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Investigating the Roles of Brain-Derived Neurotrophic Factor, Vitamin D, and Insulin Resistance in Vitiligo Patients

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ABSTRACT

Background: *Vitiligo is a skin condition where skin loses its color, presenting as macules which are smooth white patches. It is considered to affect 1% of the world's population and is associated with various factors such as autoimmunity, oxidative stress, and some mosquito psychological comorbities. Reduced levels of brain derived neurotrophic factor (BDNF) and vitamin D in addition to insulin resistance have also been impart in this disorder.* ***Objective****: The objective of this study was to determine the degree of involvement of BDNF, insulin, and vitamin D on the causation and course of vitiligo.* ***Methods****: A case control study was where 90 subjects were enrolled; 45 diagnosed with vitiligo and 45 were healthy control subjects from the dermatology clinic. Serum level of BDNF, insulin, vitamin D, and other metabolic markers were taken for evaluation through Enzyme linked immunosorbent assay (ELISA) tests. The activity and severity of the disease were evaluated using VIDA and VASI scores in that order. The parameters were then compared through statistical analysis (t-test and Pearson correlation) while the diagnostic accuracy of BDNF was evaluated with the ROC curve analysis.* ***Results****: With respect to mean serum level findings, BDNF and vitamin D were significantly lower in the vitiligo patients compared to the controls ($p<0.05$). Conversely, insulin, fasting blood glucose FBG, and HOMA-IR levels in the patient group were significantly increased ($p<0.05$). The diagnostic potential of BDNF was poor with AUC=40%. Furthermore, there were significant relationships discovered between the serum levels and duration as well as severity and activity scores of the disease.* ***Conclusion****: In reference to the above investigation, the three potential targets may be insulin resistance, BDNF, and deficient Vitamin D. These may be factors in the explanation of the pathophysiology of vitiligo. These biomarkers may be useful for strategizing therapy, disease management, and the psychological disease that accompanies vitiligo.*

Keywords*:* **Vitiligo, Brain Derived Neurotrophic Factor, ROC-Curve, Iraq.**

Article Information

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INTRODUCTION

Vitiligo is a form of skin disorder in which pigmentation is lost on certain skin areas resulting in smooth white patches or depigmented skin. It affects about one per cent of the world's population and is more conspicuous in people with darker skin [1,2]. Although vitiligo may occur at any age, most cases arise before 30 years. Different biological mechanisms have been suggested including autoimmunity, oxidative injury, neurohormonal imbalance, and autocytotoxicity; autoimmunity is the proposed theory for most vitiligo cases [3]. Brain-Derived Neurotrophic Factor (BDNF) is

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one of the most important form of neurotrophin and is responsible for the modification of synaptic plasticity during learning, memory, and behavior. Apart from that, it also assists skin homeostasis by encouraging the growth and maintenance of melanocytes and keratinocytes [4,5]. Lowered levels of BDNF activity have been linked to some forms of depression and some neuropsychiatric disorders, as well as some skin conditions such as vitiligo, acne, and psoriasis [6,7]. Research works indicate that lowered levels of BDNF may be one of the factors involved in the pathogenesis of vitiligo and may indicate the presence of psychiatric disorders in people with vitiligo [8]. Vitamin D proves to be another crucial factor as it modulates both the adaptive and the innate response through its receptors present in lymphocytes B and T, dendritic cells and macrophages [9].

There is a growing body of evidence that associates a lack of Vitamin D with autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus, and even multiple sclerosis. Concerning the vitiligo scenario, Vitamin D acts to increase the activity of melanocytes by enhancing their growth, differentiation, and melanin synthesis. On the other hand, contradictory findings have been reported on the relationship between Vitamin D and vitiligo [10,11]. Another condition that has also been associated with vitiligo is Insulin resistance (IR) – defined as the inability of the body to utilize insulin adequately. IR adds to metabolic derangements and is known to be associated with type 2 diabetes. The concept of BDNF having some relationship to the insulin sensitivity of the vitiligo patient still requires confirmation, especially in view of the fact that there could be a possible linkage [14, 32]. This study is set to investigate the likely involvement of BDNF, insulin resistance, and Vitamin D deficiency in the pathophysiology of vitiligo along with their possible usefulness as indicators of the disease and concurrent mental disorders.

METHODS

Using an observational strategy, controls and 45 patients diagnosed with vitiligo aged between 18 and 72 were recruited from Al-Sadiq Teaching Hospital and Hilla General Teaching Hospital Dermatology Clinics between June 2024 and November 2024. Clinical parameters of the patients including history of the disease, sex, age, duration of the illness, severity of the disease, etc were documented. The diagnosis and type of vitiligo was confirmed and classified by the dermatologists to restrain the disease activity. The disease activity and severity were quantified by the aid of II (13,14). VABS, also known as Vitiigo Area Scoring Index 9, was set to measure the disease severity.

All study subjects had to record their blood sample. After coagulation, the samples were kept in centrifuge for 10 minutes at 3000 *g to separate the serum from the blood and obtain it for analysis. The level of BDNF, insulin, and Vitamin D was checked using ELISA test. Metabolic parameters were analyzed alongside Fasting blood glucose levels (FBG) and HOMA-IR treatment. The data was then entered into IBM SPSS 26 for analysis and interpretation. A t-test was done to the means comparisons in the two singles groups where the null hypothesis was that all means were equal. IF the p value was smaller than 0.05, the difference was marked as significant. Adjusted parameter linear relationships were calculated by Pearson correlation. The diagnostic accuracy of BDNF was evaluated using receiver operating characteristic (ROC) curve analysis. Ethical approval was obtained from the relevant institutional ethics committees, and informed verbal consent was secured from all participants before sample collection.

Table 1: Disease severity assesses through VASI score.

Table 1: VIDA score	
Disease activity	**VIDA score**
Active in 6 weeks	+4
Active in 3 months	+3
Active in 6 months	+2
Active in 1 year	+1
Stable for at least 1 year	0
Stable for at least 1 year and spontaneous repigmentation	−1

Every participant had a blood sample drawn from their vein. The sample was centrifuged for ten minutes at 3000 x g after the blood was gently pumped into a gel tube and allowed to coagulate for ten to fifteen minutes at room temperature. Next extract serum and put it in Eppendorf tube, the amount of BD NF, Insulin and Vit D were determining by enzyme-linked immunosorbent assay (ELISA) kits.

Ethics approval

Before collecting samples, all study participants were informed and allowed to verbally consent. A local college and hospital ethics committee examined and approved the study protocol.

Statistical analysis

The current study's results, which compare the patient and control groups, were statistically calculated using the t-test to find the mean difference between the two groups (p-value ≤ 0.05), which is significant. Pearson correlation was also used to determine the correlation between the parameters under study. The IBM Statistical for the Social Sciences (SPSS V. 26) was used to conduct Brain-Derived Neurotrophic Factor level ROC curve analysis.

RESULTS

a. The demographic characteristics of study contributors

The mean difference between the control and vitiligo groups, as well as the correlation between the various patient parameters, were computed statistically using the t-test in the current comparative analysis of the patient and control groups. 45 subject as vitiligo group and 45 control group in all enrolled in this study. It has been no certain change in age across control in addition to patients with vitiligo as it was shown in table 2.

Age: The mean age of patients (34.75 ± 9.41 years) and controls (35.14 ± 8.91 years) is comparable. The p-value (>0.05) suggests no significant difference in age distribution between the two groups.

Sex Distribution: Among patients, 40% (17/45) are male, and 60% (28/45) are female. Among controls, 44% (21/45) are male, and 56% (24/45) are female. The p-value (>0.05) indicates no significant difference in sex distribution between the groups.

Family History: Family history of the condition is present in 26% (12/45) of the patients and absent in 74% (33/45). Family history data for controls is not provided.

Duration of Disease: The mean duration of disease in patients is 8.14 ± 4.56 years, with a range of 3.7–14.58 years. Duration of disease is applicable only to the patient group and is not relevant for controls.

VIDA Score (Vitiligo Disease Activity Score): The mean VIDA score for patients is 2.71 ± 1.49, ranging from -1 to 4.3. This score reflects disease activity, with positive scores indicating active disease and negative scores indicating stabilization.

VASI Score (Vitiligo Area Scoring Index): The mean VASI score for patients is 26.2 ± 23.5, with a range of 11–91. VASI measures the extent and severity of depigmentation in patients. No significant differences in age or

sex distribution are observed between patients and controls. Family history, disease duration, VIDA, and VASI scores provide additional insights into the patient group, emphasizing disease characteristics and activity levels **Table 2**.

Table 2: Comparison between cases and controls regarding their demographic data.

Demographic data	Patients (Mean ± SD) N=45	Control (Mean ± SD) N=45	P-value
Age (years)	34.75±9.41	35.14±8.91	>0.05
Sex n (%): Male Female	17 (40%) 28 (60%)	21 (44%) 24 (56%)	>0.05
Family history Present Absent	12 (26 %) 33 (74 %)	-	
Duration of disease (years) Range	8.14±4.56 (3.7-14.58)	-	
VIDA score Range	2.71±1.49 (-1 – 4.3)	-	
VASI score Range	26.2±23.5 (11-91)	-	

Patients with vitiligo have significantly reduced levels of BNFI when compared to healthy subjects supporting the possibly of BDNF playing a role in vitiligo. The elevated fasting blood glucose levels in vitiligo patients point to possible insulin resistance or metabolic disorders due to the illness. The considerably greater levels of insulin in patients are suggestive of insulin resistance which might play a role in the pathology of vitiligo. A greater HOMA IR in patients indicates higher insulin resistance and further strengthens the association between insulin dynamics and vitiligo. The significantly lower serum vitamin D levels in patients with vitiligo suggests that there is a deficiency that could be unfavorable to the immune system and the skin **Table 3**.

Table 3: Comparison between cases and controls regarding BNFI, FBG, HOMA-IR and vitamin D.

Variable	Patients	Control	P-value
BNFI (n g /ml)	8.035 ± 1.23	9.45 ± 1.67	<0.05
FBG (mmol/L)	6.2±2.01	7.4 ±2.4	<0.05
Insulin (mIU/mL)	16±1.6	8.9 ±4.6	<0.05
HOMA IR	4.9 ± 1.3	7.1±0.71	<0.05
Serum vitamin D (ng/ml)	14.4 ± 10.7	35.3 ± 16.3	<0.05

* Significant at p<0.05

Table 4 shows the relationship of the Brain-Derived Neurotrophic Factor Index (BNF) and the Homeostasis Model Assessment of Insulin Resistance (HOMA IR) with vitamin D and patient characteristics (age, the duration of the disease, and Vitiligo disease severity) of the patients. There is no strong evidence in the relationship between age and BNFI or HOMA IR. But instead there exists moderate positive relationship between age

and vitamin D levels which indicates that elderly patients will have increased vitamin D levels. Significant positive correlation can be established between the duration of the disease and BNFI, HOMA IR and the level of vitamins. This explains as the duration of vitiligo impairment increases the levels of BDNF, insulin resistance and vitamin D will increase. There is moderate positive correlation between the activity of the disease (VIDA score) and HOMA IR as well as vitamin D levels which demonstrates high activity of the disease could mean that there is more insulin resistance and a change in vitamin D level. The correlation with BNFI is not so great. All three have weak to moderate positive correlation with the VASI score which means that more severe disease (using VASI score quantitative) are having elevation of insulin resistance and reduction of BDNF and vitamin D Levels **Table 4**.

Table 4: Correlation between BDNF, HOMA-IR and Vit D, age, duration of diseases, vitiligo disease activity score, and vitiligo area scoring index score among patients.

variable	BNFI	HOMA IR	vitamin D
Age (years)			
r	0.01	0.051	0.31
p-value	0.73	0.53	0.44
Duration of disease (years)			
r	0.62	0.41	0.61
p-value	0.039*	0.042*	0.03*
VIDA score			
r	0.37	0.62	0.42
p	0.4	0.31	0.62
VASI score			
r	0.31	0.26	0.328
p-value	0.04*	0.02*	0.017*

The obtained data indicates that BDNF holds little promise as a reliable diagnostic marker for benign skin neoplasms considering the overall analysis of BDNF demonstrated low sensitivity and specificity **(Figure 1).** Additionally, these results serve as evidence that BDNF is not able to differentiate between normal and diseased skin. **Table 5** highlights further detail on the specificity of BDNF.

Table 5: Receiver operating characteristic (ROC) analysis of the Brain Derived Neurotrophic Factor.

Parameters	AUC	p-value	Sensitivity	Specificity	Cut off value	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
BDNF	40%	0.082	44%	45%	8.95	0.278	0.511

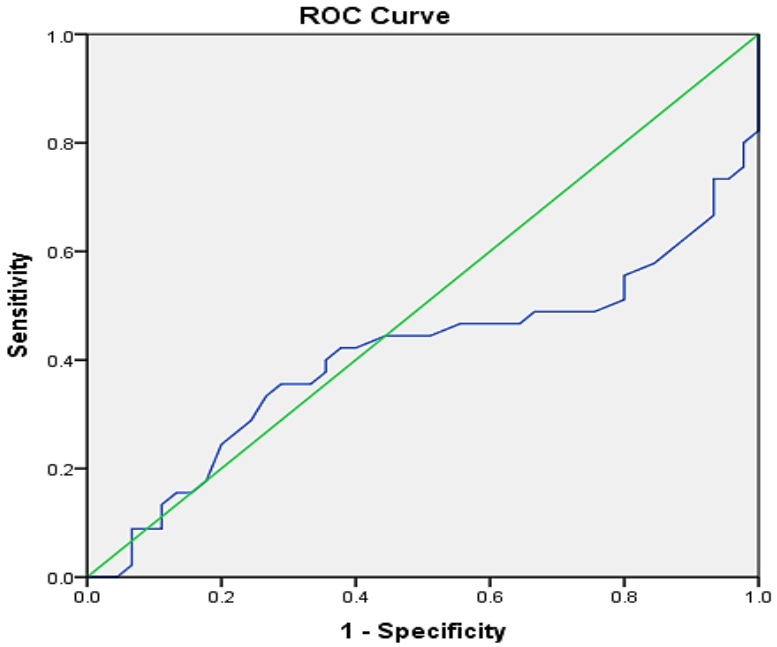

Figure (1): **ROC curve for the sensitivity and specificity of Brain Derived Neurotrophic Factor.**

DISCUSSION

This study demonstrated that vitiligo patients had significantly lower serum levels of Brain-Derived Neurotrophic Factor (BDNF) (3.16 ± 1.83, $p < 0.05$) compared to healthy controls, as shown in Table 2. BDNF is a vital neurotrophin that regulates synaptic plasticity, learning, memory, and mood. It equally affects skin homeostasis by increasing the proliferation and survival of both melanocyte and keratinocyte cells [15,16]. This came from vitiligo patients were demonstrated Yanik et al. [17] and Kussainova et al. [18] noted lower levels of BDNF. These were consistent with our findings where it was noted that BDNF could be a depression and psychological distress marker in vitiligo patients. Furthermore, other skin disorders such as psoriasis and acne, which are depression and mood disorder comorbidities, have been associated with BDNF deficiency [19,20].

There was no significant correlation between BDNF levels and VIDA scores (disease activity) while a significant correlation was noted between BDNF levels and VASI scores (disease severity). This concurs with the idea that reduced BDNF levels may annually inflame vitiligo but most of the time remain dormant. These results corroborate those regarding the role of BDNF in psychological well-being and quality of life of dermatological patients [21,22]. Moreover, BDNF deficiency is in connection with IR and other metabolic changes. Research using animal models indicate that BDNF is related to higher glucose metabolism and lower insulin resistance, phenomena that are typical of type 2 diabetes. From our results, it was also found that reduced levels of BDNF are highly correlated to increased HOMA-IR values in patients with vitiligo, implying the potential involvement or ‘pathogenic role’ of BDNF in metabolic dysregulation and the aforementioned disease. Similar findings were reported by Boyuk et al. [24], who demonstrated a correlation between reduced BDNF levels and increased IR. Vitamin D deficiency was another prominent finding in this study. Vitiligo patients exhibited significantly lower serum Vitamin D levels, which were associated with disease activity. These findings support prior research by Aly et al. [25] and Amer et al. [26], who observed an association between Vitamin D deficiency and

vitiligo. Vitamin D is known to regulate both innate and adaptive immune responses and promote melanocyte maturation, proliferation, and melanin synthesis [27]. However, conflicting results have been reported by studies such as those by Singla et al. [28] and Doss et al. [29], which found no significant relationship between Vitamin D levels and vitiligo progression.

Vitamin D deficiency also plays a critical role in neuropsychiatric health. Studies have shown that Vitamin D supplementation can improve mood and reduce symptoms of depression by regulating intracellular calcium levels, serotonin production, and neuronal activity [30]. In this context, Vitamin D therapy has been shown to elevate BDNF levels and reduce oxidative stress, suggesting its dual benefit in addressing both vitiligo and associated psychological conditions [31]. The ROC curve further established that BDNF had great difficulty distinguishing vitiligo patients from normal controls, with a specificity and a sensitivity of 44% and 45%, respectively, and an AUC of 40%. In spite of the fact that BDNF is unlikely to be a standalone diagnostic biomarker, its utility in the pathophysiology of vitiligo and its psychological comorbidity components requires additional studies.

CONCLUSION

This study notes the vital roles that BDNF or Brain Derived Neurotrophic Factor and vitamin D have in the pathophysiology of vitiligo, and how these factors can be markers for the vitiligo disorder itself as well as any psychological impacts it carries. The studied drop observed with BDNF levels in vitiligo patients suggests it plays a part in not only the severity of the disease, but also in the increased chances of depression and other psychological disorders. Equally, the evidence that links Vitamin D deficiency with activities of vitiligo further proves its function in the immune reaction and the activity of pigment cells. The results mark an intricate connection between BDNF and insulin resistance, hinting that some form of metabolic disturbance could be a factor in the development of vitiligo. This brings out the necessity of a multidisciplinary approach towards patients suffering from vitiligo since it seems that the condition has both a dermatological as well as a metabolic side to it. These studies recommend broader longitudinal studies to check the practicability of BDNF and Vitamin D for use in the treatment of vitiligo. Further, combining BDNF intake through vitamin D with existing vitiligo treatments methods poses as a great potential for improving overall health and wellbeing of the affected individuals. Strategies, these forms of personalized therapy which use the markers or predictive tools aimed at more effective management of the disease, are bound to become more common place.

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Conflicts of interest

The authors declare that they have no competing interests and no conflicts of interest in the current study.

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