Original Article

# A Celiac Disease Marker: Serum Immunoglobulin A Anti-Tissue Transglutaminase in Vitiligo Cases and Controls in a Hospital in South-West Nigeria

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## Abstract

**Background:** Vitiligo is an autoimmune disorder resulting from the destruction of melanocytes of affected patients. Celiac disease (CD) is characterised by autoimmune inflammation of small intestinal mucosa specifically triggered by the gluten consumption in susceptible individuals. Immunoglobulin A (IgA) anti-tissue transglutaminase (anti-tTG) serology is recommended as an initial test for the diagnosis of CD prior to confirmation with intestinal biopsy. **Aim:** We aimed to compare the serum IgA anti-tTG levels in vitiligo patients and controls without vitiligo in a hospital in South-West Nigeria. **Materials and Methods:** The study was a case–control study of 33 vitiligo cases and 33 controls. IgA anti-tTG was assayed in participants' sera using an enzyme-linked immunosorbent assay protocol employing recombinant human tTG. **Results:** A total of 66 participants were recruited into the study; 33 cases with vitiligo and 33 controls. The median age for cases was 50 years (range: 4–82). The median age for the controls was 55 years (range: 23–76). Generalised vitiligo accounted for 13 (40%) of vitiligo cases with the others consisting of various forms of segmental vitiligo. Anti-tTG levels were higher in cases at 6.1U/ml (8.8, 0.6–20.0) (med [interquartile range (IQR), min-max]), compared to controls 5.2 U/ml (3.7, 0.7–22.4). Difference between groups estimated using the Mann-Whitney U-test was not significant, $u = 408.0$, $P = 0.08$ ($\alpha = 0.05$). **Conclusion:** There was no significant difference in serum IgA anti-tTG in vitiligo cases and controls in this study. Further studies are required to clarify the nature of the association between vitiligo and CD.

**Keywords:** Anti-tissue transglutaminase, autoimmunity, celiac disease, endomysial antibodies, vitiligo

## Introduction

Vitiligo is an acquired depigmenting skin condition characterised by a selective loss of skin melanocytes. The pathognomonic feature is the presence of depigmented, amelonocytic, and nonscaly macules with distinct margins.[1] There are two main types of vitiligo: generalized or nonsegmental vitiligo; the most common form involves loss of pigment in patches of skin all over the body, typically on the face, neck, and scalp, and around body openings such as the mouth and genitals. Segmental vitiligo is associated with smaller patches of depigmented skin that appear on one side of the body in a limited area; this occurs in about 10% of affected individuals.

Vitiligo affects about 1% of people worldwide and has a pronounced impact on the physical and mental health of patients, including loss of skin photoprotection, compromised cutaneous immunity, and an appreciable reduction in quality of life.[2]

Several mechanisms are responsible for the melanocyte loss in vitiligo, including autoimmune responses, genetic defects, oxidative stress, generation of inflammatory mediators, and melanocyte detachment mechanisms. Innate immune response to melanocyte stress involves recruitment of natural-killer cells and release of proinflammatory cytokines

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like interleukin1-beta, interleukin 6, interleukin 8, as well as heat-shock proteins (HSPs). Inducible HSP70i has been shown to play a central role in vitiligo pathogenesis in a mouse model by inducing dendritic cells to present melanocyte-specific antigens to T-cells in the lymphoid tissues.[3] Celiac disease (CD) 8+ T-cells subsequently destroy melanocytes. Large-scale genome-wide association studies performed in Europeans and in Chinese have revealed nearly 50 different genetic loci that confer a vitiligo risk.[4] In addition, co-occurrence of vitiligo with various other autoimmune diseases, particularly autoimmune thyroid disease (both Hashimoto's disease and Graves' disease), pernicious anaemia, Addison's disease, systemic lupus erythematosus, rheumatoid arthritis, adult-onset type 1 diabetes mellitus, and psoriasis suggest shared genetic underpinnings. Association of vitiligo with another autoimmune disease, CD, has been described in the literature.[5-7] Vitiligo is often diagnosed clinically; examination of the skin under Wood's lamp may reveal the extent of lesions. There is no known cure for vitiligo at present. Management modalities include the use of corticosteroids, calcineurin inhibitors, ultraviolet phototherapy, and skin grafting. Depigmentation of residual normal skin may be employed in a widespread disease.[8]

CD, also known as "celiac sprue," is a chronic inflammatory disorder of the small intestine, produced by the ingestion of dietary gluten products in genetically susceptible people.[9] It is the end result of the three processes that culminate in the intestinal mucosal damage: genetic predisposition, environmental factors, and immunologically based inflammation.[4] Almost all CD patients have human leukocyte antigen (HLA) DQ2 and/or HLA DQ8.[10] The incidence of CD is about 1% globally. There is a global rise in the prevalence of CD likely due to the availability of screening tests and increased consumption of gluten in the diet.[11]

The clinical features of CD vary from patient to patient and include intestinal and extraintestinal manifestations. Intestinal symptoms are more common in the pediatric age group and include failure to thrive, diarrhoea, bloating, constipation, abdominal pain, and weight loss. They have been referred to as "classical" features of CD extraintestinal or "atypical" symptoms which are common in both children and adults and include iron deficiency, microcytic anemia, microcytic anaemia, osteopenia or osteoporosis, neurological symptoms such as headache anxiety and depression, as well as fertility disorders, for example, oligomenorrhea and oligospermia.[10] CD has been found in association with other autoimmune conditions including primary biliary cirrhosis, type I diabetes mellitus, autoimmune thyroiditis, Addison's disease, as well as dermatologic conditions such as alopecia areata, psoriasis, and vitiligo.[7,12,13]

Diagnosis of CD is made by clinical history, serology, biopsy, and response to a gluten-free diet. Genetic analysis may be carried out in ambiguous cases.[9] Antibodies to tTG, endomysium, and deamidated gliadin are the serologic diagnostic assays in CD. Anti tTG IgA assay is available in the enzyme-linked immunosorbent assay (ELISA) format, is highly sensitive and specific, and is the initial test of choice for diagnosing CD. Histological assessment following intestinal biopsy, however, remains the mode of diagnosis of choice in CD with the exception of specific pediatric cases.[14]

The current available treatment for CD is a lifelong gluten-free diet; other drug-based therapies include gluten degrading enzymes, probiotics, immune modulating agents, and vaccination among others.[15,16] Larazotide acetate, an inhibitor of zonulin, a protein thought to be responsible for increased intestinal permeability, is another agent that may be potent in treating.[17-19]

CD and vitiligo both have autoimmunity involved in their etiopathogenesis and have been found in association in some patients.[5,7,12,13,20] Reports of the presence of CD antibodies in vitiligo patients are equivocal, but repigmentation has been observed in isolated case reports of vitiligo patients placed on a gluten-free diet.[21,22] We assayed serum anti-tissue transglutaminase (anti-tTG) in a group of vitiligo cases and compared with those of normal controls to investigate further about the association between the two conditions.

## Materials and Methods

This was a case–control study carried out at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, between February 2018 and December 2010.

Ethical approval was given by the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC). Informed consent was sought from vitiligo patients attending the dermatology clinic at the OAUTHC used as cases for the study. Controls were selected from normal healthy individuals from the general population in the Ile-Ife environs. Thirty-three individuals were eventually selected for each group. Exclusion criteria included the presence of other autoimmune conditions, use of anti-inflammatory agents, use of immune system modulators, and use of monoclonal antibodies. No participant was on gluten restriction at the time of the study.

Five milliliters of venous blood was collected from all the participants, serum was extracted through centrifugation following clot retraction, and the samples were stored at 80°c for later analysis.

Anti-tTG IgA was carried out using a traditional ELISA format employing recombinant human tTG (Generic Assays GmbH, 15827 Dahlewitz, Germany). Manufacturer-suggested upper limit for the normal population was 20 U/ml.

Endomysial antibodies were not assayed for, and no participant had an intestinal biopsy. None of the participants had genetic typing for HLA-DQ2 and HLA-DQ8. In addition, we did not assay IgA in the participants; the prevalence of IgA deficiency was also unknown in the population.

Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY). We hypothesised that there was no difference in the serum levels of IgA anti-tTG in cases and controls. Data were checked for normality using the Kruskal–Wallis test. Nonnormal data were subsequently described using the median and IQR. The Mann–Whitney *U* test was used to compare data between the cases and controls. Statistical significance was $P < 0.05$.

## Results

A total of 66 participants, all constitutionally Negroid, were recruited into the study. 33 cases had vitiligo, and 33 controls were apparently healthy. Of the vitiligo cases, 10 (30%) were male and 23 (70%) were female. For controls, 4 (12%) were male and 29 (88%) were female. Bar diagram showing gender distribution of groups is shown in Figure 1. The median age for cases was 50 years (range: 4–82). The median age for controls was 55 years (range: 23–76). The average duration of disease persistence was 48.1 months with a least duration of 1 month and the longest duration of 32 years of vitiligo. There was no other autoimmune condition detected in any of the study participants. A participant among the vitiligo cases had type 2 diabetes mellitus. A summary of the demographic characteristics of the study participants is shown in Table 1.

### Types of vitiligo in cases were distributed as follows

Generalized: 13 (40%), segmental: 5 (15%), mixed: 6 (18%), focal: 3 (9%), acrofacial: 3 (9%), on trunk and arm: 1 (3%), on neck: 1 (3%), and vulgaris: 1 (3%). Pie chart showing frequency of the types of vitiligo in cases is shown in Figure 2.

IgA anti-tTG levels were higher in cases at 6.1U/ml (8.8, 0.6–20.0) [med (IQR, min-max)], compared to controls 5.2 U/ml (3.7, 0.7–22.4). Difference between groups estimated using the Mann-Whitney U test was, however, not significant, $u = 408.0$, $P = 0.08$ ($\alpha = 0.05$). Boxplot diagram showing the comparison of serum IgA anti-tTG in both groups is shown in Figure 3.

## Discussion

Vitiligo and CD are both conditions of autoimmune etiology that have been associated together in some cases. This study found no significant difference between the serum levels of IgA anti-tTG in patients with vitiligo and normal controls

**Table 1: Demographic characteristics of the study participants**

| | Vitiligo cases | Controls |
|---|---|---|
| Age (median) | 50 | 55 |
| Average duration of disease (months) | 48.1 | - |
| BMI (kg/m$^2$) | 24.3 | 23.7 |
| Type I diabetes mellitus | Nil | - |
| Type II diabetes mellitus | 1 | - |
| Hypertension | 3 | - |
| Smoking | Nil | - |
| Frequent alcohol consumption | Nil | - |
| IgA anti-tTg (U/mL) | 6.1 | 5.2 |

BMI: Body mass index, IgA: Immunoglobulin A

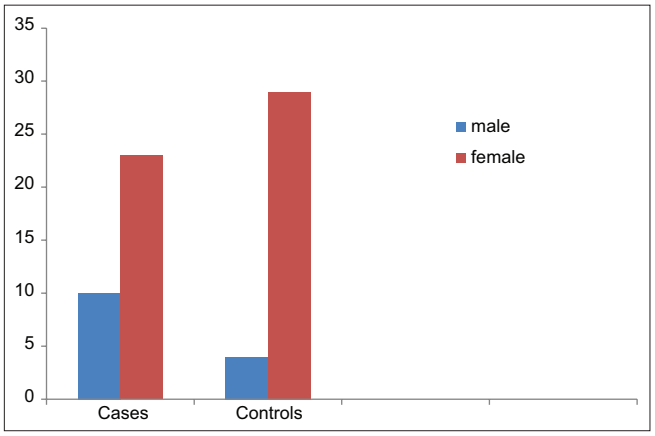


**Figure 1:** Bar diagram showing gender distribution in cases and controls

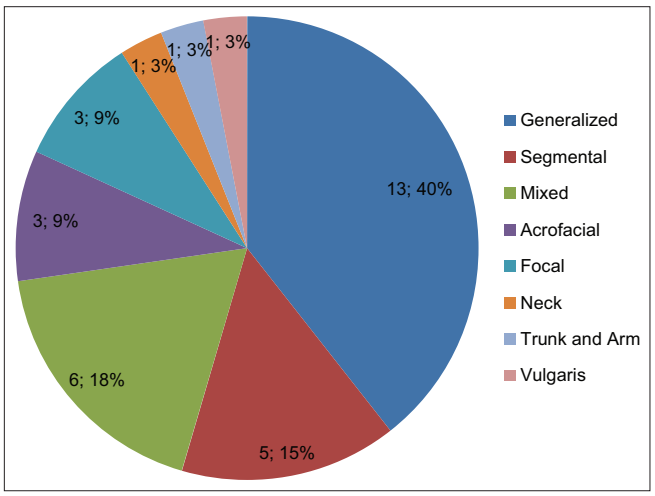


**Figure 2:** Pie chart showing the frequency of types of vitiligo in cases

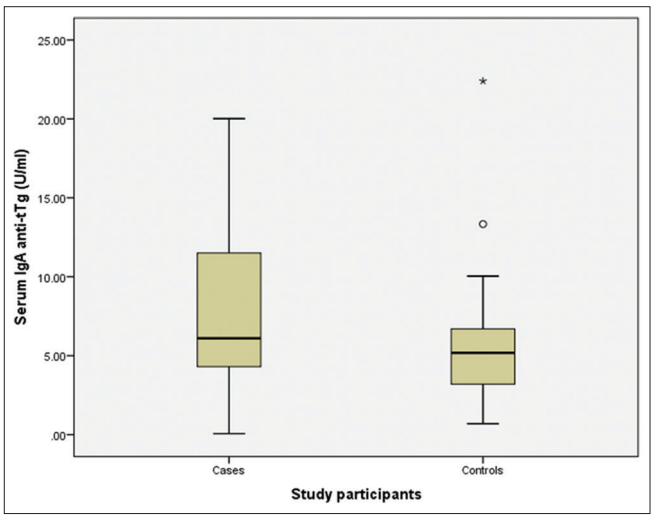


**Figure 3:** Boxplot showing the comparison of serum IgA anti-tTG in cases and controls. Anti-tTG: Anti-tissue transglutaminase, IgA: Immunoglobulin A

even though anti-tTG IgA was generally higher in the vitiligo cases group. This finding is similar to a case–control study in Turkey that found no significant difference in celiac antibody titers in the two groups. The study also found one participant in each group to have positive CD antibody titers that was eventually confirmed as CD by duodenal biopsy and histology.[23] Similarly, a study carried out in Iran on 64 vitiligo cases and 64 healthy controls found 2 (3.1%) cases to be seropositive for IgA tTG antibody as well as endomysial antibody. There was, however, no statistical difference in the antibody titers in both groups although none of the controls was positive for the antibodies.[5] Yet, another study of 198 vitiligo cases that were all seronegative for IgA antibodies to endomysium and gliadin in all the participants.[24] The same study, however, found positive IgA antibodies in two patients with alopecia areata. The researchers suggested that the association of vitiligo with CD be regarded as coincidental.

In contrast, a study of 55 children and adolescents with CD diagnoses confirmed by biopsy showing characteristic histology findings that found vitiligo in 5 (9.1%) of the patients, considered this finding to the due to the autoimmune pathogenesis of both vitiligo and CD.[25] Another study found positive IgA antibodies of CD in 5 (2.8%) of 176 patients with vitiligo and recommended routine screening for CD and trial of the gluten-free diet in vitiligo patients.[26] A case report of a 9-year-old girl with confirmed CD and vitiligo reported a sustained repigmentation following a change in the management plan to the gluten-free dietary protocol.[22]

A participant out of the cases in our study had serum anti-tTG IgA above the manufacturer-suggested cutoff value of 20U/ml for healthy population. This is, however, unlikely to be clinically significant as the same finding was present in the control group.

There was no significant difference in serum IgA anti-tTG in vitiligo cases and controls in this study. Larger standardised cohort studies and/or systematic reviews would shed much needed light on the true nature of the association between these conditions.

## Conclusion

In spite of the common autoimmune etiopathogenesis of vitiligo and CD, clinical association between the two conditions remains equivocal and may only be coincidental. Yet, the clinical finding of repigmentation in vitiligo following dietary gluten elimination suggests a yet to be identified, strong if not widespread association between the conditions. Genetic studies of such isolated cases may be of much help. Screening for CD should be considered in vitiligo patients by the prudent clinician. A trial of gluten-free diet in those vitiligo patients with confirmed CD may prove beneficial.

This study was limited by the lack of materials for further testing of participants beyond IgA anti-tTG serology. The sample size was also relatively small due to the low prevalence of vitiligo in the study population.

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### Conflicts of interest

There are no conflicts of interest.

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