

# A Study of Autoimmune Polyglandular Syndrome (APS) in Patients with Type 1 Diabetes Mellitus (T1DM) Followed Up at a Tertiary Care Hospital

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## ABSTRACT

**Background:** Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of insulin-producing  $\beta$  cells and is characterized by the presence of insulinitis and  $\beta$ -cell autoantibodies. Up to one third of patients develop an autoimmune polyglandular syndrome (APS). Presence of other autoimmune disorders in patients with T1DM has been associated with increased morbidity and mortality. Hypoglycemia resulting from concurrent hypothyroidism or adrenal crisis can be dangerous; starting replacement therapy for hypothyroidism may result in adrenal crisis if background hypocortisolism is not recognized. Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease.

**Aims:** The objectives of this study were to assess the concurrence of various autoimmune disorders in patients with T1DM, to review the concept and detect the overt forms of Autoimmune Thyroid Disease (AITD), Addison's Disease (AD), Vitamin B 12, vitiligo in T1DM and to find their correlation according to age and sex of the patients.

**Methods:** It is a retrospective study where medical records between January 2007-June 2010 of all the patients diagnosed

with T1DM, followed up at Department of Endocrinology were reviewed to find out the presence of (AD), AITD, vitiligo, Vitamin B12 deficiency and Primary Gonadal Failure, which were diagnosed clinically with available investigational procedures.

**Results:** A total of 100 cases of T1DM were evaluated during the present study. The age group of patients ranged from 8 to 40 years, with the average being 21.56 years. 64% of the patients were males and the rest were females. 29 % of T1DM subjects had AITD (Hashimoto's or Graves' disease), 5% were diagnosed with Vitamin B12 deficiency, 4% had AD, and 6% showed Vitiligo. 28 % had family history of autoimmune endocrinopathy.

**Conclusion:** The commonest autoimmune disorder associated with T1DM found in our study was AITD. Because genetic/autoantibodies testing is not a feasible option, it is important to screen them with best available laboratory facilities and clinical assessment in view of high prevalence of associated autoimmune conditions.

**Keywords:** Autoimmune endocrinopathy, Autoantibodies, Autoimmune thyroid disease, Addison's disease, Hypothyroidism

## INTRODUCTION

T1DM arising through a complex interaction of immune, genetic and environmental factors, results from autoimmune destruction of insulin-producing  $\beta$  cells. T1DM is characterized by the appearance of insulinitis and the presence of  $\beta$ -cell autoantibodies [1]. T1DM as a common autoimmune endocrine disease of children and adolescents is frequently associated with the other autoimmune disorders and autoantibodies [2]. In one third of patients the autoimmune attack is not limited to  $\beta$  cells, but expands into an APS [3-5].

In type 1 diabetic subjects, 15 to 30% have AITD (Hashimoto's or Graves' disease), 5 to 10% are diagnosed with autoimmune gastritis and/or pernicious anaemia (AIG/PA), 4 to 9% present with coeliac disease (CD), 0.5% have AD and 2 to 10% show vitiligo [6]. Presence of other autoimmune disorders in patients with T1DM has been associated with increased morbidity and mortality. Hypoglycemia resulting from concurrent hypothyroidism or adrenal crisis can be dangerous; starting replacement therapy for hypothyroidism may result in adrenal crisis if background hypocortisolism is not recognized [7]. Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease [8].

To our knowledge, there is little published Indian data on the co-

existence of Type 1 diabetes mellitus with autoimmune diseases among a large group of individuals [9]. The objectives of this study were to assess the concurrence of various autoimmune disorders in patients with T1DM, to review the concept and to find their correlation according to age and sex.

## METHODS

Hundred cases of T1DM diagnosed during a period of three and half years duration (January 2007-June 2010) which were registered in medical records of Department of Endocrinology in a tertiary care hospital were included for the study. The institutional clearance was obtained and 100 patients with T1DM diagnosed during a period of three and half years duration (January 2007-June 2010) in the age group of 8-40 years were reviewed to find out the presence of AD, AITD, vitiligo, Vitamin B12 deficiency and Primary Gonadal Failure. All the patients with autoimmune disorders were diagnosed clinically with available investigation procedures. We analyzed the coexistence of putative autoimmune diseases in persons with diabetes from these medical records, as well as the coexistence of diabetes mellitus among persons with hypothyroidism or hyperthyroidism, vitiligo, Vitamin B12 deficiency and AD.

## STATISTICAL ANALYSIS

SPSS Version-16 (2007) was employed for statistical analysis. The One-Way ANOVA test was used for quantitative dependent variable by a single factor (independent) variable. Microsoft Word and Excel have been used to generate graphs and tables.

## RESULTS

A total of 100 cases were evaluated during the study. 64% (n= 64) of the patients were males and 36% (n=36) were females. The age group of patients ranged from 8 to 40 years, with the average being 21.56 years and maximum number of patients were between the age group of 20-30 years.

Out of 100 patients with Type 1 diabetes, autoimmune diseases were diagnosed in 52% (n=52) cases. Out of 52 cases; 28 female patients and 24 male patients had associated autoimmune diseases.

Out of 25 hypothyroid patients associated with T1DM, three patients were associated with vitiligo and one case was associated with Vitamin B12 deficiency. Hypothyroidism, vitiligo and Vitamin B 12 were the three common conditions coexisting in persons with Type 1 diabetes.

Five patients had evidence of Vitamin B12 deficiency on biochemical testing. All patients were symptomatic.

Four of the patients documented with evidence of AD had inadequate response to synacthen test. Other associated conditions were Graves' disease, goiter, candidiasis and SLE (Systemic Lupus Erythematosus). Details of diseases are given in [Table/Fig-1].

Condition	Total no of patients n=100	Males n=64	Females n=36
Hypothyroidism	25	5	20
Graves' Disease	2	1	1
Goiter	2	2	0
Vitamin B12 deficiency	5	4	1
Addison's Disease	4	3	1
Vitiligo	6	4	2
SLE	2	1	1
Candidiasis	6	4	2
Family h/o of autoimmune endocrinopathy	28	20	8

**[Table/Fig-1]:** Autoimmune diseases associated in patients with Type 1 diabetes mellitus

## DISCUSSION

In the majority of T1DM patients, the associated autoimmune disease follows the onset of diabetes. Patients with T1DM are known to have a higher risk of developing associated autoimmune disorders [2,3]. T1DM is associated with other autoimmune endocrine disorders as well as autoimmune impairment of nonendocrine tissue. Autoimmune Polyglandular syndrome (APS) consists of multiple coexisting autoimmune disorders principally affecting the endocrine glands. APS is commonly associated with autoimmune thyroiditis, adrenocortical insufficiency, and Type 1 diabetes mellitus [10]. APS-I is defined by the presence of two or three of the following components: mucocutaneous candidiasis, adrenal insufficiency and/ or hypoparathyroidism. It usually manifests in infancy at the age of 3 to 5 years or in early adolescence. The APS-II is defined as the association of an autoimmune endocrine disorder with an additional autoimmune disease but not meeting criteria for APS-I and not having an identified mutation of the AIRE gene. APS-II is a complex polygenic disorder. APS-2 is characterized by presence of AD, AITD, T1DM, oophoritis, malabsorption, hepatitis, asplenism, alopecia, vitiligo, keratitis, enamel dysplasia. This syndrome has a peak incidence between the ages of 20 and 60 years, mostly in the third or fourth decade [4-5].

In a retrospective analysis of patients from an endocrine polyclinic, 151/~15,000 had coexisting autoimmune endocrine disorders. 61% (n = 92) had T1DM, 33% (n = 50) had thyrotoxicosis, and 20% (n = 30) had vitiligo. The common association was of T1DM and AITD [11].

In another small report of 10 persons with coexisting diabetes mellitus and hyperthyroidism; eight of them (80%) developed both the diseases at the same time [12]. Similarly, type 2 diabetes mellitus (T2DM) was present in 7.6% (n = 49) of persons with Graves' disease [13]. Graves' disease was the commonest form of thyrotoxicosis in diabetes mellitus, outnumbering toxic adenomas by nearly three times [14].

In a large series of 1,436 persons with Vitiligo, 5 had coexisting diabetes mellitus (0.35%), 7 had thyroid disorders (0.5%) and 6 had alopecia (0.4%). Myasthenia gravis and Graves' disease may occur together with other autoimmune diseases [9].

In our series, among 100 cases with type 1 diabetes, autoimmune diseases were diagnosed in 52 % (n= 52) patients which involved both endocrine and non-endocrine tissues. The various autoimmune disorders are represented in the [Table/Fig-1]. Hypothyroidism was the commonest autoimmune disorder found in our study with 20 females and 5 males. 28 % (n= 28) patients reported of family history of autoimmune endocrinopathy. The rest 20% (n= 20) of T1DM patients had no associated autoimmune disorders.

In a study done among 1310 individuals with diabetes mellitus of adult onset, the overall prevalence of thyroid diseases was 13.4%. Hypothyroidism occurred in 0.9% and hyperthyroidism in 0.5%. Clinical hypothyroidism and hyperthyroidism were reported in 5% to 8% of persons with T1DM [15].

In the present study we found that, out of 52 cases diagnosed with autoimmune disorders highest incidence was in females (28 cases), when compared to male patients (24 cases). Our finding correlates with other studies which have reported a increased prevalence of Type 1 diabetes associated autoimmune disorders in females when compared to males [5,16].

In addition; in the present study we found that three patients of hypothyroidism were associated with vitiligo and one patient of hypothyroidism was associated with Vitamin B12 deficiency. Hypothyroidism, vitiligo and Vitamin B 12 were the three common conditions coexisting in persons with Type 1 diabetes. Five patients had evidence of Vitamin B-12 deficiency on biochemical testing. All patients were symptomatic. Two patients had symptoms of neuropathy and one patient had symptoms of hypopigmentation with normal adrenal function, none of the patients had anemia. There have been earlier reports of diabetes mellitus with thyroid disorders and of vitiligo and autoimmune endocrine disorders [10].

In the present analysis four patients were documented with evidence of AD with inadequate response to synacthen test with three males and one female. Other associated conditions were of Graves' disease and goiter, two patients each, six patients of candidiasis and two cases of SLE.

The commonest autoimmune disorder associated with T1DM found in our study was AITD. The results indicate that all T1DM patients should undergo anti TPO antibody assay to screen for thyroid autoimmunity. Thyroid peroxidase antibodies (aTPO) are present in 25 to 30% of adults and in 5 to 22% of children with Type 1 diabetes, compared with 2 to 10% and 1 to 4%, respectively, in matched controls. Cross-sectional analysis has shown that hypothyroidism is present in 4 to 18% of subjects with T1DM. Long-term follow-up suggests that as many as 30% of patients with T1DM will develop AITD [16].

T1DM subjects with GADA (Glutamic Acid Dehydrogenase) positive, in contrast to Insulinoma-associated protein 2 antibody (IA2A) positive patients, are more prone to have aTPO [5]. The

association of GADA with thyrogastric antibodies might be explained by the fact that GAD-65 is not exclusively present in the brain and pancreas but can also be found in the thyroid gland and stomach. Other factors such as age, diabetes duration, and gender (female preponderance) influence the link between T1DM and AITD [17] which correlate with our findings.

Thus T1DM patients should undergo anti TPO antibody assay to screen for thyroid autoimmunity and also for serum Free T4 and TSH to detect asymptomatic thyroid dysfunction particularly in those with positive anti TPO antibodies. This will help us to detect any thyroid disease at the earliest and achieve better glycaemic control and prevent diabetic complications due to thyroid dysfunction.

## CONCLUSION

Type 1 diabetic patients exhibit an increased risk of other autoimmune disorders. Approximately 25 to 30% of patients with T1DM have thyroid antibodies, and up to 50% of such patients progress to clinical AITD. The commonest autoimmune disorder associated with T1DM found in our study was AITD. Most common occurrence of associated autoimmune diseases was seen in females. Because genetic/ autoantibodies testing is not a feasible option it is important to screen them with best available laboratory facilities in view of high prevalence of associated autoimmune conditions. Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease.

Limitation of our study was a smaller study group (100 cases), a larger study group along with estimation of autoantibodies would further help in better assessment and treatment of associated autoimmune disorders in T1DM.

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