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Screening for Celiac Disease Using Anti Tissue Transglutaminase in Patients with Esophageal SCC between 2004 and 2009

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ABSTRACT

Introduction: Esophageal Squamous-Cell Carcinoma (SCC) is one of the most common malignancies in Iran. To reduce the incidence of esophageal SCC, it is important to recognize the controllable risk factors and prevent them. Celiac disease is widely known as a possible risk factor for esophageal SCC. Thus, we decided to assess the frequency of celiac disease in esophageal SCC patients in North east of Iran in order to suggest correlation between two diseases.

Materials and Methods: In a Cross-sectional study one hundred and forty-three cases of esophageal SCC were examined for anti tissue transglutaminase antibody (anti-tTG) between the years 2004 and 2009 in Ghaem and Omid Hospitals of Mashhad University of Medical Sciences, Iran. The enzyme-linked immunosorbent assay was the test of choice in this study since it provides the sensitivity and specificity needed for the diagnosis and screening of celiac disease. The results of this test were compared with those of the control group which were compatible in terms of sex and age. Data were analyzed through SPSS software and statistical analysis such as x2, exact x2 and T-test.

Results: 19.6% patients (SCC) had positive anti-tTG (>20) which was significantly different to 7.9% in control group (p -value=0.005). Comparing age groups of patients for positive anti_tTG using exact x square test showed significant difference in patients with <40 years old (P value=0.005).

Conclusion: There seems to be a correlation between positive anti_tTG and esophageal SCC; that is to say, celiac disease might play a role in the earlier manifestations of esophageal SCC.

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Introduction

Esophageal cancer is one of the most dominant types of cancer in the world. It is known as the 6th main cause of death in women and 9th in men due to cancer. Esophageal

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Squamous Cell Carcinoma (SCC) is the most common type of esophageal cancer. However, its prevalence has diminished since 1970. Geographically speaking, Esophageal SCC mostly occurs along the "esophageal cancer belt" from China through North of Iran and South of Turkey to North of Africa with incidence rates greater than 100 per 100,000. These geographic differences are thought to be due to genetic factors, diet, environmental factors and alcohol and tobacco consumption (1).

Esophageal SCC is related to such conditions or disorders as: diet, food processing and maintenance, inadequate consumption of fruits and vegetables (1,2), drinking hot beverages (North of Iran and Turkey) (1,3-5), cigarette smoking and addiction (5-8), alcohol consumption (5,9), achalasia (5,10), caustic injuries to the esophagus (1,5,11)and any history of radiotherapy especially in the head and neck (5). Malabsorptive disorders like celiac disease are mentioned as risk factors for esophageal SCC in some references (1,12-14). However, further evidence is required in order to prove the theory.

The core of assessing the risk factors of the diseases, especially in case of malignant disorders, is to extend our knowledge of predisposing factors in order to prevent the disease if possible. Since the disease is really fatal and most of the symptomatic patients are at late stages of the disease when it is diagnosed, it is crucial to know more about the risk factors of esophageal SCC so they could be annihilated at the right time.

The prevalence of celiac disease is different in different parts of the world. Today, however, the disease seems to be more prevalent than before. Assessing the specimens of blood donors all around the world indicates that the prevalence of the disease to be about 1:250 in Sweden, 1:524 in Denmark, 1:333 in Netherland,1:100 in England (15,16), 1:157 in Israel, 1:250 in USA and1:681 in Brazil (17). The first study which was performed on healthy male blood donors in Tehran revealed a prevalence of 1:166(18). Another study from Shiraz (South Iran) showed the prevalence of %0.5 (19). The reports are quite different from northern to southern parts of Iran (17) as other studies from Gonbad_Kavoos (20) and Sari (21) (North Iran) showed a prevalence of 1:100 for the celiac disease. The survey was conducted on some geographical region of Asian belt on esophageal SCC and the authors suggested that the celiac disease could not be a major risk factor for esophageal SCC as it had the same prevalence as in the other parts of Iran (20). However, a more valid study on the epidemiology of the celiac disease in Iran seems to be a multi-centric one on different geographical locations of the country which revealed a prevalence of 1:104 (22). Consequently, considering Iran's large habitat and different geographical regions with a variety of ethnicities, the prevalence of the celiac disease seems to be %.05-1.

Nowadays, fewer patients manifest with the classic presentation of the disorder and there is a remarkable shift to the diagnosis via screening tests (23).

Celiac Disease and Esophageal SCC

The incidence of cancers, particularly malignant lymphoma and small intestinal adenocarcinoma, are heightened in the celiac disease (24,25). Earlier studies from the United Kingdom have also suggested a link between the celiac disease and esophageal carcinoma. Although this increase of malignancy rate has not been confirmed in some reports from long-term follow-ups of celiac patients (26), numerous studies revealing the relationship between the celiac disease and esophageal SCC identify that celiac can raise the risk of malignancy.

In one study which was performed on celiac patients, Green PH et al demonstrated malignant events in 11% of the patients. Intestinal lymphoma, esophageal SCC and small intestine cancer were the most common malignancies in that study (27).

Askling et al claimed that adults (but not children and adolescents) with the celiac disease had an elevated overall risk for cancer which declined with time and eventually reached unity. Elevated risks were found for malignant lymphomas, small-intestinal, oropharyngeal, esophageal, large intestinal, hepatobiliary and pancreatic carcinomas (12). Dr Ferguson et al published the results of one study on celiac patients which demonstrated that at a mean of 13.5 years, the overall mortality of celiac was 1.9-fold of the general population. Much of the increased mortality from malignant disease was accounted for by deaths from lymphoproliferative disorders and esophageal cancer (13). Collins et al considered celiac disease a premalignant disorder based on an increased frequency of intestinal lymphoproliferative condition and esophageal SCC in these patients (28).

Disagreements between many studies considering the increased risk of malignancy – especially in case of esophageal SCC- for the celiac disease and the others who do not believe in any form of elevated risk of cancers encouraged us to plan a new study on esophageal SCC patients.

Materials and Methods

A cross-sectional study was conducted on the patients with dysphagia referring to the

Table 1. Comparison of two groups for sex and age

		Case NO. (%)	Control NO. (%)	P_value
Gender	**Male**	78 (53.8%)	75 (54%)	0.978
	Female	67 (46.2%)	64 (46%)	
Age	**< 40years**	92 (64.3%)	88 (63.3%)	0.853
	40 _ 49 years	7 (4.9%)	7 (5%)	
	50_59	5 (3.5%)	6 (4.3%)	
	60_69	20 (14 %)	18 (12.9%)	
	70 years	19 (13.3%)	20 (14.4%)	

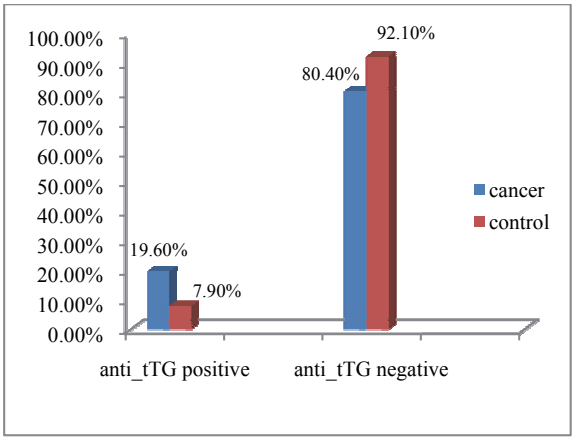

Figure 1. comparison of case and control group for anti-tTG level

Gastrointestinal Clinic of Ghaem and Omid Hospital in Mashhad, Iran between the years of 2004 and 2009. After upper GI endoscopy and biopsy, 143 of them were diagnosed as esophageal SCC. Anti-tTG test was decided upon for the patients with esophageal SCC so as to screen for the celiac disease. Since in most cases of esophageal SCC the esophageal lumen was so narrowed and the scope could not be passed through the esophagus to the duodenum to obtain biopsies for the celiac disease, most patients had been referred for chemoradiotherapy. Therefore, we passed up duodenal biopsy specimens in order to confirm the diagnosis of celiac disease and to prevent the possible adverse effects of chemoradiation to the gastrointestinal mucosa.

The control group was selected from the patients for whom anti_tTG had been requested for any reason but esophageal SCC (diarrhea, unexplained anemia, failure to thrive and malabsorption). This group was compatible in terms of sex and age with the case group. At any rate, anti-tTG was performed on all of them in Moayyed LAB/ Mashhad, Iran using Euroimmune kit.

Any patient in whom histopathologic examination showed results other than SCC and also did not will to participate in study was excluded.

Data were analyzed by SPSS ver. 16.1 using $\chi 2$ and fisher exact test and p-value=0.05 was considered significant.

Results

Distribution of age and gender between two groups of esophageal SCC and control group are shown in Table 1. As showed in this table two groups were matched for age and gender.

1) **In patients with esophageal SCC**, 80.4% were anti-tTG negative (<20) and 19.6% were anti-tTG positive (>20) (Figure 1).
2) The mean anti-tTG level of the **esophageal cancer group** was 5(3, 12). It means 50% of the patients in the study group had anti-tTG level of less than 5, 35% less than 3, and 75% less than 12.
3) **In the control group**, 92.1% were anti-tTG negative and 7.9% were anti-tTG positive (Figure 1)
4) $\chi 2$ test revealed a significant difference between the case and control group for anti-tTG level (P-value= 0.005).
5) $\chi 2$ test showed no relationships between sex and anti-tTG level in case group (P-value= 0.974).
6) Comparing anti-tTG level in age groups using fisher exact test revealed a significantly more frequent positive results for anti-tTG level in SCC patients with less than 40 years old (P-value= 0.005). It means younger patients with esophageal cancer showed more positive results for anti-tTG.

Discussion

We found the positive results of anti-tTG among the patients with esophageal SCC significantly more frequent than in the control group (P_value=0.005). As anti_tTG test is one of the most sensitive and specific screening tests for the celiac disease with an accuracy level of more than %95, we concluded that screening for the celiac disease with anti_tTG in patients with esophageal SCC showed more positive results than in the control group**.** Control group was selected among patients in whom anti-tTG was requested because of signs and symptoms suggestive for celiac disease. This is why we found the mean amount of anti-tTG in control group higher than normal population in Iran (7.9% versus 0.5-1%) (17-22). we suppose that if we had chosen control group from normal population we could have find more significant

differences between patient and control groups. This can be a subject for future studies.

The results of this study are compatible with many previous studies from all over the world which confirmed the same theory (1, 12-14, 23-25, 27, 28). Thus, we shall consider the celiac disease as a risk factor for esophageal SCC. Moreover, we planned to study the prevalence of positive celiac screening tests among esophageal SCC patients; so, we only assessed the relationship between a few demographic factors such as age, sex and anti_tTG level. However, the authors suggest that more variables and risk factors of esophageal SCC be assessed through further studies in order to discover more risk factors of the celiac disease predisposing to esophageal SCC or other malignancies; it is because having a more extensive knowledge on any risk factors in malignancies in celiac patients could greatly serve as a preventive method for the malignant turn over in the high risk, positive anti_tTG cases.

The positive results of anti-tTG had barely correlations with sex (P-value= 0.974). It means that being male or female cannot account for any risk factors for celiac patients to get esophageal SCC in the future.

Positive results of anti-tTG also revealed a significant relationship with the age range of less than 40 years (P-value= 0.005). Whether malabsorptive effect of celiac disease, abnormal sensitivity of gastrointestinal mucosa to wheat proteins or direct contact of these proteins with the mucosa of the esophagus from early in life are factors of malignant transformation of the mucosa of esophagus is still a matter of question and it requires further scientific research.

Considering the theory that the celiac disease can be a risk factor for esophageal cancer and might lower the age of the occurrence of cancer, we recommend the screening of high risk patients for the celiac disease, paying more attention to the non-classic manifestations of the disorder and encouraging the patients to be more compliant to gluten-free diets in order to prevent esophageal cancer especially at the age of involvement.

According to many studies claiming that the risk of malignancies is not increased in childhood and it is elevated as the patient grows up (12, 24, 25), the time of gluten consumption seems to be an important factor for the health of gastrointestinal mucosa and effort should be made to diagnose the disease and start a gluten-free diet as soon as possible. Many studies reveal the preventive effects of eliminating gluten on late complications such as certain malignancies (1, 28-30). Therefore, we recommend intensive screening programs, paying more attention to non-classic manifestations of the disease, adherence to a gluten-free diet in order to decrease injuries to GI mucosa caused by gluten.

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Conflict of Interests:

The author has no conflict of interests.

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