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Review Article

Biomarker of Vitiligo: A Review Update

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ABSTRACT

The pathophysiology of vitiligo is very complex. It is an autoimmunity disease that cause white patches on the skin basically when decrease the melanin production in our body then they cause the skin depigmentation. Highly sensitive C-reactive protein is susceptible marker for the systemic inflammation in body. Interlukins-6 and TNF-alpha is the inflammation mediator they cause systemic inflammation. When the nutrient deficiency then increases the level of homocysteine because they inhibit the tyrosine enzyme by binding with copper and it is reversible hypopigmentation. The S100B Protein is increase in the patient of vitiligo this protein is react with less than 6 months in all vitiligo patient when the rapidity increases the concentration of S100B protein in the patients they cause the neuronal dysfunction and cell death it produces pro-inflammatory cytokines that are harmful for the tissue. The Neutrophil growth factor is also the factor of causing the depigmentation of skin because when the person is surfer from the schizophrenia, depression and other mental disorder they are also cause the depigmentation. When the decrease the Vitamin D level in our body then they cause the different disease such as diabetes mellitus, Rheumatoid arthritis, depigmentation, multiple sclerosis and other disease.

Keywords: Copper, Highly sensitive C reactive protein, Homocysteine, S100B protein, Vitamin D, Vitiligo, Zinc.

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INTRODUCTION

A disorder called vitiligo develops patches and regions of lighter skin by discolouring the surrounding skin. A few spots may appear on certain persons. Others have a more extensive loss of colour. Dermatologists provide treatments that might bring back the colour of missing skin. White macules and patches appear on the body as a result of vitiligo, a gain pigmentary dermis condition cause by the lack of pigmentary cells in the Epidermis. Thyroid problems are the most prevalent autoimmune issue connected with the syndrome. However, there are generally a few others. Although the cause of vitiligo is unclear, its pathophysiology can be explained by a variety of ideas. Clinically, vitiligo manifests as symmetrically distributed white patches on the body, which are more noticeable in those with darker skin. The lesions are oval, round, or linear in shape, with well define, de-pigmented pearly white patches. The borders are convex, ranging in size from a few millimetres to centimetres and they expand centrifugally. Trichrome, marginal inflammatory and Quadri chrome vitiligo are the three distinct clinical forms of the condition. Another typical clinical manifestation is the Koebner phenomenon, which is the development of vitiligo in particular trauma-prone areas, such as cuts, burns, or abrasions. First lesions are most common on the hand, feet, forearms and face, with a preference for a perioral or peri-ocular distribution. Three forms of pattern Vitiligo are distinguished according on distribution: widespread, segmental and localized. The damaged body surface area is used to assess the disease's severity. The disease's progress is frequently unexpected and changes depending on the course of therapy. Low self-esteem, social stigma and psychological suffering are frequently brought on by depigmentation. In India, vitiligo is reported to occur in 0.25-2.5% of cases. The states with the greatest frequency are Gujarat and Rajasthan (8.8%). According to certain dermatological outpatient data, vitiligo occurs in India between 3% and 4% of the population, while reports have shown that the frequency might reach 8.8%.

VARIOUS BIOMARKER OF VITILIGO

CXC Motif Ligand

Wang and colleagues identified the different components of the CXCL10 pathway. It has been determined that CXCL10 is associated with progressive instances and that there are differences in CXCL10 levels between individuals with stable and active vitiligo.[1] It is a member of the subfamily CXC. A chemokine called CXCL and its receptors are involved in ethology of a no. of autoimmune disease.[2] Interferon (IFN)-Y induces it is a various cells types included fibroblasts and lymphocytes, neutrophils, endothelial cell or another epithelial cell. It has a binding with the

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CXCR3 and CXCL 10 specific receptors through the recruit and activation of T-cells and Monocytes or Killer cells it is regulates the immunological responses.[3]A high concentration of CXCL 10 in peripheral fluid is indicative of a host immunological response, particularly a Th1-oriented immune response. Th1 lymphocytes recruited into inflammatotissues produce IFN-Y or Tumour Necrosis Factor (TNF)-alpha which is turn and trigger to CXCL10 release the identification of IFN-y signature depigmentation CXCL10 was examined.[4]

Highly sensitive C reactive protein

One sensitive sign of systemic inflammation is C Reaction Protein (CRP) This is mediated from the regulation of the hepatic production of acute phase of reactants like CRP include Interleukin (IL)1 IL6, or TNF alpha.[5] A quantitative laboratory test called the Hypersensitive CRP (hsCRP) test measure a very low amount of CRP in the serum. This test is through index for assessing coronary problem and is frequently use in a diagnostic and prognostic marker for heart disorder. The liver secretes CRP, an acute phase protein, into the blood stream to response inflammatory cytokines like IL6 or number of another systemic inflammation indications.[6,7] Standard CRP is used for patients with acute inflammation and to assess obvious chronic inflammation with typical values of 0-0.5 mg/L It is less than 1mg/L of inflammation regarded as reduce risk 1-3 mg/L as medium risk or more than 3 mg/L as high-risk .when values exceed 10 mg/L, it is necessary to identified the cause of inflammation and infection or repeat the test once the patient has recovered.[8] Another research indicated that there was no statistically difference between two groups or the local inflammation brought on vitiligo had no impact on these level of CRP. In order to shed additional light on this crucial topic, they also advice doing another study with a larger sample size, a longer illness duration and a higher percentage of people with bodily involvement.[9]

Homocysteine

Elevations of Homocysteine (Hcy) in the local environment may disrupt regular melanogenesis and contribute to the pathophysiology of vitiligo. Hcy metabolism depends on vitamin B12 or Folic acid both are deficient in the vitiligo suffers. Increased Hcy levels in the blood are the predicted consequence of a nutritional deficit in these 2 vitamins in vitiligo.[10] Additionally, it causes reversible hypopigmentation by attaching to active site of tyrosinase enzyme or inhibit. According to two investigations, the degree of disease activity in vitiligo patients was correlated with higher Hcy concentrations.[11,12] Other, more modestly sized research, however, revealed no connection between Hcy levels and vitiligo activity.[13,14]

Brainderived neutrophic growth factor

In which one key neurotrophins that controls the synaptic plasticity of Brain-Derived Neurotrophic Factor (BDNF). Additionally, it essential for memory or learning processes.[15] The human brain's BDNF signalling has been shown to influence behaviour. Apart from its function in education and recall, BDNF has also been linked to actions connected to emotions. In Neuro-psychiatric conditions in which involved bipolar disorder or major depressive disorder or schizophrenia, BDNF is extensively researched.[16] It has recently been determined that neurotrophins and their receptors regulate skin haemostasis and hair development.[17] According to one study, lower blood levels of BDNF show the risk factor of vitiligo development or may also be a sign of psychological problems in vitiligo patients down the road. It could serve as a biomarker for psychosomatic conditions that vitiligo suffers may experience.[18]

S100B protein

S100B belong to the S100 protein family, which consists of 21 low-molecular-weight proteins with 21 different genes.[19] Numerous tissues involved melanocytes or astrocytes and oligodendrocytes or Schwann cells, brain progenitor cells, or kidney epithelial cells and skeletal myofibers or Langerhans cells, adipocytes or a subset of lymphocytes, have been shown to express S100B.[20] A recent study that S100B was passively released by injured tissues and that it was expressed by melanocytes but not in a keratinocytes and fibroblasts.[21] In comparison to all other vitiligo patients Specker. it found in which patient in active depigmentation higher circulating levels S100B, or that these levels increased in a patient with recent, disease activity, (<6 months). They also found in a higher correlation between S100B serum levels or bod surface areas are affected, but not patients' stable vitiligo.[22] It has been discovered that lower S100B concentrations (micromolar levels) are advantageous while high ones (nanomolar levels) are determine.[23] Through a Inflammatory response are prompts microglia or astrocytes to recruit or produce pro-inflammation cytokines, elevated calcium levels or nitric oxide which have detrimental effect on the tissue, rapidly rising extra-cellular levels of S100B cause neuronal dysfunction and cell die.[24] Elevated blood S100B levels have been proven to be helpful tracking individually with malignant melanoma and keeping an eye on their prognosis. S100B protein is mostly derived from cell injury, necrosis or apoptosis that follows and continuous extrusion from tumour locations in these individuals.[25] S100A2 was shown to have a protective impact on melanoma cells and its overexpression was linked to higher expression of the tumour suppressor p53.[26] At lower doses, S100B protects melanocytes; but, at greater concentrations, it causes inflammation and other negative consequences.[27]

SOX10 antibodies

Embryonic Melano blasts express SOX 10, a transcription factor associated with melanocytes.[28] It is expressed throughout human embryogenesis in the sympathetic or parasympathetic ganglia and enteric ganglia in the gastrointestinal tract or the central

and peripheral nervous system. In which important to the different tissues that arose from the neural, crest. Additionally, the pancreas, heart, lung and submandibular glands exhibited it. It expressed the SOX10 in adults in which found the heart, Prostate and small intestine or colon or brain.[29] Microphthalmia associated with transcription factor is a gene critical formation of the melanocytes or other neural crest derived cell, or SOX10 It show to bind and promoter.[30] Although it incidence of SOX10 Antibodies was 3.2% in the individual's solitary depigmentation, it was found to be a autoantigen in depigmentation associated with Autoimmune Polyendocrine Syndrome type1 (APSI), Potentially indicating to general involvement in ethology of depigmentation. The study identified SOX10 as an Autoantigen in (APSI) and demonstrated its expression in mature human skin melanocytes. In which these are those protein is linked to depigmentation. A subset of individuals with idiopathic vitiligo also strong reactivity to SOX10.[31]

Interferon γ

It is a one important immunological system regulator is the pleiotropic cytokine IFN-Y.32 INF-Y stimulates the autoantibodies activates autologous, cytotoxic t-cells or induces to targeted cell death in addition to host defense. When depigmentation patients were compared to control or between active or stable cases their serum IFN-Y levels were higher. While one research supported these conclusions, another found no differences.[32,33]

Vitamin D

Autoimmune disorders such as systemic lupus and diabetes mellitus or multiple sclerosis, rheumatoid arthritis have all been linked to low vitamin D levels, additionally, it raises melanogenesis and tyrosine activity in melanocytes via binding to the vitamin d receptor, a nuclear hormone receptor.[34] Through receptors on the dendritic cell and macrophages or T and B lymphocytes it may be influence the both innate and adaptive immune responses. Although the precise method by which vitamin D influences autoimmunity is uncertain, it is evident that *in vitro* vitamin D regulates immune cells.[35] There have been few research looking at the possible link between low vitamin D levels and vitiligo, however the findings are not entirely consistent. Ustun. looked at 25 depigmentation patients or 41 controls they are found that most patients had inadequate (<30 ng/mL) and extremely low (<15 ng/mL) vitamin D level but that difference statistically significant when compare the control group low blood vitamin D levels have been linked to autoimmune disorders in a number of studies, but it's still unknown if this is cause to effect of the autoimmune diseases. Forty vitiligo suffers and forty controls were examined in another investigation. The patient blood vitamin D levels were significantly low then the control.[36,37] Another study revealed that vitiligo patients had a lower serum of vitamin D levels then controls, however this difference is not statistically significant.[38] Psoriasis and vitiligo are two skin conditions that are treated with vit D or it' analogues. Topical calcipotriene has been used to treat vitiligo in patients. Vitamin D auto ultraviolet B radiation was shown to stimulate the growth of melanocytes.[39] Numerous studies have documented that are used in vitamin D analogues alone, in conjunction with UV radiation and corticosteroids, or both, to cure depigmentation and promote repigmentation.[40]

Interleukin 23

A member of the Interlukin-12 family, Interlukin-23 stimulates Th17 cell activity to enhance inflammatory response. The develop of autoimmune illnesses, such as Psoriasis and rheumatic arthritis or inflammatory bowel disease, auto immune diabetes, has been linked to IL-23. It was previously believed that the interlukins-23 mediated autoimmune secreting members of the interlukin-17 family because this cytokine stimulates the generation of Th-17 cell.[41] The levels of serum Interlukin-17 are noted in depigmentation patients, indicating a potential function for IL-17 in the Immune responses early onset diseases. Inflammatory macrophages these are stimulated and generate IL-1, TNF-alpha or IL-23 itself express it. It appears that Il-23 is crucial for autoimmunity.[42] It has been established that IL-23 is crucial for the central control of the inflammatory cellular processes. It could cause the innate immune system to enter an autocrine loop and produce a variety of inflammatory mediators.[43] Serum IL-23 level are show the considerably greater in depigmentation patients compared to control and Vaccaro. It found a stronger positive connection between serum interlukins-23 levels or the length, extent or activity of the condition.[44]

Vitamin B12 and folic acid

Vitamin B12 deficiency or pernicious anaemia is thought to be more common in vitiligo sufferers. Hyperhomocysteinemia is the consequence of a dietary deficit in either folic acid or vitamin B12, two important factors that determine homocysteine Hcy levels.[45] Numerous investigation revealed that are vitiligo patients much higher blood level of Hcy than controls did, that vitiligo patients had significantly low serum levels of Vit B12 [10-12] Numerous studies revealed that the level of folic acid and vitamin B12 or Hcy in the serum it is didn't different from statistically between depigmentation people or control.[46]

Zinc and copper

The two trace elements that are present in extremely min concentrations in the body are Zinc (Zn) and Zopper (Cu).[47] They have a role in several homeostatic processes in the body, including oxidative stress, particular immunity and inflammation.[48] It is one of the significant trace elements joined with the health or illness is Zinc.[53] Zn is crucial to the process of melanogenesis when combined with anther micro nutrient like copper, cobalt and nickel, Iron magnesium or Ca^{++}.[49] They are possible anti-apoptotic agents that prevent cell proteins from oxidizing and antioxidants that help eliminate free radicals. Moreover,

zinc and copper contribute to melanogenesis by releasing and manufacturing melanocyte stimulating hormone, which in turn stimulates cell-mediated immune responses.[50] Numerous investigations revealed that vitiligo patients' blood zinc levels were much lower than those of control subjects.[49,50] When there is a zinc shortage, copper absorption is increased.[51,52] Consequently, increased blood Cu levels were associated with decreased serum Zn levels.[53] Cooper levels where much greater active in vitiligo people then in the control, according to research by Helmy.[59] Numerous investigations see that no statistically differ in cu level between in the control group or vitiligo patients.[54,55]

Granulocyte Macrophage Colony Stimulating Factor and its Antibodies

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) is linked to the pathophysiology of multiple sclerosis and rheumatoid arthritis, among other autoimmune and inflammatory illnesses, according to recent investigations. It has been suggested that autoimmune gastritis might result from its overexpression in the stomach. Moreover, individuals with Crohn's disease have been shown to higher levels of GM-CSF auto antibodies.[56] The conclusion of GM CSF in vitiligo is interesting because to its function in autoimmune and inflammatory illnesses. The evidence supporting this involvement involves GM-CSF gene targeting or GM-CSF antibody blocking, which worsens illness in mice.[57] It is also considered a potential predictor of prognosis following Trans Plantation of Culture Autologous, Melanocytes (TCAM), as evidenced by the fact that circulating blood level of GM CSF was significant is high in the group of depigmentation people with excellent recovery of depigmentation following TCAM treatment than in group with bad and good recovery of depigmentation. According to this study findings, high GM-CSF levels in the serum may act as indicators to determine how well TCAM patients would fare.[58]

Macrophage migration inhibitory factor

Vitiligo is show to exhibit macrophage in-filtration, with a higher concentration of macrophages in the perilesional skin. It is hypothesized that cytotoxic T lymphocytes-induced apoptosis in melanocytes is cleared by macrophages.[59] The lymphokine known as macrophage Migration Inhibitory Factor (MIF) first shown to concentrate macrophages at sites of inflammation. It is thought to be crucial for cell-mediated immunity as it is a strong *in vivo* macrophage activator.[60] A research by Sarasvan. Evaluating the blood is 30 vitiligo patients and 30 healthy controls suggested that MIF likely play a role in Patho-physiology of the vitiligo. It shows the main serum MIF level in depigmentation people was greater than in control, suggesting that MIF plays, a role in the pathophysiology of the condition. Additionally, they found a useful between, duration of the disease or MIF levels in vitiligo patients. Serum MIF levels were greater in patients with acral and acrofacial, or generalized depigmentation than in those with localized depigmentation.[61]

Some-soluble forms of tumour Necrosis factor receptor

The cytokine receptor protein super-family known as the TNF receptor superfamily (TNFRSF) is distinguished by its capacity to bind TNFs through an external cysteine-rich region.[62] Most TNF receptors in the plasma membrane form trimeric complexes when they are activated. Transmembrane Domains (TMDs) are present in the majority of TNF receptors; whereas some-like TNFR1-can be cleaved into soluble forms and others-like decoy receptor 3-do not have TMDs at all. Furthermore, for downstream signalling, the majority of TNF receptors need certain adaptor proteins including Fast-associated death, domain protein TNFR-associated factor, Death domain connected with TNF receptor and protein that interact with the receptor. TNF receptors participate in several signal transduction pathways, including those that promote proliferation, survival and differentiation, even though their primary roles are in inflammation and apoptosis. TNFR are expressed many different organs, although they are most prevalent in leukocytes.[63]

Soluble cluster of differentiation 27

Naturally killing cells T cells and B cells make CD27, a transmembrane protein that is a part of the TNFRSF. CD27 guarantees lymphocyte permanence increases T-cell growth, or the development of reminder cells via attaching to its ligand, CD70.[64] The development of helper T-cells type1 (TH1) is supported by its expression by means of alternative splicing or extra-cellular domain shedding and the membrane bound receptor protein and activated lymphocytes can release miscible Cluster of Different 27 (sCD27) in the blood stream. In a number of inflammatory illnesses, the blood CD27 levels, has been utilized as a biomarker that track immunological activation or disease burden however, it is still unknown if sCD27 plays a functional role in the illnesses and it is a consequence of T-cell activation.[65] Research conducted on animal and human models suggest that CD27 signalling might enhance IFN-γ-dependent immune responses, a finding that is especially pertinent to vitiligo. Recent research has demonstrated that sCD indicators actively participate in inflammatory processes. Among these contributions are the ways in which sCD27 stimulates the immune system by triggering T-cell activation.[66] Furthermore, sCD27 stimulates the synthesis of immunoglobulin G and gives antigen-primed B cells an activation signal.[67]

Soluble cluster of differentiation 25

There is evidence linking sCD25 to the development of autoimmunity. By preventing IL-2R's downstream signalling, sCD25 promotes the growth of TH17. The TH17 phenotype is induced in T-cell responses by functioning as a fictitious receptor

for IL-2.[68] Accordingly, elevated blood levels of IL-17 and circulating TH 17 cell have been link to active vitiligo.

DISCUSSION

The biomarkers of vitiligo show the increases and decreases of the element they cause vitiligo in the people. When there is a deficiency of vitamin B12 they are suffering from vitiligo. Folic acid and vitamin B12 are two important factors to determine the homocysteine levels. There are different autoimmune disorders linked with vitiligo such as diabetes mellitus, multiple sclerosis and rheumatoid arthritis. When the deficiency of vitamin D causes autoimmune disorder and causes depigmentation of the skin called vitiligo.

CONCLUSION

In this report we observe the various type of vitamin deficiency such as vitamin A, D and Vitamin B12, Folic acid, in our body then they will cause the vitiligo in the person and developed the auto immune disease like as Diabetes mellitus, Rheumatoid arthritis, depigmentation, multiple sclerosis and other disease. When the decrease of vitamin D level in our body they cause the autoimmune disease such as Diabetes mellitus. Zinc or Copper are present in our body very few amounts. When cause zinc deficiency then copper absorption is increase. The copper levels are increase in vitiligo patient. The S100B protein also increase in the vitiligo patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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