Association between vitiligo and diabetes mellitus: a case control study

Shahid Shahzad, MD [1]
Ahmad Reza Taheri, MD [1]
Zari Javidi, MD [1]
Akbar Dorgalaleh, MD [2]
Shadi Tabibian, MD [2]
Taregh Bamedi, MD [3]
Saeed Dorgalaleh, MD [4]
Mohammad Moemeni, MD [5]

1. Department of Dermatology, Mashhad University of Medical Sciences, Mashhad, Iran
2. Department of Hematology, Allied Medical School, Tehran University of Medical Science, Tehran Iran
3. Department of Parasitology, Allied Medical School, Zahedan University of Medical Sciences, Zahedan, Iran
4. Department of Laboratory Sciences, Zabul University of Medical Sciences, Zabul, Iran
5. Imam Ali Hospital, Sistan and Baluchistan, Chahbahar, Iran

Corresponding Author:
Ahmad Reza Taheri, MD
Department of Dermatology, Mashhad University of Medical Sciences, Mashhad, Iran
Email: hematology.1390@gmail.com

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Background: Vitiligo is a common acquired disorder of the skin. The disease is characterized by depigmented macules and patches on the skin. Autoimmunity has a crucial role in the pathogenesis of the vitiligo. Vitiligo is frequently associated with different autoimmune diseases such as thyroid abnormalities and diabetes. This study aimed to evaluate the association between vitiligo and diabetes mellitus.

Method: This case-control study was conducted on 70 patients with established vitiligo disorder and 70 non vitiligo individuals as the control group. In the case group, we performed two tests, fasting blood sugar (FBS) and oral glucose oral tolerance test (OGTT), while only FBS was checked in the control group.

Result: The results of our study showed that out of 70 people in the case group, 18 (25.71%) had impaired FBS while only 4 (5.7%) had impaired GTT3. Statistical analysis showed p-value=0.015 which indicated a significant difference in impaired FBS between case and control groups. We had half and 1 hour GTT data (GTT1 and GTT2) and all patients with impaired GTT1 (4 individuals) and GTT2 (5 individuals) were females with a significant difference (P-value = 0.021 and 0.017, respectively).

Conclusion: Periodical laboratory investigation for diabetes mellitus in vitiligo patients, particularly in females, seems to be necessary.

Keywords: diabetes mellitus, fasting blood sugar, glucose tolerance test, vitiligo

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INTRODUCTION

Vitiligo is a common acquired hypomelanotic disorder of the skin with an estimated prevalence of 0.5-2% in the general population worldwide [1-2]. The disease is characterized by depigmented macules and patches that can appear anywhere on the skin [3]. It affects both sexes equally and may appear at any age and race [3-4]. Although the precise mechanism of vitiligo is unknown, several theories have been proposed for the pathogenesis of the disease such as autoimmune, genetic, neural, viral, biochemical and autocytotoxic mechanisms [5-7].

Several Studies have shown that autoimmunity has a crucial role in the pathogenesis of the vitiligo [8-9]. Autoimmune theories have proposed the

role of B and T cell. The presence of autoreactive T cells in the peri-lesional skin and peripheral blood and the presence of anti-melanocyte autoantibody in the patient's serum contribute to the destruction of melanocytes. The precise role of autoantibodies remains unclear but it may be a signal for autoreactive cytotoxic T cells to identify melanocyte antigen [10].

The treatment of vitiligo is often difficult and encompasses several methods such as narrow UVB phototherapy, excimer laser therapy, topical corticosteroids, topical immunomodulators, and surgical therapy [3,11]. Vitiligo is frequently associated with different autoimmune diseases with thyroid abnormalities being the most common. Other autoimmune diseases that are associated with vitiligo include alopecia areata, addison's disease, pernicious anemia, grave's disease, Hashimoto's disease, and diabetes mellitus [9,12].

Diabetes mellitus is a common endocrine disorder with the phenotype of hyperglycemia. It appears in 2 categories:

1. Diabetes mellitus type 1 (T1DM) or juvenile-onset diabetes is a lifelong metabolic disorder that is identified by autoimmune destruction of insulin- producing beta cells of the pancreas. The marker of beta cells destruction is circulatory islet cell and insulin autoantibodies and the rate of this destruction can be rapid (in infants or children) or slow (in adults). In this type of diabetes, some patients present with unpredictable hyperglycemia that can change to ketosis and some develop ketoacidosis as the first symptom [13-14].
2. Diabetes mellitus type 2 (T2DM) or adult-onset diabetes is a chronic, progressive disease characterized by hyperglycemia due to insulin resistance. It comprises 90-95% of the cases of diabetes. The exact etiology of this form is unknown. Most patients with this type of diabetes are obese; thus, obesity can be the primary cause. The patients with T2DM are at risk of cardiovascular diseases. Other risk factors are lack of physical activities, poor diet, and stress [13,15].

The American Diabetes Association (ADA) has proposed FPG (fast plasma glucose) and OGTT (oral glucose tolerance test) as the diagnostic criteria for diabetes mellitus [13,16]. During OGGT, a standard dose of glucose is ingested and blood glucose levels are checked after 2 hours. FPS is a test which measures plasma or blood glucose levels after a fasting period of at least 8 hours. The international expert council of ADA published a new cut point of ≥126 mg/dl (7.0 mmol/l) for FPS and ≥ 200 mg/dl for 2-hour plasma glucose (11.1 mmol/l) on OGTT. The patients whose plasma glucose is above the normal level but not high enough for the diagnosis of diabetes having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Impaired fasting glucose is defined as glucose levels between 100 mg/dl (5.6mmol/l) and 125 mg/ dL (6.9 mmol/L) in fasting patients and impaired glucose tolerance is defined as two-hour glucose levels between 140 mg/dl (7.8mmol/l) and 199 mg/dL (11.0 mmol) on the oral glucose tolerance test. Patients with IFG or IGT have a significant risk of progression to diabetes.The HBA1C is also added as a diagnostic method for diabetes mellitus, it reflects plasma glucose level over a 2-3 months period [13,16].

The association between diabetes and vitiligo has been proposed by several studies [17]. The occurrence of vitiligo and diabetes mellitus may be the result of autoimmune mechanisms in the same patient. Long standing diabetes mellitus impairs melanocytes, resulting in anti-melanocyte antibody formation and destruction of melanocytes which causes vitiligo [18]. From the first report of Lerner up to now, attention has been given to the association of vitiligo and diabetes mellitus and several studies have shown this relationship. In the same way, we performed this study to evaluate the laboratory association between vitiligo and diabetes mellitus.

PATIENTS AND METHODS

This case-control study was conducted on 70 patients with established vitiligo disorder who were referred to the dermatology ward of Imam Reza Hospital, Mashhad, from 2009 to 2010. We also randomly chose an additional 70 non vitiligo individuals as the control group. Written consent was obtained from each participant and the study was approved by the medical ethics committee of Mashhad University of Medical Sciences. We measured FBS and OGGT in the case group while only FBS was measured in the control group because of ethnic issues. OGTT is also costly and time

consuming as compared to FBS. The laboratories used 4 specimens (FBS, GTT1, GTT2, GTT3) for GTT while according to the latest reference of endocrinology, the main criteria for the diagnosis of diabetes mellitus is FBS, GTT3 (2 hour glucose tolerance test), or random BS with symptoms, and there is no mention of half and 1 hour glucose tolerance tests (GTT1, GTT2).

Normal values of these tests are as follows:

FBS: (normal=70-110 mg/dl), (impaired=100-125 mg/dl), (>126 mg/dl =diabetes)

GTT1: (normal=140-170 mg/dl)

GTT2: (normal=130-160 mg/dl)

GTT3: (normal=< 140 mg/dl), (impaired=140-200 mg/dl), (>200 mg/dl =diabetes)

The patients with the following factors, due to their influence on the glucose level, were excluded from study:

1. Physical inactivity like bed rest over a long period of time.
2. Infectious diseases and surgery or other traumas.
3. Drugs like salicylates, estrogens, oral contraceptives, thiazides diuretics, phenytoin, acetaminophen, L-dopa and corticosteroids.
4. Pregnancy and endocrine disorders.

After exclusion, 70 patients with vitiligo have guided for a restricted diet for this test in order to obtain a true response to the test. This diet, which contains a minimum of 150 g of carbohydrate per day, should be used for at least 3 days before the test. The excessive intake of sucrose or glucose should be avoided. The case and control groups were fasting for at least 8 but not more than 16 hours before the test. The test was performed in the morning between 7 to 9 am with no food taken after the previous midnight. Initially, the technicians first took blood samples from the patients who were fasting for at least 8 hours; then, the patients were given 75mg glucose dissolved in 300cc water. The patients consumed this solution within 5 minutes and the second sample was taken 30 minutes after the first sample. After that, 60-minute and 120-minute samples were also taken from the patients. For each sample, the serum was separated within 30 min and then, the glucose level was measured with Hitachi autoanalyzer.

In this research, we used the SPSS statistical software to analyze our collected data. Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level of significance. All the statistical analyses were performed by SPSS software. Discrete variables were analyzed by the $\chi 2$ test. The relationship between FBS, GTT1, GTT2, and GTT3 levels and the risk of vitiligo was calculated using logistic regression and expressed as an OR (Odds Ratio) with a 95% confidence interval (CI). We used chi-square, t-test, and one-way ANOVA statistical methods to evaluate data. One-way ANOVA and t-test were used to compare the mean age of the patients in different ranges of FBS and GTT3. We used LRT (Likelihood ratio test) for comparison between gender and GTT because more than 5% of the cells were less than 5.

RESULT

In this study, 70 vitiligo patients with a mean age of 25.43 years (ranging from 14 to 58 years) and a control group with a mean age of 29.83 years (range: 12 to 84 years) were chosen. 74.29% (n=52) of the patients in the case group had normal FBS and 25.71% (n=18) had impaired FBS values while in the control group, 90% (n=63) of the participants showed normal FBS and 10% (n=7) had impaired FBS values, which showed a significant difference in impaired FBS between case and control groups (p=0.015) (Figure 1).

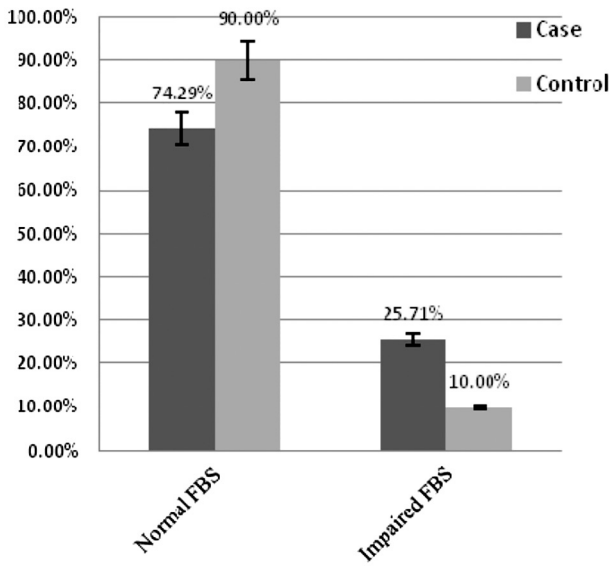

Figure 1. Comparison of normal and impaired FBS between case and control groups

Sixty six (94.3%) patients had normal values of GTT3 and only 5.7% (N=4) had impaired GTT3. Moreover, we had 36 females and 34 males in the case group of whom 33 females and 33 males had normal values of GTT3 while 3 females and 1 male had impaired GTT3 values. Statistics analysis showed that the gender had no effect on GTT3 values (Fisher exact test P-value=0.615). We also used T-test to compare age and GTT3 and found no statistical difference in age between patients with normal and impaired GTT3 values (T-test P-value=0.693). Four patients had GTT1 more than normal value and all of them were females. It means that gender was important in GTT1 (p-value=0.021). There was no statistical difference between the age of the patients in the categorized GTT1 levels (p-value = 0.670). GTT2 was higher than normal values in 5 patients who were all female (p-value=0.017). According to ANOVA, there was no statistical difference between the patients' age in the categorized GTT2 levels (p-value = 0.151) (Table1).

DISSCUSION

Vitiligo as a common disorder of the skin is characterized by depigmented macules and patches on the skin [1-2]. Vitiligo is frequently associated with different autoimmune diseases such as thyroid abnormalities, pernicious anemia, and diabetes mellitus among which diabetes mellitus is more common in vitiligo patients. The current study was based on the findings of other studies and intended to evaluate the relationship between vitiligo and diabetes mellitus. The results of our study showed from a total of 70 cases, 18 (25.71%) had impaired FBS while only 4 (5.7%) had impaired GTT3. As we had half and 1 hour GTT data (GTT1 and GTT2), their statistical analyses showed a significant difference between gender and GTT1 (P-value = 0.021 using LR test) and GTT2 (p-value=0.017). All patients with impaired GTT1 and GTT2 were female.

In 1999, a similar study performed in Kerman showed 8.2% diabetes and glucose tolerance test abnormalities in vitiligo patients, indicating that vitiligo patients have more abnormal glucose values than normal healthy persons [19]. Another study performed on 750 diabetes patients in Iran, showed 32 out of 750 (4.3%) diabetic patients had vitiligo [20]. In 2010, 80 vitiligo patients were investigated in Turkey, and it was found that only 2 of them (2.5%) had diabetes mellitus [1]. In another study in India, 100 vitiligo patients were studied and an association with systemic diseases like diabetes mellitus was found in 9 (9%) cases [21]. A study performed in Belgium in 2009 showed that 2-10% of type 1 diabetes mellitus subjects had vitiligo [22]. In a study in USA in 2010, the authors performed a genome-wide association study of generalized vitiligo in 32 vitiligo and 50 healthy persons and found a linkage and association signal for type1 diabetes and rheumatoid arthritis in vitiligo patients [23].

According to the results of this study and other similar studies, it seems necessary to perform periodical laboratory checkup for diabetes mellitus in vitiligo patients, especially in female patients. Moreover, it seems useful for diabetic patients to be regularly examined by a dermatologist for the probable signs of vitiligo. However, future controlled study especially with controlled measurement of OGTT could be more helpful to elucidate the possible association of vitiligo with diabetes mellitus.

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Table 1. OGTT in vitiligo patients.

		GTT1	GTT2	GTT3
Normal	Male	25 (35%)	28 (40%)	33 (47.1%)
	Female	18 (25.7%)	22 (31.4%)	33 (47.1%)
Impaired	Male	9 (12.8%)	6 (8.5%)	1 (1.4%)
	Female	14 (20%)	9 (12.8%)	3 (4.3%)
Diabetic	Male	0	0	0
	Female	4 (5.7%)	5 (7.1%)	0

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