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Association of Vitiligo with Thyroid Dysfunction and Thyroid Autoimmunity: A Case-Control Study

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ABSTRACT

Objective: To assess the association of thyroid dysfunction and thyroid autoimmunity with vitiligo.
Study design: A case-control study.
Place and Duration of Study: Outpatient of Dermatology Department of a tertiary referral hospital Bahawalpur, Pakistan, from Jan to Dec 2023.
Methodology: A total of 207 vitiligo patients (Group-A) and 207 controls (Group-B) of similar age and gender were enrolled. Pregnant females, patients already getting any form of treatment for vitiligo and those with any diagnosed autoimmune disease were excluded. The onset age, sites involved by the disease and associated diseases were noted. Thyroid profile and anti- thyroid peroxidase antibodies were tested in all patients and controls. A p-value less than 0.05 was considered statistically significant.
Results: Out of 207 patients, 117(56.521%) were male patients and 90(43.478%) were female. Mean onset age was 27.320±10.467 years and mean disease duration was 4.700+5.996 years. Generalized vitiligo was the most common type found in 120 (57.971%) patients. Sixty-eight (32.850%) patients had a positive family history and associated diseases were found in 25 (12.077%) patients. Thyroid dysfunction manifested by deranged Thyroid Hormone Levels was found in 20 (9.662 %) patients and 4 (1.932%) controls (p=0.001). Level of Anti-TPO Antibodies was raised in 17 (8.212 %) patients and in 3 (1.449%) controls (p=0.001).
Conclusion: Vitiligo is significantly associated with thyroid dysfunction and thyroid autoimmunity.

Keywords: Anti-TPO Antibodies, Subclinical Thyroid Disease, Thyroid Autoimmunity, Vitiligo.

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INTRODUCTION

Vitiligo is an acquired chronic skin disease characterized by depigmented patches. It is caused by progressive loss of melanocyte activity. It affects any part of the body and most commonly presents as bilaterally symmetrical non-scaly, chalky-white macules with distinct margins.[1,2] Around 0.5–2% of the population is affected by this disease worldwide with no predilection for gender, race, ethnicity, skin type or geographic area.[1,2]

The disease occurs with a higher frequency in patients with other autoimmune diseases compared to general population, and destruction of functional melanocytes by T-cell mediated mechanism in genetically predisposed individuals is thought to be responsible for depigmentation.[3,4]

A number of immune mediated diseases including thyroid dysfunction, alopecia areata, diabetes mellitus type 1, Addison's disease, and myasthenia gravis, occur more frequently in vitiligo patients.[3-6] One study reported some autoimmune problem in 20% of their vitiligo patients.[4]

Autoimmune diseases also occur more frequently in close relatives of vitiligo sufferers.[4-6]

Thyroid disorders may manifest clinically, but subclinical disease which is detected only by abnormal Thyroid function tests is more common.[6-8]

Anti-Thyroid peroxidase antibodies (anti-TPO antibodies) have been reported in up to 40.3% of vitiligo patients.[5] Thyroid autoimmunity, which encompasses conditions such as Hashimoto thyroiditis and Graves' disease is of particular relevance.[5-7] A number of authors have explored association between vitiligo and thyroid disease.[4-8] Very few studies have evaluated the frequency of thyroid dysfunction in vitiligo from our country and there is a gap in knowledge regarding the association of these disorders.[9-10] We conducted this study to find the association of thyroid dysfunction and thyroid

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autoimmunity with vitiligo patients in comparison to normal controls.

METHODOLOGY

This case-control study was conducted at the OPD of the Dermatology Department of a tertiary referral hospital in Bahawalpur, from January 2023 to December 2023. Ethical approval was given by the Hospital Ethical Committee vide (certificate number 19 dated 21 December 2022).

Inclusion Criteria: Patients of all age groups and either gender diagnosed with vitiligo were included.

Exclusion Criteria: Pregnant females and patients already getting any form of treatment for their vitiligo (either topical or systemic) during last one month and those with any associated autoimmune disorder were excluded.

OpenEpi software was used for sample size calculation, with prevalence of thyroid autoimmunity detected previously in vitiligo patients at 16%, which came to 400.[11] We enrolled a total of 414 patients, with 207 being cases, and 2027 being ctrols Figure.

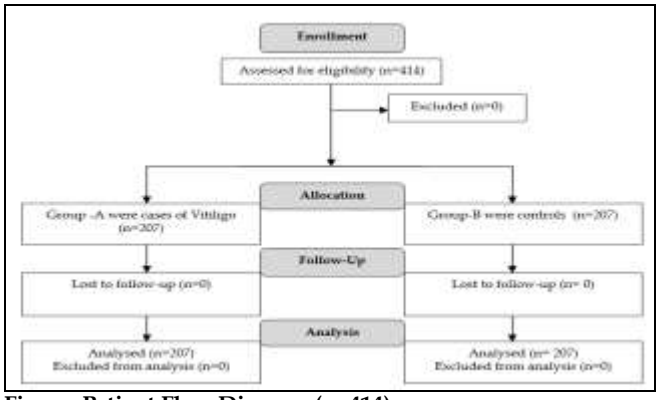

Figure: Patient Flow Diagram (n=414)

A total of 207 vitiligo patients were recruited from dermatology outpatient using a non-probability convenience sampling approach, after obtaining informed consent (Group-A).

An equal number (n=207) of age and sex-matched controls with unrelated disease were also selected by non-probability convenience sampling, from the patients visiting dermatology OPD (Group-B).

Age, gender, the age at onset of disease, any associated diseases and history of vitiligo in the family was taken from each patient. Patients were examined to know the type of vitiligo, involved sites and any signs of any other cutaneous or systemic disease.

Venous samples were taken from the participants for thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) levels and Anti-TPO antibodies. Normal values included 0.4 to 4.5 mIU/L for TSH), 1.1 to 2.7 nmol/L for T3 and 8–21 pmol/L for T4. Cobas E 441random access autoanalyzer (Roche Diagnostics) was used for measuring the hormone levels. Preci-Control Universal were used for quality control. Thyroid autoimmunity was defined as detection of elevated anti-thyroid peroxidase auto-antibodies titres. A deviation of 5% above or 5% below the normal values were considered as abnormal.[11]

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 23. Frequency and percentages were computed for qualitative variables which included thyroid dysfunction (normal and deranged) and Anti-TPO tests (positive or negative), while Mean±SD was used for quantitative variables. Chi-square test was used for qualitative data and Independent Samples t-test was used to compare means. A *p*-value less than 0.05 was considered statistically significant. To quantify the strength of association between group (patient vs. control) and the categorical outcome variables (thyroid dysfunction and thyroid autoimmunity), Odds Ratios (OR) with 95% confidence intervals (CI) were calculated using 2x2 contingency tables.

RESULTS

Out of 207 vitiligo patients, 117(56.5 %) were male and 90(43.5 %) female. Male: female ratio was 1.3:1. Mean age of female patients was significantly less than male patients (p=0.028). There was no significant difference in onset age of vitiligo in two genders. (p-value=0.774). Mean duration of the disease at presentation in females was significantly less than males (p=0.006), which can be seen in Table-I.

Table-I: Effect of Gender on Disease Characteristics (n= 207)

Parameters	Study Groups		*p*-value
	Males (n=117) (Mean±SD)	Females (n=90) (Mean±SD)	
Age in years	33.29+13.01	30.46+12.84	0.028
Age in years at onset of Vitiligo	27.50+10.231	27.08+10.818	0.774
Duration of the disease at presentation in months	5.6479+6.93	3.4596+4.23	0.006

In 147 patients (71.0%) the disease started before the end of third decade of life, in 177 patients (85.5%) it started before the end of fourth decade and in 198 patients (86.1%) it started before the end of fifth

decade of life. The disease started after 40th year of life in only 28 patients (14.5%).

Generalized vitiligo was the most common type found in 120(58.0%) patients (Table-II). Sixty-eight (32.85%) patients gave a history of vitiligo in the family out of which 37(54.4%) were male and 31(45.58%) were female. This difference was not statistically significant (*p*=0.668).

Table-II: Morphological Types of Vitiligo (n= 207)

Type of vitiligo	Male n=117 n (%)	Female n=90 n (%)
Generalized	68(58.1%)	52(57.8%)
Acrofacial	21(17.9%)	17(18.9%)
Focal	16(13.7%)	16(17.8%)
Segmental	7(6.0%)	3(3.3%)
Universalis	5(4.3%)	2(2.2%)

Associated diseases were found in 25(12.1%) patients. Out of the 25(12.1%) patients with associated diseases 10(4.8%) had diabetes mellitus and 7(3.4%) had hypertension.

Thyroid dysfunction was found in 20(9.66%) Group-A participants and 4(1.93%) Group-B participants. One Group-A participant had hyperthyroidism. Clinical thyroid disease was not detected in any Group-B participant. Deranged thyroid function tests were found in 20(9.66%) Group-A and 4(1.93%) Group-B participants (*p*=0.001). There was a significant difference in the frequency of presence of thyroid dysfunction between groups: Anti-TPO antibody levels were raised in 17(8.21 %) Group-A and in 3(1.45 %) Group-B participants (*p*=0.001). Thyroid autoimmunity, manifested by raised Anti-TPO antibody, levels was detected in 17(8.2%) Group-A and 3(1.4 %) Group-B participants. Thyroid autoimmunity was significantly more commonly detected in Group-A as compared to Group-B. The Odds Ratio was 5.40 (1.81–16.14), representing a five-time greater risk of thyroid disease in patients with vitiligo as compared to controls (*p*=0.001), as seen in Table-III.

Table-III: Comparison of Thyroid Dysfunction and Thyroid Autoimmunity in Cases and Controls (n=207)

Parameter	Results	Group-A (n=207) n (%)	Group-B (n=207) n (%)	OR (95% CI)	*p*-value
Thyroid Dysfunction	Normal	187 (90.34%)	203(98.06%)	5.40 (1.81–16.14)	0.001
	Deranged	20 (9.66%)	4(1.93%)		
Thyroid autoimmunity	Present	17 (8.21%)	3(1.45%)	6.44 (1.82–22.75)	0.001
	Absent	190 (91.79%)	204(98.55%)		

Out of 20 patients with deranged thyroid functions tests, 8(40%) were male and 12(60%) were female. There was no significant difference in frequency of Thyroid dysfunction between genders (*p*>0.05). Out of 4 controls with deranged thyroid functions tests, 3(75%) were male and 1(25%) was female (Table-IV).

Table-IV: Comparison of Thyroid Dysfunction across Genders

Parameters	Study Groups		*p*-value
	Males n=11 n (%)	Females n=13 n (%)	
Thyroid Dysfunction in patients (n= 20)	8 (40.0%)	12 (60.0%)	0.118
Thyroid Dysfunction in controls (n= 20)	3 (75.0%)	1 (25.0%)	0.454

DISCUSSION

This study was carried out to investigate the association between vitiligo and thyroid dysfunction and thyroid autoimmunity, and confirmed the previously established link between vitiligo and thyroid dysfunction and thyroid autoimmunity. Deranged thyroid function tests (thyroid dysfunction) were found in 20(9.7%) cases and 4(1.9%) controls. A significant majority of vitiligo patient found to have thyroid disorder had subclinical thyroid dysfunction (19 out of 20 affected patients). The findings were consistent with previous studies which explored the increased risk of thyroid dysfunction and autoimmunity in vitiligo.[8-10,13-20] Kasumagic-Halilovic *et al*., and Sedighe *et al*., reported higher rates of thyroid function test abnormalities (18.18% and 17%, respectively), while Hasan *et al*., found a lower prevalence (3.7%).[19,21,22] These differences in prevalence of thyroid dysfunction may be due to the influence of genetic, environmental, and geographical factors on the expression of these autoimmune disorders in different populations. Our findings point to the likely shared autoimmune pathogenesis between vitiligo and thyroid disorders and underscore the importance of routine screening, for subclinical disease even in the absence of overt clinical symptoms.

A number of authors have described raised anti-TPO-Ab levels in vitiligo patients but only few case-control studies have explored the association of vitiligo and thyroid autoimmunity. The reported frequency of raised titres of anti-TPO-Ab titres in vitiligo has ranged between 14.8-36.7% in various studies conducted worldwide.[16-24] Eight-point two percent of our vitiligo patients had elevated Anti-TPO antibodies, which was significantly higher as compared to healthy controls (*p*=0.001). Our findings

were in agreement with other international studies, which also found a significantly higher frequency of Anti-TPO antibody positivity in vitiligo patients.[14,19,20] Similarly, a study conducted by Motamed *et al.*, reported that 16% of their vitiligo patients had positive Anti-TPO antibodies, while Yang *et al.*, reported that 70% of vitiligo patients with positive TPO-Ab and TG-Ab, eventually developed autoimmune thyroid disease.[9,14]

Anti-TPO antibodies are a sensitive marker for subclinical autoimmune thyroiditis and are a strong predictor of subsequent development of overt throid dysfunction over time.[12-15] Screening for thyroid autoimmunity in vitiligo patients with Anti TPO antibodies is important for early diagnosis of thyroid diseases.[14] Presence of anti-TPO antibodies should be considered as an early marker of clinical autoimmune thyroid disease.[14,21,25]

Given the increased risk of subclinical thyroid dysfunction and thyroid autoimmunity in vitiligo patients, routine screening for thyroid function and thyroid antibodies should be carried out in all patients diagnosed with vitiligo. Early detection of the thyroid abnormalities could potentially improve the overall prognosis.

LIMITATIONS OF STUDY

Anti-thyroglobulin antibody (TgAb) titres and anti-thyroid-stimulating hormone receptor (TSHR) antibody titres were not measured because of non-availability of test facilities in the hospital lab. Measuring antibody levels for anti-thyroglobulin (TgAb) and anti-thyroid-stimulating hormone receptor (TSHR) might reveal a higher frequency of thyroid autoimmunity in vitiligo patients.

CONCLUSION

Vitiligo has significant association with thyroid dysfunction and thyroid autoimmunity. Thyroid function tests and Anti-TPO antibody tests should be performed in all cases of vitiligo for early detection.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AH & SS: Data acquisition, data analysis, critical review, approval of the final version to be published.

NA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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