Increased prevalence of thyroid dysfunction and diabetes mellitus in Indian vitiligo patients: A case-control study

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ABSTRACT

Background: Though it is well-known that vitiligo is associated with other autoimmune disorders, few Indian studies have focused on the relation between vitiligo, autoimmune thyroid dysfunction and diabetes mellitus. **Materials and Methods:** This case-control study included 150 new cases of vitiligo and 100 age and sex-matched controls. A complete history and thorough dermatological examination was done. Serum samples from both patients and controls were collected and assayed for triiodothyronine, thyroxine, thyroid-stimulating hormone, anti-thyroid antibodies—anti-thyroid peroxidase and anti-thyroglobulin and fasting plasma glucose. **Results:** Thyroid hormonal profile revealed autoimmune thyroid dysfunction manifesting as hypothyroidism in 30 (20%) vitiligo patients and two controls (2%). Diabetes mellitus was present in 24 (16%) vitiligo patients and five controls. Seven (4.7%) patients had both hypothyroidism and diabetes mellitus. **Conclusion:** There is a clear association between vitiligo, autoimmune hypothyroidism and diabetes mellitus. It would be very useful to screen for thyroid dysfunction and diabetes mellitus in all patients with vitiligo.

Key words: Autoimmune thyroid dysfunction, diabetes mellitus, vitiligo

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INTRODUCTION

Vitiligo is a common, acquired, depigmentary disorder of the skin that affects 1-2% of the general population, without racial or sex differences.[1,2] Recent studies show that complex autoimmune, neural and self-destructive mechanisms are involved in its pathogenesis.[3-5] Numerous studies from abroad have described an association of vitiligo with other autoimmune disorders such as thyroid disease (Hashimoto's thyroiditis and Graves' disease), Addison's disease, pernicious anemia, insulin – dependent diabetes mellitus and alopecia areata.[6-8] In India however, few studies have focused on the association of autoimmune thyroid dysfunction with vitiligo and no studies have been done to know the association of diabetes mellitus and vitiligo.[9,10] We therefore undertook this study of the prevalence of autoimmune thyroid dysfunction and diabetes mellitus in vitiligo patients in and around North Coastal Andhra Pradesh.

MATERIALS AND METHODS

This study was conducted simultaneously at an urban skin-care and research clinic and at the Dermatology Department of a suburban medical college between January and December 2008. The study was approved by the Institutional Ethics Committee. This case-control study included all eligible new cases of various types of vitiligo attending the above centers over the 12-month period. A total of 100 age and sex-matched non-vitiligo cases, presenting with other common dermatological conditions were included as controls. Enrollment of lesser number of controls than cases was done due to cost factor. Pregnant women, children below 5 years of age and individuals with known endocrine dysfunction were excluded from the study. Written informed consent from all patients and controls was obtained prior to the study. In all patients, a complete history was taken including age of onset, duration, family history of vitiligo and personal or family history of common systemic diseases associated with

vitiligo such as anemia, alopecia areata, thyroid dysfunction and diabetes mellitus. A thorough dermatological examination was done and an approximate percentage of the body surface involved was calculated using the "rule of nine". All the vitiligo patients were classified into four groups: focal, segmental, acrofacial and generalized vitiligo. For statistical analysis, focal and segmental vitiligo were considered under localized vitiligo whereas acrofacial and generalized vitiligo were considered under generalized vitiligo. A complete general examination and clinical examination of the thyroid gland was done in all cases and controls. All routine investigations such as complete hemogram and serum biochemistry profile were carried out in all patients and controls. Serum samples from both patients and controls were collected and assayed for triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) and antithyroid antibodies – antithyroid peroxidase and antithyroglobulin. Thyroid hormones were assayed using radioimmunoassay kits (RIAK 5/5A; Board of Radiation and Isotope Technology, BARC, Navi Mumbai, India). The normal range for serum T3 was 70-200 ng/dl, for serum T4 was 5-13 ng/dl and for serum TSH was 0.5-5 micro U/ml. A diagnosis of hypothyroidism was made when thyroid function tests showed a raised TSH with or without low T3/T4 levels. Hyperthyroidism was diagnosed if T3/T4 levels were raised with associated lowered levels of TSH. Antithyroid antibodies were assayed by enzyme-linked immunosorbent assay using commercial kits (Varelisa TPO and Varelisa TG Antibodies, Pharmacia and Upjohn diagnostics GmbH Co. KG, Freiburg, Germany). All patients and controls were also subjected to fasting plasma glucose examination using the glucose oxidase method. A diagnosis of diabetes mellitus was made when fasting plasma glucose was more than 126 mg/dl. Both Type I and Type II diabetes mellitus cases fulfilling the above criteria were included. Numerical and graphical techniques have been used to summarize and present the quantitative data of this study. Chi-square test (c2) and Fisher's exact probability test were used for statistical analysis.

RESULTS

Out of the 150 vitiligo patients, 83 were males and 67 were females. The age of the patients varied from 9 to 63 years, the mean age being 24 years (SD = 10.28 years). Peak age of onset of vitiligo was between 11 and 20 years. Out of the 100 controls, 54 were males and 46 were females. The age of the controls varied from 8 to 61 years, the mean age being 26 years (SD = 9.81 years). Out of the 100 controls, 18 had superficial fungal infections, 17 had acne, 16 presented with melasma, 24 had pattern hair loss and 25 suffered from eczemas.

The duration of the disease ranged from 3 weeks to 26 years with a mean duration of 3.4 years (SD = 1.77 years). Duration of vitiligo was <5 years for 106 patients and ≥5 years for 44 patients.

Twenty two patients had focal vitiligo, 22 had segmental vitiligo, 35 had acrofacial vitiligo and 71 had generalized vitiligo. 54 (36%) vitiligo patients had a positive family history of vitiligo with at least one affected first-degree relative in 33 (22%) and second degree relatives in 21 (14%) cases. Anemia was present in 30 (20%) vitiligo patients and three (3%) controls, which was statistically significant (P = 0.0011). Alopecia areata was seen in 11 (7.4%) vitiligo cases and none of the controls (P = 0.0078).

None of the vitiligo patients and controls was found to have specific signs and symptoms of thyroid disease such as palpitation, tremor, insomnia, goiter, exophthalmos, etc. Thyroid hormonal profile revealed a statistically significant relationship between an autoimmune thyroid dysfunction and vitiligo as hypothyroidism was seen in 30 (20%) vitiligo patients and two controls (2%) (P = 0.004) [Table 1]. Antithyroid peroxidase antibodies were present in 17 cases as compared to three controls. Antithyroglobulin antibodies were present in eight cases as compared to two controls. Five of the cases and none of the controls had both antithyroid peroxidase and antithyroglobulin antibodies. Thus, all the 30 vitiligo cases found to have hypothyroidism by thyroid hormonal profile and five controls were positive for at least one thyroid antibody, which was statistically significant (P = 0.007). Hypothyroidism was seen in both sexes and in all age groups. Out of the total of 39 cases under the age of 18 years, 13 (30%) were found to have hypothyroidism, which was higher than the overall prevalence (20%) and prevalence in pediatric controls (5%) [Figure 1]. Hypothyroidism was not related to the duration and severity of vitiligo [Tables 2 and 3]. Hyperthyroidism was not detected in any of the cases or controls.

Diabetes mellitus was present in 24 (16%) vitiligo patients and five controls, which was statistically significant (P = 0.006) [Table 4].

Table 1: Hypothyroidism in vitiligo patients and controls

	No. of patients examined	Patients having hypothyroidism			% of patients having hypothyroidism
		Males	Females	Total	
Cases	150	14	16	30	20
Controls	100	2	0	2	2

(P=0.004)

Table 2: Relationship of type of vitiligo with hypothyroidism

Type of vitiligo	Hypothyroidism present		Hypothyroidism absent		Total
	No.	%	No.	%	
Localized	6	13.63	38	86.36	44
Generalized	24	22.64	82	77.35	106

(P=0.061)

Table 3: Relationship of duration of vitiligo with hypothyroidism

Duration of vitiligo	Hypothyroidism present		Hypothyroidism absent		Total
	No.	%	No.	%	
More than 5 years	12	27.27	32	72.72	44
Less than 5 years	18	16.98	88	83.01	106

(*P*=0.0139)

Table 4: Diabetes mellitus in vitiligo patients and controls

	No. of patients examined	Patients having diabetes mellitus			% of patients having diabetes mellitus
		Males	Females	Total	
Cases	150	14	10	24	16
Controls	100	3	2	5	5

(*P*=0.006)

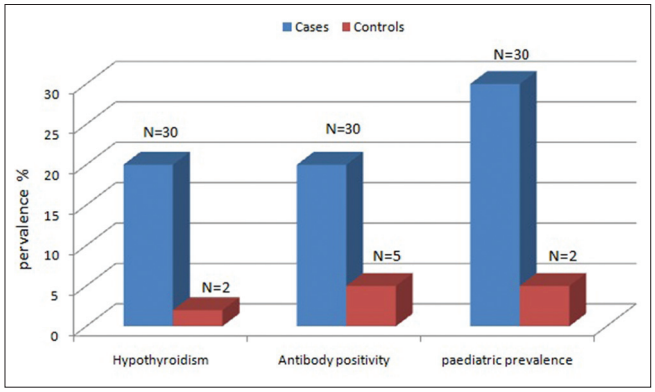

Figure 1: Prevalence of hypothyroidism, thyroid antibody positivity and hypothyroidism in pediatric age group

Twenty one (19.8%) patients of generalized vitiligo and 3 (9.8%) patients with localized vitiligo had diabetes mellitus, this difference being statistically significant (*P* = 0.048) [Table 5]. There was no statistically significant correlation between the presence of diabetes mellitus and the duration of the disease [Table 6]. Seven (4.7%) patients had both hypothyroidism and diabetes mellitus. All the seven patients had generalized vitiligo. None of the patients found to have hypothyroidism or diabetes mellitus had segmental vitiligo.

Thus, out of 106 cases with either generalized or acrofacial vitiligo, 38 (35.84%) had either hypothyroidism, diabetes mellitus or both compared to 9 (20.45%) out of 44 cases with localized vitiligo. Peak incidence of the two diseases was in the 10-20 year age group followed by 20-30 year age group [Figure 2].

DISCUSSION

Pathogenesis of vitiligo involves complex genetic, immunological, neural and self-destructive mechanisms.[11] Higher prevalence

Table 5: Relationship of type of vitiligo with diabetes mellitus

Type of vitiligo	Diabetes mellitus present		Diabetes mellitus absent		Total
	No.	%	No.	%	
Localized	3	6.81	41	93.19	44
Generalized	21	19.81	85	80.19	106

(*P*=0.048)

Table 6: Relationship of duration of vitiligo with Diabetes mellitus

Duration of vitiligo	Diabetes mellitus present		Diabetes mellitus absent		Total
	No.	%	No.	%	
More than 5 years	10	22.72	34	77.27	44
Less than 5 years	14	13.21	92	86.79	106

(*P*=0.061)

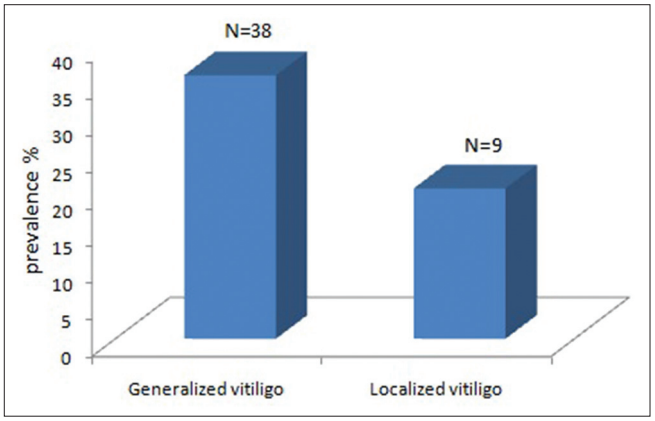

Figure 2: Prevalence of hypothyroidism, diabetes mellitus or both in generalized and localized vitiligo

of vitiligo in patients with autoimmune diseases (10-15%) in comparison with the general population (1-2%) and high prevalence of autoantibodies to melanocytes in the serum of patients with vitiligo support the autoimmune hypothesis.[1,12] The majority of vitiligo patients are healthy and have no associated pathology, but it is well-known that vitiligo is frequently associated with other autoimmune disorders such as thyroid dysfunction, Addison's disease, insulin – dependent diabetes mellitus, alopecia areata etc.[13-16]

In our study, though none of the cases had specific clinical signs of thyroid disease, autoimmune thyroid dysfunction manifesting as hypothyroidism occurred in 30 (20%) vitiligo patients and in two out of 100 controls, this difference being statistically significant (*P* = 0.004). Similar higher prevalence of hypothyroidism resulting from autoimmune thyroiditis in vitiligo patients has been reported by Kumar *et al*. (40%),

Akay *et al*. (31%) and Iacovelli *et al*. (16%) though a lower occurrence was noted by Narita *et al*. and Handa and Kaur.[8,9,17-19] The presence of hypothyroidism was unrelated to sex, duration and type of vitiligo but a higher prevalence of hypothyroidism in the pediatric age group (<18 years) was noticed. Some authors have noticed an association of vitiligo with hyperthyroidism and a female preponderance in vitiligo patients with autoimmune thyroiditis, but these findings were not noticed in our study.[15,18]

Even though, none of our vitiligo patients and controls were known diabetics, findings of fasting plasma glucose examination revealed diabetes mellitus in 24 (16%) vitiligo patients and five controls, which was statistically significant ($P = 0.006$). These findings were consistent with the results of previous studies by Dawber and Laberge *et al*.[20,21] The presence of diabetes mellitus was unrelated to age, sex and duration of vitiligo, but a statistically significant association was seen between the extent of vitiligo and diabetes mellitus. A higher prevalence of hypothyroidism, diabetes mellitus or both was seen in generalized or acrofacial vitiligo (35.84%) compared to localized vitiligo (20.45%) suggesting that there is a positive correlation between the existence of other autoimmune diseases and the severity of vitiligo. None of the patients detected as having hypothyroidism or diabetes mellitus had segmental vitiligo which suggests that segmental vitiligo is a unique subtype of vitiligo caused by alteration in neural peptides and not involving autoimmune pathomechanisms.[22]

All the above findings establish a clear association between vitiligo, autoimmune hypothyroidism and diabetes mellitus. These associations indicate that vitiligo shares a common genetic etiologic link with these autoimmune disorders. Gene expression studies and genomic analysis of families with generalized vitiligo and associated autoimmune disorders will be important in shedding light on the mechanisms of vitiligo pathogenesis. These studies will in turn provide novel approaches to the prevention and treatment of vitiligo and associated autoimmune diseases.[14,23]

Previous studies have shown that vitiligo precedes thyroiditis by 4-35 years in nearly 50% of the subjects.[6,18] Various studies in pediatric patients have also shown that vitiligo usually appears before the development of autoimmune thyroiditis.[15] Insulin-dependent diabetes mellitus is found in 1-7% of patients with vitiligo and conversely 4.8% of all diabetic patients were found to have vitiligo.[11,20] These findings in conjunction with ours clearly establish that it is very useful to screen all patients with non-segmental vitiligo for thyroid dysfunction and diabetes mellitus. We suggest that all pediatric patients with vitiligo should be routinely subjected to thyroid screening as the diagnosis of autoimmune thyroiditis is particularly important in this age group to avoid the negative impact of hypothyroidism on growth and health status. Prompt treatment in all detected cases will prevent long-term morbidity and complications. More Indian studies with a larger sample size will shed further light on the association of hypothyroidism and diabetes mellitus in vitiligo patients.

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