VITILIGO AND THE PREVALENCE OF AUTOIMMUNE THYROID DISEASE AND DIABETES MELLITUS IN VITILIGO
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ABSTRACT

BACKGROUND
Vitiligo is an acquired pigmentary disorder characterised by the development of white macules related to the selective loss of melanocytes residing in the interfollicular epidermis and occasionally in the hair follicles as well. Exact aetiology of vitiligo is not known. A convergence theory, which states that stress, infection, mutations, autoimmunity, accumulation of toxic compounds, altered cellular environment and impaired melanocyte migration or proliferation- all can contribute to development of vitiligo. However, most favoured hypothesis is autoimmune because vitiligo is frequently associated with other disorders, which have an autoimmune origin such as Autoimmune Thyroid Disease (AITD) and Diabetes Mellitus (DM). Recent studies suggest that vitiligo is not just a cutaneous disorder, but a systemic disorder of the pigmentary system.

MATERIALS AND METHODS
This is a hospital-based one year cross-sectional study of all vitiligo patients attending the outpatient wing of a tertiary care centre in Kerala. Patients were included after getting the written consent and those patients who had under gone thyroid surgery and on drugs that can interfere with thyroid function were excluded.

RESULTS
After meeting the criteria, only 122 patients out of 61,750 outpatients (0.19%) were included in this study. The youngest participant was 4 years, while the eldest was 69 years old. Most common age group- 10-19 years. 56.6% were females. Duration of disease was less than 2 years in 61.8%. Majority (36.9%) patients were students. A personal history of thyroid disease was obtained in 12.29%. 55.7% had positive family history of diseases like diabetes, thyroid disease, vitiligo and rheumatoid arthritis. Among the diseases noted in family members, diabetes was the commonest accounting for 32%. Though vitiligo vulgaris was common, percentage of focal and acrofacial vitiligo was higher than other studies. Vitiligo vulgaris was more commonly seen among females with a significant p value of 0.007. Infertility was observed in a significant proportion of vitiligo vulgaris patients (p=0.021). 58.9% had generalised vitiligo was more common among those who had an earlier onset of disease (p=0.013). Statistically significant correlation was obtained between generalised vitiligo and other concurrent diseases- Diabetes mellitus (p=0.010), AITD (p=0.003) and thyroid diseases taken together (hyper/hypothyroidism + AITD) (p=0.016).

CONCLUSION
The observed associations of vitiligo in our study indicate the need for screening vitiligo patients for diabetes and thyroid disease, at least in those with a generalised disease.

KEYWORDS
Autoimmune Thyroiditis (AITD), Diabetes Mellitus (DM), Systemic Disorder of the Pigmentary System Vitiligo.

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of melanin synthesis, cell adhesion, immune regulation and so forth, the probable association between ZAG and vitiligo.4

Since, all of these theories are plausible, it is most likely that the loss of melanocytes in vitiligo arises through a combination of pathogenic mechanisms that act in concert and that vitiligo may indeed include a spectrum of disorders that manifest as a common phenotype.5

Clinical types of vitiligo are focal, segmental, generalised and universal.6 It shows depigmented well-defined macules that gives a bluish white fluorescence in Wood’s light examination. The natural course of the disease is unpredictable. Total spontaneous regression in vitiligo vulgaris is rare and evolution to vitiligo universalis is unusual, though not rare.

Prevalence of AITD in vitiligo patients is an area of recent research interest. Many studies have shown a positive correlation with the occurrence of AITD in vitiligo.7 Vitiliginous diabetics commonly report a personal or close family history of other autoimmune diseases.8

A study of different types of vitiligo and prevalence of AITD and DM among them becomes important in this context. Hence, we decided to study the clinical patterns of vitiligo and to estimate the prevalence of AITD and DM in these patients.

MATERIALS AND METHODS
This is a hospital-based one year cross-sectional study of all vitiligo patients attending the outpatient wing of a tertiary care centre in Kerala. Patients were included after getting the written consent, but those patients who had undergone thyroid surgery and on drugs that can interfere with thyroid function were excluded.

History was obtained regarding age and site of onset of vitiligo, duration and course of the disease, detailed family and personal history. History of precipitating factors especially trauma, stress, sun exposure, contact with chemicals, etc. were also noted.

All patients underwent detailed clinical examination including sites of involvement, body surface area involved, type of vitiligo and any special features of vitiligo. Vitiligo was classified as stable if no extension of the lesions or new lesions appeared within last 2 years.

Investigations including routine blood and urine, RBS, FBS/PPBS, TFT (which included FT3, FT4, and TSH) with anti-thyroglobulin (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were performed in all cases. USG of neck and serum insulin levels were done in selected cases.

Hypothyroidism was diagnosed with elevated TSH along with decreased FT3 and FT4, whereas hyperthyroidism was diagnosed on the basis of decreased TSH along with elevated FT3 and FT4 from the given range of normal lab standards. AITD was diagnosed in a patient who is positive for either anti-TPOAb, anti-TgAb or both antibodies.9 Diabetes mellitus was diagnosed based on recommendations of American Diabetes Association, 2011.10

Criteria for the Diagnosis of Diabetes Mellitus-
1. Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) or diabetes.
2. Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), or
3. HbA1c >6.5% or
4. Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test.

Data entered in excel sheet and statistical analysis was performed using Microsoft Excel.

RESULTS
Out of 61,750 patients attended during the study period 189 were diagnosed to have vitiligo (0.29%). After meeting the criteria, only 122 patients (0.19%) were included in this study.

The youngest participant was 4 years, while the eldest was 69 years old. Mean age observed was 32.34, most common age group was 10-19 years. 56.6% were females. Duration of disease was less than 2 years in 61.8%. Among them, 2.5% had disease of less than 1 month. But, 12.3% had vitiligo for more than 10 years. 41% patients had the onset of disease in 10-19 years of age. Proportion of ‘late-onset vitiligo, i.e. after 50 years was 13.9%. 84.4% of the patient had onset of the disease at single site. The commonest site was head and neck area (46.7%), followed by upper and lower extremities (21.3%; 18%). Trunk and mucosal involvement at the outset of the disease was noted only in a minority. Out of total 66 married couples, 12.1% (7 females and 1 male) had history of infertility. Among these, 6 patients had vitiligo vulgaris. Majority (36.9%) of the patients were students followed by housewives and manual labourers.

Various aggravating factors noted were stress, trauma, contact with chemicals like phenol, sunburn, etc. Most of the subjects identified stress as a major trigger for either the onset or rapid progression of their disease. Diet was not identified by any patients as a contributory factor in their disease process.

A personal history of thyroid disease was obtained in 12.29%. 55.7% had positive family history of diseases like diabetes, thyroid disease, vitiligo and other autoimmune diseases like rheumatoid arthritis. Among the diseases noted in family members, diabetes was the commonest accounting for 32%.

40.2% of the patients had depigmentation limited to a single site, lips were the commonest involved (66 cases) site, followed by upper limbs (57 cases) and lower limbs (54 cases) and trunk was involved in 42 cases and scalp in 18 cases. Periorificial distribution was noted in 15 cases (12.3%). Among the study population, 45.1% had less than 5% body surface area involvement, while severe involvement with more than 20% was seen in 5.7%.
Vitiligo vulgaris was more commonly seen among females with a significant p-value of 0.007. Infertility was observed in a significant proportion of vitiligo vulgaris patients (p=0.021). 58.9% had generalised vitiligo.

![Figure 1. Type of Vitiligo](image1)

Generalised vitiligo was more common among those who had an earlier onset of disease, especially those with onset before 20 years (p=0.013). Chi-square test done on various diseases with positive family history and their association with generalised vitiligo showed no statistically significant correlation. DM (p=0.524), thyroid diseases (p=0.085) and vitiligo (0.558). But, statistically significant correlation was obtained between generalised vitiligo and other concurrent diseases- Diabetes mellitus (p=0.010), AITD (p=0.003) and thyroid diseases taken together (hyper/hypothyroidism + AITD) (p=0.016).

Segmental vitiligo was seen to involve face in three, among them 1 showed extension onto neck. Others were, one on the buttock along L1 and one on trunk along T8 dermatome. Special features noted were shown in the table below.

<table>
<thead>
<tr>
<th>Special Features</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Quadrichrome</td>
<td>20</td>
<td>16.4</td>
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<tr>
<td>Pentachrome</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Erythema</td>
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<td>4.1</td>
</tr>
<tr>
<td>Blue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukotrichia</td>
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<td>28.7</td>
</tr>
<tr>
<td>Koebnerization</td>
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<td>27.9</td>
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<tr>
<td>Halo nevus</td>
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<td>2.5</td>
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<tr>
<td>Photosensitivity</td>
<td>6</td>
<td>4.9</td>
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</table>

**Table 1. Vitiligo Special Features**

6.6% of the cases had recurrent lesions, 3% had progressive disease. By investigating the patients, hypothyroidism was detected in 17 patients and hyperthyroidism in 5. USG neck done in 6 patients, 4 had diffuse swelling, 1 had nodule and 1 had colloid goitre. 22 were detected to have diabetes mellitus and all were adults. 6 patients in whom serum insulin was done showed normal levels. Statistically significant correlation was obtained between generalised vitiligo and other concurrent diseases- Diabetes mellitus (p=0.010), AITD (p=0.003) and thyroid diseases taken together (hyper/hypothyroidism + AITD) (p=0.016).

**Thyroid Autoantibodies and Generalised Vitiligo**

Antithyroid antibodies was positive in 68 patients, anti-TPO alone in 21 (17.2%) patients, anti-TG alone in 23 (18.8%) patients and both antibodies positive in 24 (19.7%) patients.

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Yes</th>
<th>No</th>
<th>Pearson Chi-Square Value</th>
<th>df</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Anti-TPO</td>
<td>Yes</td>
<td>32</td>
<td>13</td>
<td>5.499</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>38</td>
<td>39</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anti-TG</td>
<td>Yes</td>
<td>34</td>
<td>13</td>
<td>5.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>36</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>Yes</td>
<td>19</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>51</td>
<td>47</td>
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</table>

**Table 2. Generalised Vitiligo**

Thyroid autoantibodies and their association with generalised vitiligo showed significant correlation.

**DISCUSSION**

In this study, clinical analysis was conducted in 122 patients diagnosed to have vitiligo. The mechanisms by which the melanocytes are lost in vitiligo maybe multiple, but is not yet identified unequivocally. There is existing evidence to suggest that vitiligo is not just a cutaneous disorder, but a systemic disorder of the pigmented system. Vitiligo is associated with high degree of stigma.

In India, the reported prevalence rate is 3-4%. The highest prevalence in the world at about 8.8% have been reported from Gujarat. Female preponderance was noted in most studies including in this study is probably due to the fact that females are cosmetically concerned and hence are likely to seek treatment early though the incidence of vitiligo is reported to be equal among both sexes. Nearly, 80% of the adult patients in this study were married. This may be due to increased awareness among the people regarding the benign and non-infectious nature of this disease secondary.
to improved educational and socioeconomic profile of the general population as our institution caters to the part of the state with the highest literacy rate. 12.1% married couples had history of infertility. Although, vitiligo is a disease thought to be purely of cosmetic concern. This study has observed a significantly increased rate of infertility among the patients with vitiligo, especially among those with vulgaris type. Hor et al reported 2.5% infertility among vitiligo patients.14

Majority of the patients were students reflecting the commonest age-group of this study. The proportion of ‘late-onset vitiligo’ was 13.9%. Relatively, higher proportion of late-onset cases in this study compared to other study probably parallels the increasing population of elderly citizens in this part of the state due to migration of younger population to other countries and increasing in the average life expectancy of the general population owing to the better healthcare system. Duration of disease was less than 2 years in 61.8% cases. This indicates that there is an early recognition of the symptom and increased cosmetic concern among general population. 6.6% of the cases had recurrent lesions, 62.3% had a progressive disease relatively similar to other studies.15 This could be a selection bias as the patients seeking treatment may do so because of the spreading lesions or newer lesions.

40.2% of the patients had depigmentation limited to a single site. This might have resulted from the patients seeking treatment at the initial stage of the disease itself.

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</thead>
<tbody>
<tr>
<td>Vitiligo vulgaris</td>
<td>36.8%</td>
<td>45.7%</td>
<td>69.8%</td>
<td>64.73%</td>
</tr>
<tr>
<td>Acrofacial</td>
<td>22.1%</td>
<td>14.3%</td>
<td>NA</td>
<td>13.73%</td>
</tr>
<tr>
<td>Focal</td>
<td>33%</td>
<td>11.5%</td>
<td>14.9%</td>
<td>8.42%</td>
</tr>
<tr>
<td>Segmental</td>
<td>4.9%</td>
<td>5.7%</td>
<td>5.0%</td>
<td>5.71%</td>
</tr>
<tr>
<td>Mucosal</td>
<td>3.2%</td>
<td>22.8%</td>
<td>NA</td>
<td>1.6%</td>
</tr>
<tr>
<td>Universal</td>
<td>0%</td>
<td>NA</td>
<td>NA</td>
<td>5.81%</td>
</tr>
</tbody>
</table>

Table 3. Table Showing Compared to Other Studies

Compared to others, focal vitiligo and acrofacial types made up a significant proportion, 33% and 22.1%, respectively.

Among the study population, 45.1% had less than 5% of body surface area involved as lips were the single most common site involved in most of our patients. Severe involvement with more than 20% of the body surface area involvement was seen in 5.7%. Similar observation was made by Handa and Kaur.15

A higher percentage of koebnerization (27.9%) seen in our study probably reflects the higher proportion of active or progressive disease (62.3%) among this group. Nail changes were observed in 44.3%. Nails are found to be involved in psoriasis, alopecia areata and other autoimmune diseases of the skin, particularly pitting of the nails, which was also commonly observed in vitiligo, points towards the autoimmune basis of this disease.

An 18% had associated diabetes mellitus. Vitiligo patients has definitely an increased incidence of diabetes mellitus, but a higher incidence noted among this study subjects reflects the higher prevalence of lifestyle diseases in our general population.8,17

By investigating the patients, hypothyroidism was detected in 17 patients and hyperthyroidism in 5, thus detecting thyroid dysfunction in 22 patients (18%). USG neck done in 6 patients, 4 had diffuse swelling, 1 had nodule and 1 had colloid goitre.

Antithyroid antibodies was positive in 68 patients (55.7%), anti-TPO in 21 (17.2%) patients, anti-Tg in 23 (18.8%) patients and both antibodies positive in 24 (19.7%) patients. Thus, AITD was diagnosed in 55.7%.

Comparison with Other Studies

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<tr>
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</thead>
<tbody>
<tr>
<td>Anti-TPOAb</td>
<td>17.2%</td>
<td>5.7%</td>
<td>6%</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-TgAb</td>
<td>18.8%</td>
<td>14.3%</td>
<td>2%</td>
<td>NA</td>
</tr>
<tr>
<td>Both</td>
<td>19.7%</td>
<td>11.4%</td>
<td>2%</td>
<td>NA</td>
</tr>
<tr>
<td>AITD</td>
<td>55.7%</td>
<td>31.4%</td>
<td>8%</td>
<td>25.7%</td>
</tr>
</tbody>
</table>

Table 4. Comparison with Other Studies

The higher percentage of thyroid antibody positivity and AITD among the study population probably has arisen due to the genetic variation of the people of this geographic area as presence of various HLAs has been proven to predispose the individual to the acquisition of this disease. We could not find any similar studies in this part of the state to compare the results of our study.

Vitiligo Vulgaris and Female Sex- Vulgaris type of vitiligo was more commonly seen among females with a significant p-value of 0.007. Infertility was observed in a significant proportion of vitiligo vulgaris patients with (p=0.021). Hor et al studied pregnancy outcomes of vitiligo patients and reported incidence of infertility to be 2.5% among the females.14 Thus, generalised vitiligo showed significantly higher incidence in females who also showed greater incidence of infertility, thus highlighting the importance of generalised vitiligo in females.

Generalised Vitiligo and Early-Onset Disease- Generalised vitiligo was more common among those who had an earlier onset of disease, especially those with onset before 20 years (p=0.013), while there was no statistically significant incidence of the same among late-onset vitiligo (p=0.086). As the onset of vitiligo usually precedes thyroid disease, it is better to screen annually for thyroid function and antithyroid antibodies to assist in the early diagnosis of AITD especially girls and those with generalised or vulgaris type of vitiligo.7

Though, there is no significant association was seen with family history of DM, AITD and vitiligo, the proportion of cases in this study with a positive family history shows that the tendency for autoimmunity runs in families and hence a screening for autoimmune diseases at least among
the first-degree relatives of the vitiligo patients especially with extensive diseases might help to identify them earlier.

**Generalised Vitiligo and Diabetes Mellitus**- Statistically significant correlation was obtained between generalised vitiligo and diabetes mellitus (p=0.010). Previous studies reported higher prevalence of DM among late-onset vitiligo that developed after the age of 40. Although, the prevalence of diabetes is higher in the general population in our geographical area, the association found remains significant as common HLA types are shown to indicate the susceptibility of an individual to both these diseases.

Our study showed a higher prevalence of diabetes mellitus and autoimmune thyroid diseases among the vitiligo patients. Our findings were comparable with most of the reported studies regarding the coexistent autoimmune disorders, especially thyroid disease and diabetes. The observed associations of vitiligo in our study indicate the need for screening vitiligo patients for diabetes and thyroid disease, at least in those with a generalised disease.

**CONCLUSION**

Our study showed a higher prevalence of autoimmune thyroid disease and diabetes mellitus among the vitiligo patients particularly in those with a generalised disease. Statistically significant higher percentage of infertility was noted in our patients with vitiligo vulgaris. The observed associations of vitiligo in our study indicate the need for screening vitiligo patients for comorbidities, especially in those with a generalised disease, so that treatment for these can be initiated at an early stage. However, small sample size and short duration were the limitations of this study. Further studies are to be carried out in this regard before we generalise our findings.

**REFERENCES**


