair follicle melanocyte involvement; limited progression.
2. Non-segmental Vitiligo (NSV)	Bilateral acro-facial or scattered symmetric distribution; can evolve to generalized or universal forms; predilection for extensor surfaces.
3. Mixed Vitiligo (MV)	Coexistence of NSV and SV; specific criteria include absence of segmental distribution at birth, SV followed by NSV with a delay, SV affecting at least 20% of an adermatomal segment, and response to treatment.
4. Focal Vitiligo	Small, isolated, acquired hypo-pigmented lesions not fitting a segmental distribution; no evolution into NSV after 1-2 years; diagnosis after ruling out other causes.
5. Mucosal Vitiligo	Involvement of oral and/or genital mucosa; rarely diagnosed in fair-skinned individuals; classified as undetermined vitiligo when presenting in isolation).
6. Universal Vitiligo	Complete or nearly complete depigmentation of skin, body hair, and sometimes oral/genital mucosae; scalp hair may be involved; distinct from 'fulminant' vitiligoid conditions.
Unclassified Conditions:	- Vitiligo Punctata: Sharply demarcated depigmented punctiform macules - Vitiligo Minor/Hypochromic: Limited to dark-skinned individuals, partial pigmentation defect - Follicular Vitiligo: Involves follicular reservoir primarily - Occupational/Contact Vitiligo: Induced by exposure to certain chemicals (Ezzedine et al., 2012)

Precipitating factors of vitiligo:

Stress-Increased levels of catecholamines and neuropeptides may have a role in triggering

vitiligo, which has been related to immunological abnormalities that may have an impact on other autoimmune illnesses. Feelings of shame, anger, and stigmatisation are common among people with vitiligo, and these emotions may have a negative impact on the patient's quality of life, psychosocial functioning, and overall health [14]. Table 2

Table (2) Precipitating factors of vitiligo [3]:

Precipitating Factors	Description
1) Psychological Factors	- Stress may trigger vitiligo through increased catecholamines and neuropeptides, potentially influencing immune abnormalities. - Patients with vitiligo often experience psychosocial impairments, emotional disturbances, and negative impacts on social and sexual relationships, leading to impaired quality of life.
2) Nutrition	- Vitiligo patients may have pernicious anemia and vitamin B12 deficiency, contributing to elevated homocysteine (Hcy) levels. - Elevated Hcy levels may lead to reversible hypopigmentation by inhibiting the tyrosinase enzyme.
3) Drug-Induced Vitiligo	- Several drugs have been associated with vitiligo development, including anticonvulsants, antimalarials, anti-neoplastic agents, antiparkinsonian medications, and miscellaneous drugs.
4) Pregnancy	- Most vitiligo patients experience stable disease during pregnancy and the six-month period after delivery. - Vitiligo has significant psychological and social implications during pregnancy.

Pathogenesis of vitiligo

Table (3) The pathogenesis of vitiligo based on the provided information [4]:

Pathogenic Mechanism	
Genetic Susceptibility	Vitiligo is a polygenic, multifactorial disorder with a strong familial clustering.
Autoimmune Hypothesis	Autoimmune mechanisms play a significant role in generalized vitiligo.
Innate Immunity	Innate immune activation and natural killer (NK) cells infiltration may contribute to vitiligo.
Cell-Mediated Immunity	CD4+ and CD8+ T cells, regulatory T cells (Treg), and cytokines are implicated in vitiligo.
Humoral Immunity	Various antibodies are detected in vitiligo patients, including anti-melanocyte antibodies.
Neural Theory	Neuropeptides and neurotransmitters, such as catecholamines, may be involved in vitiligo.
Oxidative Stress Theory	Oxidative stress and reactive oxygen species (ROS) contribute to melanocyte damage in vitiligo.
Apoptosis and Reduced Survival	Apoptosis and impaired melanocyte survival mechanisms play a role in vitiligo progression.
Melanocytorrhagy Hypothesis	Weak basal attachments of melanocytes may lead to their migration and loss (melanocytorrhagy).
Convergence Theory	Multiple factors, including stress, genetics, toxins, and autoimmunity, may converge in vitiligo.

Diagnosis:

Wood's The diagnosis of pigmentary diseases is based on light assessment. Lesional enhancement is a common finding in vitiligo when examined with a Wood's light. Many enhancing lesions on the skin turn out to be false positives [5].

Histopathological analysis reveals long-standing and well-established patches lack melanocytes and involve the loss of melanocytes at the dermo-epidermal interface [6].

Dermoscopy has the potential to be helpful in tracking the course of the illness and its treatment (stability, progression, repigmentation). Perifollicular pigmentation in progressing lesions and perifollicular depigmentation in stable/resolving lesions are the most informative dermoscopy findings.on [7].

Assessment Methods in Vitiligo

Table (4) The assessment methods used in vitiligo evaluation [8]:

Assessment Method	
Vitiligo Disease Activity (VIDA)	A six-point scale based on patient reports to evaluate vitiligo activity. - +4: Activity of 6 weeks or less - +3: Activity of 6 weeks to 3 months - +2: Activity of 3 to 6 months - +1: Activity of 6 to 12 months - 0: Stable for at least 1 year - -1: Stable for at least 1 year with spontaneous repigmentation
Vitiligo Area Scoring Index (VASI)	Divides the body into regions and calculates the percentage of vitiligo involvement for each region. Residual depigmentation is expressed in percentages (0%, 10%, 25%, 50%, 75%, 90%, or 100%). VASI is calculated by multiplying the values assessed for each body site and summing them up.
Vitiligo European Task Force (VETF)	Evaluates extent, stage, and progression of vitiligo lesions. - Extent assessed using the rule of nines. - Staging based on cutaneous and hair pigmentation (Stage 0, 1, 2, 3). - Spreading assessed as (+1: progressive; 0: stable; -1: regressive).

Treatment

Table (5) The treatment options for vitiligo [9]:

Treatment	
Medical Treatment	
1. **Topical Treatment**	
a. Topical Corticosteroids	Commonly used but with concerns about side effects like skin atrophy and hypertrichosis.
b. Topical Vitamin D Analogues	Used alone or in combination with steroids to affect melanocyte and keratinocyte growth and differentiation.
c. Topical Calcineurin Inhibitors	Tacrolimus and pimecrolimus block cytokine production and T cell activation, effective especially on the face.
d. Topical 5-Fluorouracil	May stimulate melanocytes and increase melanosomes in keratinocytes.
e. Topical Latanoprost	Used for glaucoma, stimulates melanocytes and immunomodulation, easy self-application.
2. **Systemic Treatment**	
a. Systemic Corticosteroids	Used for disseminated vitiligo with rapid progression, with side effects like weight gain and sleep disturbances.
b. Systemic Antioxidants	Vitamin E and Ginkgo biloba may be beneficial, especially in combination with phototherapy.
3. **Janus Kinase (JAK) Inhibitors**	Modulate immune response and stimulate melanocyte growth, effective in combination with light exposure.
Phototherapies and Photochemotherapies	
- Narrowband UVB (NB-UVB) Phototherapy	Effective and well-tolerated treatment for vitiligo, promoting melanocyte growth and migration.
Depigmentation	Considered in extensive or disfiguring vitiligo, including therapies like monobenzyl ether of hydroquinone.
Camouflage	Use of temporary or permanent methods like foundation, sunless-tanners, or micropigmentation (tattooing).
Psychological Support	Psychotherapy, such as cognitive behavioral therapy (CBT), can help address the emotional impact of vitiligo.

Co-enzyme Q10 (Co Q10)

Co Q10 is a substance found in cell membranes and mitochondria that acts like a vitamin and is soluble in lipids. Co Q10's principal role is to deactivate inflammatory pathways [10], protect mitochondria and DNA

from oxidative damage, and facilitate energy generation through the mitochondrial electron transport chain.

It plays a crucial function in the generation of cellular energy in the form of ATP by being tightly attached to the inner mitochondrial membrane and taking part in the electron transport chain and oxidative phosphorylation. Tissues with a high metabolic activity, such the heart, kidney, liver, and muscle, have more of it [10].

However, its physiological concentrations may be lowered by a variety of causes, including heredity, age, and therapy with statins. Coenzyme Q10 (CoQ10) is not an FDA-approved medicine, although it has been suggested as a possible option for the treatment of many disorders. This product is not intended to diagnose, treat, prevent, or cure any illness; it is marketed only as a dietary supplement. However, many clinical studies have shown that oral administration of Co Q10 improved a variety of conditions, including mitochondrial, cardiovascular, and neurodegenerative illnesses, that have been linked to low Co Q10 levels and high oxidative stress [11].

All tissues and organs, but notably those with a high energy demand, need Co Q10 for optimum functioning since it is the sole lipid-soluble antioxidant generated endogenously and plays a vital role in ATP production [12].

Activated CoQ10

Coenzyme Q10 (CoQ10) may be found in a variety of dietary sources, including both plant and animal tissues. Vegetables, fruits, and grains have low levels of CoQ10 (1-10 mg/kg), whereas meat, fish, nuts, and certain oils contain 10-50 mg/kg. Animal hearts and livers, which contain 30–200 mg/kg of Co Q10 due to their concentration in high energy-demanding tissues, are the best sources of this bioactive chemical. CoQ10 has no set dietary reference value; nevertheless, the average daily consumption for men and women is 5.4 mg and 3.8 mg, respectively [13].

But as a non-essential nutrient, it is thought to be produced mostly by endogenous synthesis. The body of a healthy adult stores between 0.5 and 1.5 g of Co Q10, however this amount may be lowered by a number of causes. Inadequate Co Q10 or its dietary precursors, excessive utilisation of the molecule due to ageing and oxidative stress, or a combination of these factors can all lead to deficiency [14]. Deficiency can also occur as a result of physiopathologic conditions such as acquired or genetic alterations in metabolism or biosynthesis.

Skin absorption and dispersion

Oral administration of CoQ10 has been shown to enhance blood and organ CoQ10 concentrations, including those of the liver, heart, and brain. However, research of the concentration in skin was lacking. Coenzyme Q10 (Co Q10) raises Co Q10 levels in blood and basal keratinocytes after oral treatment. Supplementation at a greater dose may be necessary to significantly reduce protein oxidation in corneocytes, the body's outermost organ [15].

Coenzyme Q10 (Co Q10) levels were shown to rise in both sebum and stratum corneum when it was applied orally and topically at the same time, but only in sebum when applied topically alone [16].

Roles in energy generation and antioxidant defence

Coenzyme Q10 (Co Q10) serves as a carrier in the mitochondrial electron transport chain, which is its primary function. Coenzyme Q10 (Co Q10) shuttles electrons between complexes I (NADH dehydrogenase) and II (succinate dehydrogenase), maintaining a stable equilibrium between its reduced (Ubiquinol) and oxidised (Ubiquinone) forms. This redox cycle produces the semiquinone intermediate in the respiratory chain by a two-step transfer of one electron each. Coenzyme Q10 (Co Q10) also has essential responsibilities in the provision of cellular energy [17], such as facilitating the transport of protons to the mitochondrial intermembrane space, where they may be used to generate the energy needed to make adenosine triphosphate (ATP).

The significance of its antioxidant effects as a result of its electron transport characteristics cannot be overstated. It is found in all tissues and has been proven to protect cell membranes against lipoperoxidation due to free radicals (FR). Most of Co Q10's actions are thought to involve ubiquinol, its reduced form, a potent antioxidant agent. Mitochondrial glycerol 3-phosphate dehydrogenase, mitochondrial dihydroorotate dehydrogenase, and electron-carrying flavoprotein dehydrogenases all contribute electrons to the redox process that reduces CoQ10 to CoQ10H2 (ETFDHs). Therefore, oxidoreductases such cytochrome b5 reductase (CytB5) and NAD(P)H quinone dehydrogenase 1 (NQO1) are essential components of the Co Q10 redox cycle, which occurs in cellular membranes. In turn, ubiquinol interacts with alpha-tocopherol and vitamin C radicals, lowering OS [18]. This allows the active form of Co Q10 to be recovered.

Immune and anti-inflammatory properties

It had previously been shown that CoQ10 had a preventative function in a number of physiological and pathological processes. Coenzyme Q10 (Co Q10) has been shown in several trials to have anti-inflammatory effects. But how exactly they work is still a mystery. There are a few possible processes that might help explain it. Inhibiting NF-kappaB gene expression, dampening miR-146a and IL-1 receptor associated kinase modulation, and decreasing the secretion of macrophage inflammatory protein-1 alpha and regulated upon activation normal T-cell expressed and secreted factors are all ways in which Co Q10 may play a role in lowering the production of pro-inflammatory cytokines [15].

Several studies have shown that adiponectin correlates negatively with inflammatory markers (TNF-, IL-6, CRP). An increase in adiponectin caused by coenzyme Q10 leads to a reduction in inflammatory factors such tumour necrosis factor alpha. [15]

Vitiligo and coenzyme Q10:

The self-destruction theory postulates that melanocytes in vitiligo lack a natural defence mechanism that gets rid of harmful byproducts of the melanogenesis process. Several studies show that people with vitiligo have elevated levels of oxidative stress across their whole epidermis. Patients with active vitiligo show higher oxidative stress, however this is likely linked to increased generation of intracellular reactive oxygen species (ROS) in these patients' tissues [19].

Vitiligo may be associated with a reduction in superoxide dismutases (SOD) and an increase in xanthine oxidase (XO) activities, both of which contribute to free radical production and subsequent lipid peroxidation. In addition, these results are corroborated by an elevated amount of malondialdehyde (MDA). Depigmentation in widespread vitiligo may be caused, in part, by lipid peroxidation in the membranes of melanocytes [20].

Co Q10's therapeutic potential was studied in vitiligo sufferers. Skin contains the antioxidant coenzyme Q10 (Co Q10). Hydroquinone (ubiquinol), the reduced form of CoQ10, is a powerful lipophilic antioxidant that can recycle and regenerate other antioxidants like tocopherol and ascorbate. Co Q10 may protect cultured epidermal keratinocytes and dermal fibroblasts from the damaging effects of hydrogen peroxide and ultraviolet A (UVA) [21].

However, there were also reports of negative effects from using topical Co Q10. The likely mechanism of Co Q10-induced facial vitiligo was investigated by Schallreuter (2013). The author hypothesised that in susceptible people, applying topical Co Q10 caused the production of hydrogen peroxide (H_2O_2), which in turn caused facial vitiligo. Spectroscopic in vivo studies of epidermal H_2O_2 showed its existence in all instances [22].

Interleukin-6 (IL-6)

The gene for human IL-6 has been located on chromosome 7p21; the protein itself consists of 212 amino acids, the first 28 of which make up the signal peptide. Natural IL-6 is 21–26 kDa in size; this is due to glycosylation, while the core protein is just 20 kDa. IL-6 is a Th2 cytokine with many different biological functions, including modulation of the immune system, hematopoiesis, inflammation, and more. Multiple autoimmune and inflammatory diseases, including type 1 diabetes, atherosclerosis, SLE, RA, gout, periodontitis, and others, have been linked to IL-6 [23].

The progression from innate to acquired immunity involves IL-6. A similar immunological imbalance between Th17 and Treg cells, leading to autoimmune disease, may be induced by IL-6. The immune system is modulated by IL-6, which plays a critical role in dendritic cell development (DCs). DCs, especially plasmacytoid dendritic cells (pDCs), release IL-6, which is essential for B-cell differentiation into plasma cells and antibody production [23].

IL-6 plays a crucial role in connecting the innate and acquired immune responses by encouraging the specialised development of naïve CD4+ T cells. Th17 development from naïve CD4+ T cells requires IL-6 and TGF-, although IL-6 also suppresses Treg differentiation when TGF-b is present. Disruption of immunological tolerance, and hence pathogenic involvement in the development of autoimmune and chronic inflammatory disorders, is thought to result from an up-regulated Th17/Treg balance. The production of IL-21, which controls immunoglobulin (Ig) synthesis and, in particular, IgG4 production, and T-follicular helper-cell differentiation have both been found to be facilitated by IL-6. CD8+ T cells may be induced to become cytotoxic T cells by IL-6 [24].

Enhanced angiogenesis and increased vascular permeability are pathological features of inflammatory lesions, and are observed, for example, in the synovial tissues of rheumatoid arthritis (RA) or the edoema of remitting seronegative symmetrical synovitis with pitting edoema syndrome. IL-6 induces excess production of vascular endothelial growth factor. Systemic sclerosis patients may see alterations to their skin because IL-6 promotes

keratinocyte proliferation or collagen synthesis in dermal fibroblasts [24].

Function of IL-6 in Vitiligo:

Patients with vitiligo have been shown to have elevated IL-6 expression in their skin and serum. However, findings of cytokine levels in vitiligo patients are inconsistent. The aetiology of vitiligo, in particular, has been linked to changes in Treg and Th2 cell responses to T helper type 1 (Th1) and type 17 (Th17) antigens. Vitiligo skin has a higher concentration of T cells, which persist in the lesional region but seem to move along with the epidermal border as it loses colour. The first hint suggesting the role of cellular immunity in the aetiology of vitiligo was the identification of a T-cell infiltration in the margins of lesions in inflammatory vitiligo [25].

Th1 responses are bolstered by the generation of TNF- and IFN- by both helper and cytotoxic T cells. Patients with vitiligo had elevated IL-6 and IL-8 production but decreased TNF- and IFN- release, suggesting IL-6's potential importance in melanocytic cytotoxicity. The fact that IL-17A and IL-17F Th17 cells generate IL-6, IL-21, IL-22, and TNF- is well established.α [26].

5. Conclusion

Vitiligo the complexity of its causes makes it difficult to diagnose and treat. Melanocyte dysfunction is fueled by a complex web of elements including genetic susceptibility, autoimmune processes, oxidative stress, and environmental influences. In order to choose the best course of therapy for vitiligo, the severity and duration of the condition must be evaluated. Treatment for this ailment includes a combination of medicinal, phototherapeutic, and psychosocial approaches. Additional research into the roles of coenzyme Q10 and interleukin-6 in the development of vitiligo is warranted.

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