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Transglutaminase and its specific antibodies: A key to sharing celiac disease and *Candida* spp

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ABSTRACT
Antibodies to tissue transglutaminase (tTG) are well used for diagnosis of celiac disease (CD). The TG enzyme can be found in human tissues and in the cellular wall of *Candida albicans*. Its presence in human tissues can lead to the development of CD, while it is helpful for several physiological activities in *C. albicans*. Detection of anti-tTG antibodies supports evidence that *C. albicans* is considered to be a cause of CD. The influence of TG and its antibodies on the relationship between CD and *C. albicans* has been reviewed.

Keywords: Transglutaminase, celiac disease, Candida.

INTRODUCTION

Tissue transglutaminase (tTG) is an active enzyme present in several human tissues and has eight types [1-2]. Transglutaminase-2 (TG2) is an important type of tTG that has a variety of functions [2-4]. It has been found in inactive form that may activate in the presence of its substrate such as gliadin protein after binding to and inducing histological characters of CD [1,3-4]. Antibodies to tTG are one of the most abundant features of CD [1,3-5]. Thus, detecting these antibodies with other serological tests is now more accepted for CD diagnosis. The new type of recombinant human TG is more preferred for the diagnosis of CD than older animals extracted from guinea pigs because of the high sensitivity and specificity [1-2,6].

The TG enzyme can be a significant sharing point between CD and *C. albicans* [7-8]. It occurs in numerous human tissues [9-11], while it occurs in the cell wall of *C. albicans* [7]. In addition to other antibodies, anti-tTG is found at high levels in patients with CD or *C. albicans* infection than in healthy individuals [8]. Anti-TG IgA antibodies are also detected at elevated levels in patients with CD or *C. albicans* infection [8]. *C. albicans* may be responsible for CD, as indicated by anti-tTG detection in patients with CD who are infected with candidiasis [7-8].

Anti- tissue transglutaminase antibody

Transglutaminase-2 (TG2) or tissue transglutaminase-2 (tTG2) is a protein that belongs to the family of eight enzymes in the transglutaminase which have a covalent function and irreversibly catalyze the cross-linked protein containing glutamine amino acid to another protein with lysine residue [1-2]. The tTG2 found in almost all types of cells has many other functions in addition to enzyme activity such as its association with cell adhesion, cell signaling, G-protein activities, tissue repair, and removal of cell debris after cell apoptosis [2-4]. The condition of tTG2 is usually inactive in the intracellular region of the tissue and becomes active because of many mechanical or inflammatory factors

[1]. Lack of lysine, necessary by the cells, is one of the activating factors that enable tTG2 to work on protein deamidates like produce a negative charged glutamic acid from gliadin enriched with glutamine [1]. Thus, gliadin will cross-linked with tTG2 to form a complex form taken by B-cells to promote its production of autoantibodies against CD, including tTG2 (anti-tTG2) and endomysial antibodies (EMA) [1,3-4]. T cells are also associated with the production of tTG2 antibodies by B cells through recognition of the gluten complex on the HLA-DQ peptide in CD patients and that what makes the production of anti-tTG2 is more specific to CD patients [4]. These antibodies have been used as specific assays in the diagnosis of CD since 1997 [1,3-5]. The test for tTG2 and endomysial antibodies revealed greater sensitivity (93% for both) and specificity (>99% for EMA and >98% for anti-tTG2) for the diagnosis of CD [6]. IgA antibodies for tTG and EM also showed sensitivity and specificity of 90% [12]. In general, anti-tTG testing has more advantages than EMA because anti-tTG is easier to standardize and automatically detect without having to use primate tissue [1]. Thus, detection of anti-tTG becomes a first-line test for diagnosis of CD and could also be more specific than histological analysis [4-5].

The first type of tTG used as antigen in the anti-tTG assay was that extracted from the liver of the guinea pig which has subsequently been replaced by purified human tTG or recombinant human tTG [1]. Nowadays, recombinant human TG is better than that of guinea pigs due to the high sensitivity and specificity of the first one in diagnosis of CD in children and adults [1-2,6]. Recombinant human TG has also a number of economic and practical advantages in diagnosing patients with asymptomatic CD [6]. In addition, test of anti-tTG from guinea pig can give a false positive result in patient with chronic liver diseases without CD because of the liver proteins contained in the guinea pig diagnostic kit that are not found in the recombinant human kit [3].

Anti-TG IgA is a more sensitive and specific marker for CD diagnosis using an ELISA test [4]. Human recombination IgA-tTG has a sensitivity of 90.2% and a specificity of 95.4% in adults and children, while their sensitivity is 95% to 100% and specificity ranged from 97% to 100% in adult [2, 13]. In the review of 5 studies on the diagnostic value of anti-tTG, IgA-tTG of guinea pig liver showed sensitivity of 88-100% and specificity of 92-97% in adult and it showed 93.1% sensitivity and 96.3% specificity in children, while recombinant human anti-tTG in adults demonstrated 98.1% sensitivity and 98% specificity and in children approximately 95.7% and 99%, respectively [13].

It is difficult to achieve 100% sensitivity and specificity from the CD serologic test [1]. This is also true for the anti-tTG test, in which false positive or negative results are noted in some cases with diseases unrelated to CD. The IgA and IgG classes of anti-TG2 are observed in patients with viral infection, inflammatory bowel disease or those with end-stage heart failure [14]. Chronic liver disease and myeloma may lead to false positive IgA-tTG, while false negative outcomes can also be observed in patients with positive histology and other serological CD markers [1]. In this case, the results should be clarified by biopsy analysis [4].

Anti-tTG and *Candida* spp

Specific antibodies to tissue transglutaminase enzyme are one of the key traits of CD. This enzyme can represent a sharing point between CD and many species of *Candida*, especially *C. albicans* [7-8]. Human epithelial tissues of more than one organ contain a variable amount of TG such as intestinal and buccal epithelial tissues [9-11]. It also found as one of the constituents of the cell wall of *Candida albicans* [7]. In *C. albicans*, it plays a role in a variety of activities such as fungal cell wall stability, yeast-mycelium transition and fungal growth [15-16]. TG, also known as Enolase 1, is encoded with *C albicans* by the *ENO1* gene [7, 16].

Hwp1 is a specific wall protein of hyphal cells of *C. albicans* that can be a substrate to human TG [8-9, 11, 17]. Binding of human TG to Hwp1 may produce a complex which has the ability to stimulate CD development and the production of anti-tTG antibodies [7, 9]. This proposed mechanism has been demonstrated by finding higher levels of specific antibodies to anti-Hwp1, anti-gliadin and anti-tTG in the presence of *Candida* spp in the patient with CD compared with healthy individuals [18]. In addition to other antibodies, anti-tTG IgA is found in high levels in either patients with CD or with *C. albicans* infection than in healthy individuals [8]. Thus, *C. albicans* can be one of causative agent of CD [7-8].

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Human tissue TG may be activated by *Candida* spp. to cause tissue damage by producing reactive oxygen species (ROS) [19].

In conclusion; Detection of anti-tTG is the most significant test for diagnosis of CD. A false result can be expected from anti-tTG test as well as other serological tests. *C. albicans* can play a role in the development of CD, as evidenced by the presence of the TG enzyme and its antibodies in both CD patient and cells of *C. albicans*.

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