Thyroid Disease and Indicator of Autoimmune Illness Among Vitiligo Patients

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ABSTRACT

BACKGROUND: The precise pathogenesis remains not fully understood. However, it is thought to involve an autoimmune process directed against melanocytes. Thyroid disorders and autoimmune thyroid diseases have been shown in some reports to be associated with vitiligo. Additionally, there is limited and conflicting data examining the association of antinuclear antibodies (ANA) with vitiligo. **METHODS:** We conducted a cross-sectional study among 50 vitiligo patients diagnosed according to established clinical criteria at King Khalid University Hospital, Riyadh from January 2008 through December 2010. Blood samples were obtained from the study participants and were tested for antinuclear antibodies (ANA), thyroid stimulating hormone (TSH) and free thyroxin hormone (T4). **RESULTS:** Males represented 62% and the mean age was 28.2±11.0 years. A total of 20 (41.7%) had positive ANA values (titer ≥1:40). The mean TSH level was 2.69±2.17 µIU/mL. The mean free T4 level was 16.40±2.74 pmol/L and all patients were in the normal range (10.3-25.8 pmol/L). There were no statistically significant associations between ANA and age, gender, extent of skin lesion, face inclusion, and free thyroxin levels. On the other hand, positive ANA level had significant association with TSH level (p=0.041). With exception of ANA, TSH level had no statistically significant associations with the above variables. **CONCLUSIONS:** The results of the current study showed higher prevelance of ANA in vitiligo patients, probably suggesting autoimmune process. The current finding may need to be confirmed in a larger prospective multicentric study before recommending periodic screening of patients with vitiligo for thyroid function and antithyroid antibodies.

Key words: Vitiligo; autoimmune ; thyroid disease; antinuclear antibodies

الملخص

مقدمة: بالنسبة لمرض البهاق لم تعرف بدقة الية المرض ولكن يظن أنها خلل ذاتي في جهاز المناعة ضد الخلايا الصبغية. افادت بعض التقارير وجود علاقة بين البهاق وأمراض و اضطرابات الغدة الدرقية الناتجة من الخلل الذاتي في جهاز المناعة, بالإضافة لوجود بيانات محدودة ومتضاربة فيما يخص العلاقة بين البهاق والاجسام المضادة للنواة. **المنهج:** دراسة مقطعية لعدد 50 مريض بالبهاق تم تشخيصهم سريريا في مستشفى الملك خالد الجامعي بالرياض في الفترة من يناير 2008 الي ديسمبر 2010. تم سحب عينات دم للمشاركين بالدراسة لتحليل الاجسام المضادة للنواة و الهرمون المحفز للغدة الدرقية وهرمون الثيروكسين الحر. **النتائج:** كانت نسبة الذكور بالدراسة 62% ومتوسط اعمارهم 28,2 ± 11سنة . وجد ان الاجسام المضادة للنواة ايجابية في 20 من المشاركين (41.7%) (العيار: ≤1:40. متوسط الهرمون المحفز للغدة الدرقية 2,69 ± 2,17 ميكرو وحدة دولية لكل ملم , وهرمون الثيروكسين الحر 16,40 ± 2,74 pmol/L وقد كان كل المرضي في المستوي الطبيعي (10,3 الي 25,8 pmol/L). لا توجد علاقة ذات دلالة احصائية بين مضادات النواة والعمر او الجنس او الاصابات الخارجية في الجلد او الوجه او مستوي هرمون الثيروكسين الحر. من ناحية اخري توجد علاقة ذات دلالة احصائية بين ايجابية الاجسام المضادة للنواة ومستوي الهرمون المحفز للغدة الدرقية (p=0.041). بإستثناء الأجسام المضادة للخلية فان مستوي هرمون الثيروكسين الحر لا توجد لديه علاقة ذات دلالة احصائية مع المتغيرات اعلاه. **الإستنتاج:** نتائج الدراسة أوضحت وجود معدل انتشار عالي للأجسام المضادة للنواة لمرضي البهاق , مما يؤشر لإحتمال الخلل الذاتي لجهاز المناعة . هذه النتائج تحتاج لدراسات مستقبلية متعددة قبل التوصية بعمل مسوحات لمرضي البهاق لمعرفة وظائف الغدة الدرقية ومستوي الاجسام المضادة بها

INTRODUCTION

What's known?

The causes of vitiligo are unknown. However, it has been reported that vitiligo is associated with other autoimmune diseases, with thyroid disease being the commonest.

Vitiligo is an acquired, non-contagious disorder of the skin and mucous membranes that is characterized by progressive, well circumscribed, depigmented macules and patches that occurs secondary to selective destruction of melanocytes, apparently

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on an autoimmune basis [1]. Vitiligo is the most common pigmentation-related disorder that varies based on region [2] with a prevalence of 0.06 to 2.28% among adults whereas this was 0.0 – 2.16% in children/adolescents populations [3] Gujarat, India is considered to have the highest prevalence in the world, at about 8.8% [4]. Men and women are equally affected, but young Females (< 30 years of age) usually acquire the disease earlier than males [5,6]. The average age of onset of vitiligo among patients with a positive family history (seen in up to 20% of them) is younger than sporadic ones (18.7 ±12.5 vs. 20.4 ±13.9 years) [7,8].

The pathogenesis of this disease is still not clear and is thought to be multifactorial and polygenic; however, several theories have been proposed to explain the loss of epidermal melanocytes in this disorder [1,9]. There is substantial evidence for the immune mediated destruction of melanocytes [10]. Although the triggers and specific nature of the autoimmune response remain unknown, circulating autoantibodies to melanocytes and various melanocytic proteins components, detectable in many patients, have been considered to be secondary humoral responses to melanocyte destruction rather than primary cause [11].

It is also suggested by the concomitant occurrence of other autoimmune diseases in patients with vitiligo. Some of them is well established for example thyroid disorders, particularly Hashimoto's thyroiditis and Graves' disease, are commonly associated with vitiligo, as are other endocrinopathies, such as Addison's disease and diabetes mellitus. Alopecia areata, pernicious anemia, systemic lupus erythematous, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and autoimmune polyglandular syndrome also are associated, though the significance of some of these associations is debated [12-14].

The association of vitiligo with these disorders suggests the presence of shared genetic factors that contribute to the development of these diseases. In a genome wide association study, several genes with known associations with other autoimmune disorders were identified as potential susceptibility loci for generalized vitiligo, including PTPN22, LPP, IL2RA, UBASH3A, C1QTNF6, and genes encoding MHC I and MHC II molecules[15, 16]. These genes provide potential therapeutic targets for treatment as well as for approaches to presymptomatic diagnosis and disease prevention in individuals with inherited susceptibility to autoimmune diseases [17].

Autoimmune thyroid disorders have been associated with vitiligo, and the incidence of clinical or subclinical involvement of the thyroid is more common in patients with vitiligo as compared to healthy subjects [18]. Autoimmune thyroid disease is seen in approximately 21% of children and adult patients with vitiligo compared to 3% in non-vitiligo patients [19,20]. It was found predominantly among older women and in subjects with a positive family history of thyroid disease [21]. Thus, screening of patients with vitiligo for thyroid function and antithyroid antibodies to diagnose early changes in the function of this gland becomes relevant and necessary [22].

Given the frequency with which concomitant autoimmune disorders occur in patients with vitiligo, it was suggested to screen for selected diseases (eg, thyroid function, CBC, and fasting blood glucose level), especially in children and young women [23]. There is limited data examining the association of antinuclear antibodies (ANA) and vitiligo. In a recent retrospective study performed among 135 patients with vitiligo, ANA were found in 33% of patients and the highest proportion of thyroid abnormalities was found among patients aged 21-30 years [23]. However, other studies could not detect association of ANA with vitiligo neither in children nor in adults [24].

We conducted this study among a group of vitiligo patients with the following objectives:

1. To estimate the prevalence of positive antinuclear antibodies (ANAs), as indicator of autoimmune illness
2. To estimate the level of thyroid stimulating hormone (TSH) and free thyroxin hormone (T4), as possible indicators of thyroid disease
3. To evaluate the association of ANA, TSH, and T4 with demographic (age and gender) and clinical (body site affected and percentage of affected body surface area) characteristics of vitiligo patients, and finally
4. To study the association between ANA level and levels of TSH and T4.

METHODS

Design and population:

We conducted a cross-sectional study among a group of patients diagnosed with vitiligo. We examined 50 consecutive patients with vitiligo diagnosed according to established clinical criteria [1], of both sex, irrespective of age, and attending the dermatology outpatient clinic of the King Khalid University Hospital, Riyadh from January 2008 through December 2010. Data collected in the current study included demographic, clinical, and laboratory data. Demographic and clinical data included age, sex, site of skin lesion and the percentage of body surface area affected.

Laboratory methods:

Blood samples were obtained from the study participants to separate serum and were tested for ANA, TSH, and T4. ANA tests were performed by indirect immunofluorescence (IIF) technique for the detection of autoantibodies using the following dilutions 1:40, 1:80, 1:160, and 1:320 (INOVA Diagnostic Inc., San Diego, CA). According to manufacturer, detectable ANA (fluorescence observed) at titer ≥1:40 was considered positive results. Positive levels were further categorized as mildly elevated (titers 1:40 and 1:80) and elevated (titers 1:160 and 1:320).(25, 26) Serum TSH and T4 were estimated using electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). According to manufacturer references, normal values for TSH were between 0.25 and 5.0 µIU/mL (milli-international units per liter) while normal values for free T4 were values between 10.3 and 25.8 pmol/L (picomole per liter). Therefore, low TSH values were considered at <0.25 µIU/mL while higher values were considered at >5.0 µIU/mL. Likewise, low free T4 values were considered at <10.3 pmol/L while high free T4 values were considered at >25.8 pmol/L.

STATISTICAL ANALYSIS

Patient's demographic, clinical, and laboratory data were described as mean and standard deviation or median and inter-quartile range for continuous data or proportion for categorical data. The differences of age, affected body surface area, TSH, and T4 levels by two-level groups (such as gender and ANA groups) were examined using student t-test for parametric data and Mann-Whitney U test for non-parametric data, as appropriate. The differences of age, affected body surface area, TSH, and T4 levels by three-level groups (such as affected body surface area groups) were examined using one-way analysis of variance (ANOVA) for parametric data and Kruskal-Wallis ANOVA for non-parametric data, as appropriate. The associations between categorical data were examined using Chi-square or Fisher exact, as appropriate. All tests were two-tailed and p-value of <0.05 was considered significant. SPSS software (release 18.0, SPSS Inc., Chicago, U.S.) was used for all statistical analyses.

ETHICAL STATEMENT

This study was conducted on hospital patients. Appropriate ethical committee approval and patient consent were obtained before actual data collection. All the data were securely maintained by separating participants' identification and associated clinical and laboratory data. All the data were anonymously analyzed so as to maintain individual privacy. All records with results and progress both electronic and written were maintained by the researchers in a secured place with a lock. At the end of the study, summary of the result was sent to advisor committee. Upon completion of the study the final report was submitted to the Saudi Commission for Health Specialization.

RESULTS

Table 1 showed demographic and clinical characteristics of vitiligo patients seen at King Khalid University Hospital, Riyadh from January 2008 through December 2010. A total 50 patients were included in the study. Males represented 62% while females represented 38%. The mean age was 28.2±11.0 years. The age range was between 12 and 68 years. The majority of patients (82%) were less than or equal to 35 years. The majority (83.3%) of vililigo patients had whole body skin lesions including the face while the minority (16.7%) had whole body skin lesions sparing the face. The average percentage of affected body surface area was 31.7±10.3.

A total of 20 (41.7%) out of 48 vitiligo patients had ANA elevated values (titer ≥1:40). Three-fourth (15/20, 75%) of these patients had mildly elevated values (titers 1:40 and 1:80) while one-fourth (5/20,

25%) of these patients had moderately elevated values (titers 1:160 and 1:320) (Table 1).

Table 1: Demographic and clinical characteristics of vitiligo patients seen at King Khalid University Hospital, Riyadh from January 2008 through December 2010

Characteristics	N (%) or mean±SD
Age (mean±SD, years)	28.2±11.0
Age (median & IQR, years)	27.0 (21.0-33.3)
Age groups (%)	
≤25 years	21 (42%)
26-35 years	20 (40%)
>35 years	9 (18%)
Gender	
Male	31 (62%)
Female	19 (38%)
Body site affected	
Whole Body	40 (83.3%)
Whole Body without face	8 (16.7%)
Body Surface Area affected (mean±SD)	31.7±10.3
Body Surface Area affected	
<30%	17 (34%)
30%	18 (36%)
>30%	15 (30%)
Antinuclear Antibody (ANA)	
Negative (<1:40)	28 (58.3%)
Elevated (>1:40)	20 (41.7%)
Antinuclear Antibody (ANA)	
Negative (<1:40)	28 (58.3%)
Mildly elevated (titers 1:40 and 1:80)	15 (31.2%)
Elevated (titers 1:160 and 1:320)	5 (10.4%)
TSH (mean±SD, µIU/mL)	2.69±2.17
TSH (median & IQR, µIU/mL)	2.44 (1.25-3.03)
TSH groups	
Low (<0.25 µIU/mL)	2 (4.2%)
Normal (0.25-5.0 µIU/mL)	41 (85.4%)
High (>5.0 µIU/mL)	5 (10.4%)
T4-Free thyroxine (mean±SD, pmol/L)	16.40±2.74
T4-Free thyroxine groups	
Normal (10.3-25.8 pmol/L)	48 (100.0%)
High (>25.8 pmol/L	0 (0.0%)

The mean TSH level was 2.69±2.17 µIU/mL. Since the distribution of TSH level was skewed to the right with a lot of value toward the zero side, we calculated the median and inter-quartile range at 2.44 (1.25-3.03) µIU/mL. A total of 5 (10.4%) out of the 48 vitiligo patients had high TSH values (>5.0 µIU/mL) while only 2 patients (4.2%) had low TSH value (<0.25 µIU/mL).

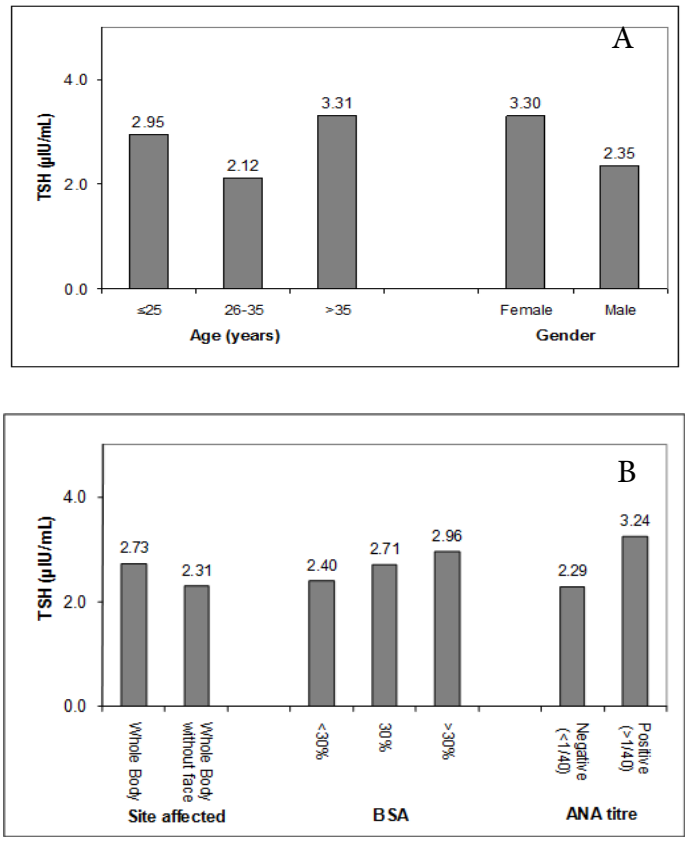


Figure 1: Thyroid stimulating hormone (TSH, µIU/mL) by demographic (A), clinical and laboratory characteristics (B) among vitiligo patients seen at King Khalid University Hospital, Riyadh from January 2008 through December 2010

ANA levels were categorized as negative and positive. Tables 2 showed the differences in demographic, clinical, and laboratory characteristics of vitiligo patients by ANA groups. Those who had positive ANA were slightly older (29.2±12.4 year) than those who had negative (27.8±10.4 year) ANA. However, there were no statistically significant associations between ANA groups and age or sex (p=0.670 and p=0.959, respectively). The frequency of those who escaped the skin lesions in face were more common among those who had negative results of ANA (22%) compared to those who had positive ANA levels (10%).

Table 2: Demographic and clinical characteristics by ANA groups among vitiligo patients seen at King Khalid University Hospital, Riyadh from January 2008 through December 2010

Characteristics	Antinuclear Antibody (ANA)		P value
	Negative (<1/40)	Positive (>1/40)	
Age (mean±SD, years)	27.8±10.4	29.2±12.4	0.670
Age groups (%)			
≤25 years	12 (42.9%)	8 (40.0%)	0.974
26-35 years	11 (39.3%)	8 (40.0%)	
>35 years	5 (17.9%)	4 (20.0%)	
Gender			
Male	18 (64.3%)	13 (65.0%)	0.959
Female	10 (35.7%)	7 (35.0%)	
Body site affected			
Whole Body	21 (77.8%)	18 (90.0%)	0.437*
Whole Body without face	6 (22.2%)	2 (10.0%)	
Body Surface Area affected (mean±SD)	30.1±8.2	34.5±12.6	0.149
Body Surface Area affected			
<30%	11 (39.3%)	5 (25.0%)	0.585
30%	9 (32.1%)	8 (40.0%)	
>30%	8 (28.6%)	7 (35.0%)	
TSH (mean±SD, µIU/mL)	2.29±1.93	3.24±2.40	0.135
TSH (median & IQR, µIU/mL)	1.68 (0.96-3.00)	2.73 (2.12-3.47)	0.041
TSH groups			
Low (<0.25 µIU/mL)	2 (7.1%)	0 (0.0%)	0.447
Normal (0.25-5.0 µIU/mL)	24 (85.7%)	17 (85.0%)	
High (>5.0 µIU/mL)	2 (7.1%)	3 (15.0%)	
T4-Free thyroxine (mean±SD, pmol/L)	16.54±2.78	16.21±2.75	0.682

However, this finding did not reach statistical significance (p=0.437). The median and inter-quartile range of TSH level was statistically significantly (p=0.041) higher among those who had positive ANA level (2.73, 2.12-3.47 µIU/mL) compared to those who had negative ANA levels (1.68, 0.96-3.00 µIU/mL). The levels of free thyroxin were similar among both who had positive and negative ANA levels (16.21±2.75 and 16.54±2.78 pmol/L, p=0.682, respectively).

We examined the differences in demographic, clinical, and laboratory characteristics of vitiligo patients by affected body surface area groups (data are not shown). There were no statistically significant associations among ANA, TSH, and free thyroxin levels and the degree of affected body surface area (p=0.585, 0.846, 0.940, respectively). Gender was the only significant characteristics observed in relation to affected body surface area. Those who had 30% affected body surface area were more likely to be females than males (61% versus 39%, p=0.041). Figure 1 showed the TSH levels by demographic, clinical, and laboratory characteristics. TSH levels were lower among those aged 26-35 years compared to other ages and in males compared to females (Figure 1A).

TSH levels were higher among patients with whole body vitiligo including the face compared to patients with whole body vitiligo sparing face and in patients with more affected body surface area compared to those with less affected body surface area (Figure 1B).

However, all the above differences were not statistically significant using non-parametric tests (Mann-Whitney U test and Kruskal-Wallis ANOVA). On the other hand, TSH levels were significantly higher in those who were ANA positive compared to those who were ANA negative (p=0.041). There were no statistically significant differences in free thyroxin levels by age groups, gender, body site affected, percentage of affected body surface area, or ANA levels using parametric tests (student t-test and ANOVA). On the other hand, free thyroxin levels was significant higher among patients with normal and higher TSH compared to those with lower TSH (p<0.001).

Discussion

In a cross-sectional study done among Saudi patients with vitiligo, 41.7% had mild to moderate ANA

elevation defined as titer ≥1:40. The prevalence of ANA in our study was generally higher than reported in many other studies suggesting an autoimmune origin of vitiligo. For example, ANA were found in 33% of patients in a recent retrospective study performed among 135 patients with vitiligo (80 women and 55 men with mean age of presentation of 36.8 years). [23] In another study among 55 Iranian patients with vitiligo, ANA was found in only 7.3% of the patients [27].

ANA are frequently found in healthy populations. Although a positive ANA test, by itself, does not establish a diagnosis of a certain autoimmune disease, it can be helpful when used with other clinical features. Moreover, some studies reported similar levels of ANA among vitiligo patients compared to the general population [14,20,24]. Additionally, it was suggested that positive ANA finding in the absence of physical signs and symptoms has limited diagnostic utility [25]. However, the higher prevalence of ANA in our study may suggest that autoimmunity might plays an important role in the pathogenesis of vitiligo. Supporting this finding, it was shown that vitiligo appears to be an autoimmune disease involving T-cell mediated melanocytes destruction [25,28].

The current study showed a weak non-significant association between ANA and older age. This finding was in accordance with that reported by previous studies [29]. It was reported that ANA was more common in adults with vitiligo compared to children with vitiligo[29]. Interestingly, it was shown that the frequency ANA positivity do not differ significantly across the age range of healthy individuals aged 20 to 60 years [26].

The current study showed non-significant associations of both TSH and ANA with the extent of skin lesions. The non-significance is probably due to the small sample size. Similar to our findings, it was also observed that vitiligo patients with autoimmune thyroid disease were more likely to have more than 25% of their body affected by skin lesions compared vitiligo patients without autoimmune thyroid disease but did not show statistical significance (67% vs. 21%, p=0.083) [30]. Unfortunately there is lack of data evaluating the association between the ANA level and extent of lesion in vitiligo patients.

A recent study examined 186 adult vitiligo patients for the differences between familial and sporadic cases of vitiligo [31]. In this study, patients in familial group showed more widespread depigmentation compared with sporadic cases. Additionally, the widespread depigmentation was associated with the presence of autoantibodies (p = 0.03) including ANA (p<0.001) in sporadic cases of vitiligo.

The current study showed non-significant associations of both TSH and ANA with the extent of skin lesions. The non-significance is probably due to the small sample size. Similar to our findings, it was also observed that vitiligo patients with autoimmune thyroid disease were more likely to have more than 25% of their body affected by skin lesions compared vitiligo patients without autoimmune thyroid disease but did not show statistical significance (67% vs. 21%, p=0.083) [30]. Unfortunately there is lack of data evaluating the association between the ANA level and extent of lesion in vitiligo patients. A recent study examined 186 adult vitiligo patients for the differences between familial and sporadic cases of vitiligo [31]. In this study, patients in familial group showed more widespread depigmentation compared with sporadic cases. Additionally, the widespread depigmentation was associated with the presence of autoantibodies (p = 0.03) including ANA (p<0.001) in sporadic cases of vitiligo.

Approximately 15% of our vitiligo patients had abnormal TSH level. This was higher than subclinical hypothyroidism or hyperthyroidism observed in many studies examining adult vitilgo patients where these rates ranged between 2.1 and 5.6% [32,33]. However, our TSH rate was lower than reported before among vitiligo patients where 20-22% had abnormal TSH level [30]. The difference between this study and other studies may be partially explained by the different age, gender, and nationality of studied patients in these studies. Thyroid disorders and autoimmune thyroid diseases have been associated with vitiligo, and the incidence of clinical or subclinical involvement of the thyroid is more common in patients with vitiligo as compared to healthy Subjects [34]. A recent systematic review estimated the prevalence of thyroid disease, autoimmune thyroid disease and presence of thyroid-specific autoantibodies in patients with vitiligo at 15.1%, 14.3% and 20.8%

(respectively) with significant relative risks of 1.9, 2.5 and 5.2 (respectively) [35].

The usefulness of periodic screening (at least every 3 years) to evaluate the coexistence of different auto-antibodies in patients affected by vitiligo has been suggested, to better follow-up the complexity of autoimmune diseases associated with vitiligo [14]. Since the interval between the onset of vitiligo and the occurrence of thyroid disease can be as long as 20 years, this periodic screening may useful for long period after the onset of vitiligo [36].

What's new?

The results of the current study showed higher prevelance of ANA in vitiligo patients, probably suggesting autoimmune process. The current finding may need to be confirmed in a larger prospective multicentric study before recommending periodic screening of patients with vitiligo for thyroid function and antithyroid antibodies.

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