

## Genetic and Dental Study of Patients with Celiac Disease

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**Objectives:** The aim of this work was to study the pattern of inheritance of celiac disease in a group of Saudi patients and to compare oral mucosal and dental clinical findings in these patients to those of healthy controls. **Study design:** Fifty patients suffering from celiac disease were screened for dental evaluation. They were subjected to clinical genetic examination, pedigree construction, oral mucosal and dental clinical evaluation. **Results:** An autosomal recessive mode of inheritance was evident in some of the studied cases, while others showed sporadic occurrence. Oral mucosal and dental clinical examinations revealed recurrent oral ulcerations, enamel hypoplasia in most of the celiac disease patients. **Conclusions:** Pedigree analysis of families is important to identify the mode of inheritance. Oral mucosal and dental clinical examinations are important in diagnosing and monitoring cases of celiac disease.

**Keywords:** genetic and dental study, patients, celiac disease

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### INTRODUCTION

Celiac disease (CD) is a familial, autoimmune disease caused by sensitivity to dietary wheat gliadins as well as related prolamins in rye and barley.<sup>1,2</sup> It is one of the most significant causes of chronic malabsorption in children, with symptoms including diarrhea, abdominal pain and growth failure. Symptoms in adulthood include anemia, fatigue, weight loss, diarrhea, constipation, infertility and neurologic symptoms, although occult disease is frequently present with minimal symptoms.<sup>3</sup>

The earliest evidence that genetic factors are of significance in celiac disease consisted of isolated reports of multiple cases occurring within families. Subsequently, family studies using clinical criteria to determine which family

members were affected clearly demonstrated that GSE occurred more frequently in the relatives of patients than in the general population.<sup>4</sup> In addition, most reported monozygotic twin pairs were concordant for the disorder, emphasizing the importance of genetic factors.<sup>5</sup> Despite these observations, the mode of inheritance remained unclear.

Families with multiple cases of CD are common, and estimates for the risk to siblings have ranged from less than 5% to greater than 20%, with most estimates between 10 and 12%.<sup>6-9</sup> CD has a strong genetic association with the human leukocyte antigen (HLA) class II genes DQA1 and DQB1, with approximately 90% of celiacs carrying the DQ2 genotype and 5% carrying the DQ8 genotype.<sup>10</sup> However, the HLA association alone is insufficient to explain the hereditary nature of the disease, and is estimated to explain less than half the sibling risk, indicating the presence of one or more additional susceptibility loci.<sup>11-14</sup>

The patients suffering from CD are also prone to have associated autoimmune disorders such as type I diabetes and Sjögren syndrome (SS).<sup>15</sup>

Extraintestinal manifestations such as dermatitis herpetiformis and osteoporosis are common in CD.<sup>16, 17</sup> Oral involvements consists of celiac-type dental enamel defects in permanent teeth of 50-80% of adult patients and mucosal inflammatory changes including recurrent aphtous ulcers and angular cheilitis.<sup>18-20</sup>

As oral manifestations occur frequently in individuals suffering from CD or SS, subjects having concomitantly both disorders might even be at higher risk, and require thus additional preventive measures and thorough treatment.<sup>21</sup>

The aim of this work was to study the pattern of inheritance of celiac disease in a group of Saudi patients and to compare oral mucosal and dental clinical findings in these patients to those of healthy controls.

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**MATERIAL AND METHOD**

The study population included 100 children, aged 10-18 years living in Jeddah City. The test group included 50 children with celiac disease, attending King Abdulaziz University Hospital (KAUH). All the registered children received regular disease follow-up at King Abdulaziz University. A control group of the same size as the test group was established by matching non celiac child, who did not have systemic diseases and did not receive medications. The matching criteria were age (maximum 2 months difference), gender and place of residence (urban versus rural children). The groups were considered to be similar, as all study participants came from similar living conditions. According to the questionnaire analysis of the study participants, there were no differences between the groups with regard to the reported social background and oral hygiene habits. The diagnosis of CD was based on the endoscopy and demonstration of partial villous atrophy with crypt hyperplasia in small bowel mucosal biopsy.

For each patient the following was recorded:

- a) Complete family and personal history as regards the other affected members of the family, consanguinity, causes of death of the family members, history of abortions and infections during the course of pregnancy.
- b) Clinical genetic examination with stress on presence or absence of facial dysmorphism and any congenital malformations.
- c) Pedigree construction to analyze the mode of inheritance in each case.
- d) A complete intra-oral soft tissue examination was performed according to the World Health Organization International Classification of Diseases in Dentistry and Stomatology (WHO ICD-DA) (WHO, 1978) and changes observed were grouped topographically. The test and control group were asked, whether they currently had or gave a positive history of having had oral ulceration.
- e) Intra-oral hard tissue examination was performed under standardized conditions using portable equipment with fibro-optic light, suction device and compressed air.

Oral mucosal and dental clinical examinations were always performed by one member from the oral medicine department (KAU).

**RESULTS**

**Genetic findings**

The present study included 50 cases of celiac sprue, 22 of them showed sporadic occurrence and gave no history of consanguinity among parents of affected offsprings with celiac disease, nor did they show other affected family members.

One of the studied families had an affected son and did neither show other affected family members nor had positive history of consanguinity yet had an affected sister suffering from stomach aches and has to be further evaluated.

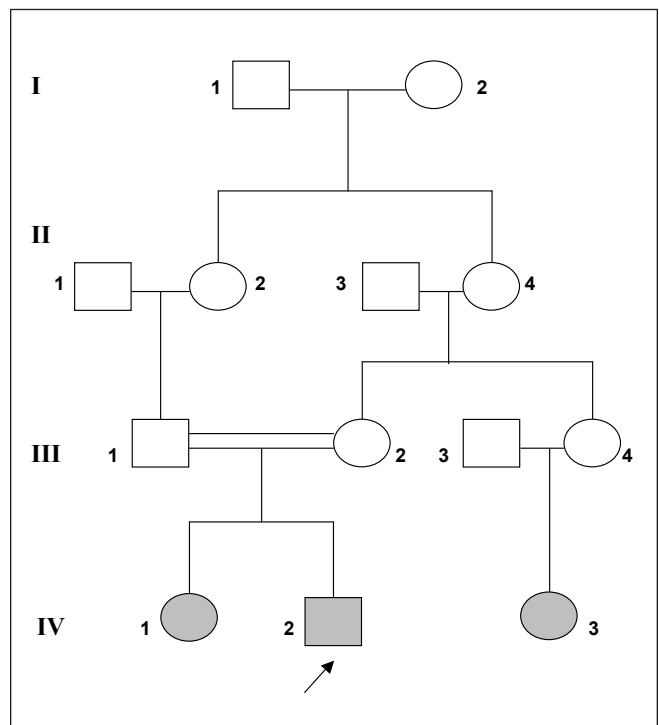
Four cases showed positive family history of consanguinity, in absence of other affected family members and thus no definite mode of inheritance was concluded.

The remaining 23 studied cases showed an autosomal recessive pattern of inheritance where the disease was found among both sexes and gave history of other affected family members (7 out of 23). Consanguinity was also a common finding (22 out of 23 families) most of which were first cousins (16 families) while others were distant relatives (6 families). The remaining family had no history of parental consanguinity yet had two affected offspring's diagnosed as celiac sprue patients, but with no similar condition within other family members.

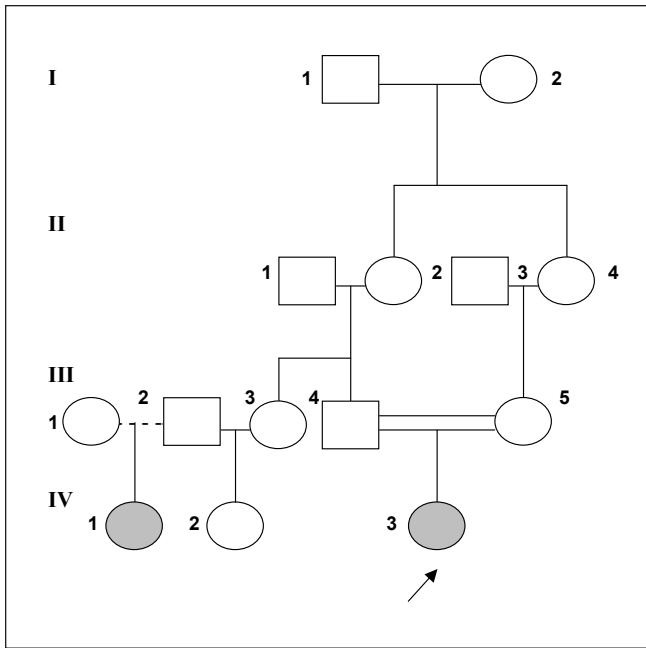
In one studied family an affected father was suffering from celiac disease, as well as his daughter.

Two cases that were diagnosed as celiac disease patients showed other affected siblings (sisters) from a second paternal marriage.

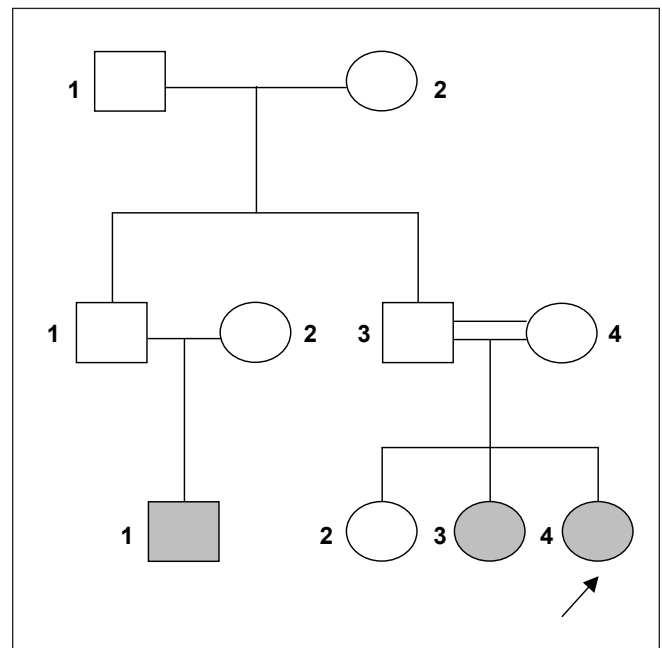
Figures (1-8), shows pedigrees of some of the studied families (shaded squares and circles show affected family members, yet only the arrowed ones are the included studied cases).



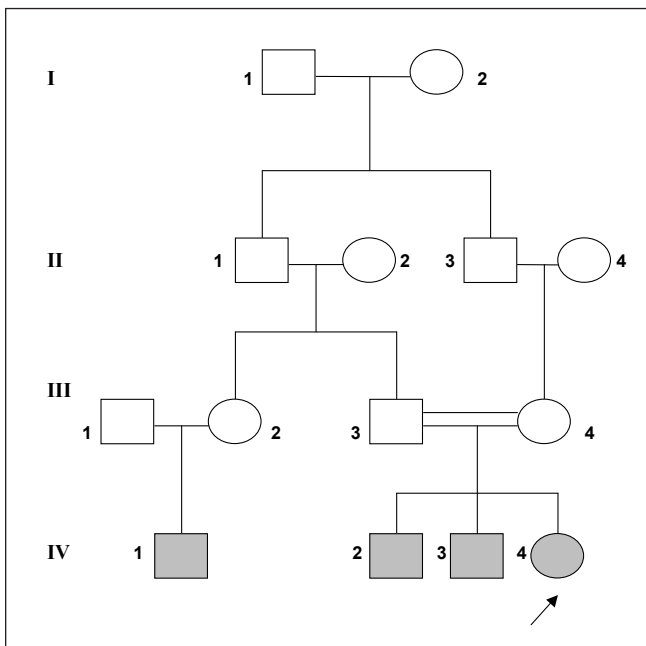
**Figure 1.** Generation IV shows affected cousins (1, 2, 3) and +ve consanguinity in generation III (1, 2)..



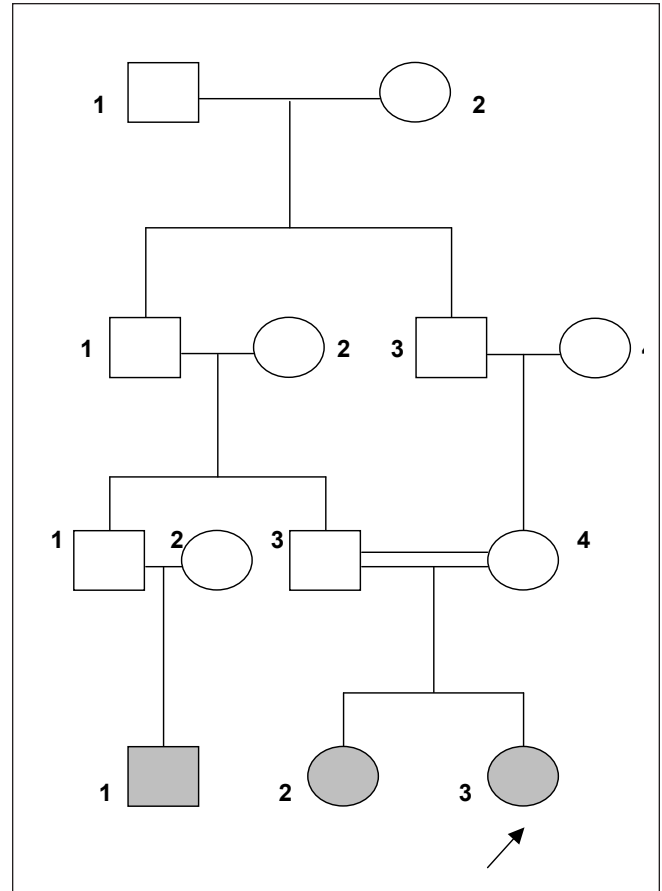
**Figure 2.** Generation IV shows 2 affected cousins (1 and 3) and +ve consanguinity in generation III (4, 5). Generation IV, 1 is the result of a 2nd marriage in generation III (1, 2).



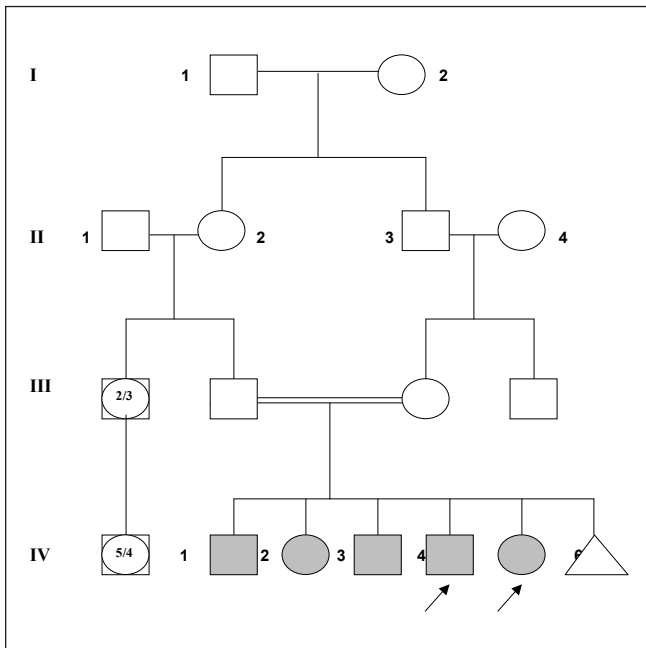
**Figure 4.** Generation III shows affected cousins (1, 3, 4) and +ve consanguinity in generation II (3, 4).



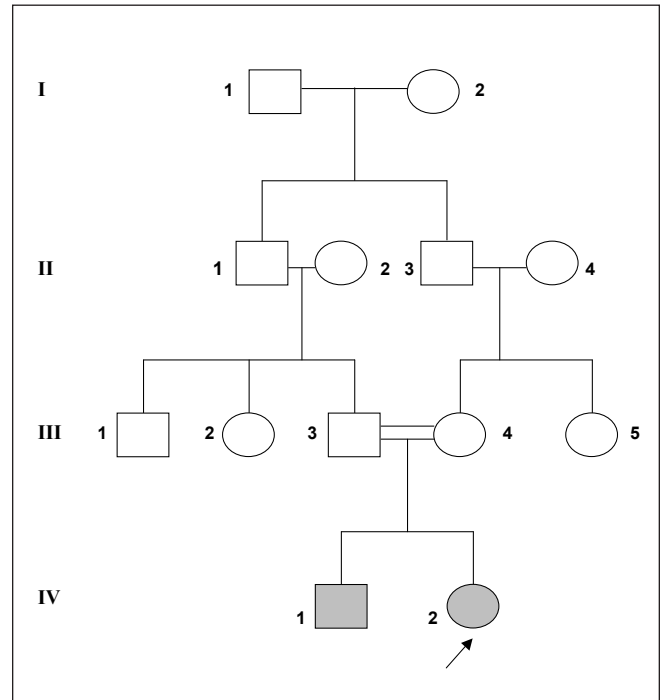
**Figure 3.** Generation IV shows affected cousins (1, 2, 3, 4) and +ve consanguinity in generation III (3, 4).



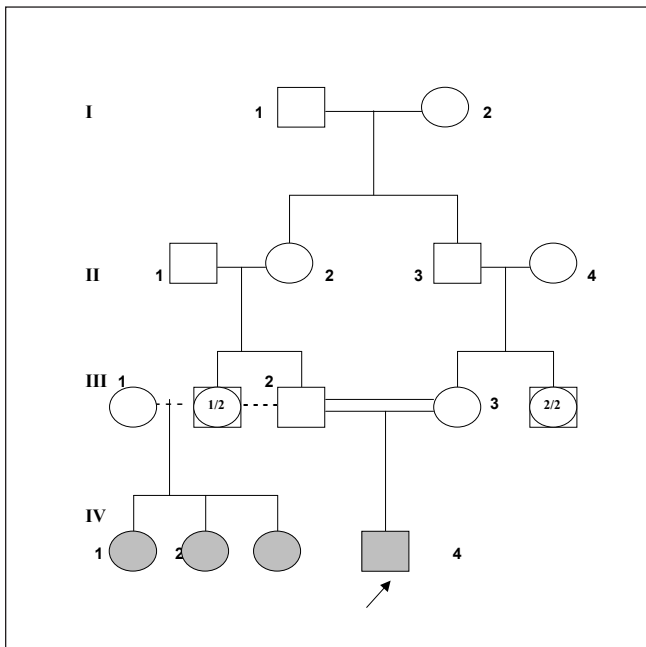
**Figure 5.** Generation IV shows affected cousins (1, 2, 3) and +ve consanguineous marriage in generation III (3, 4).



**Figure 6.** Generation IV shows multiple affected offsprings (1, 2, 3, 4, 5). Generation IV, 6 is a pregnancy ended in abortion. Generation III, 1 and 2 indicated as consanguineous marriage.



**Figure 8.** Two affected offsprings in generation IV (1, 2) as a result of consanguinity in generation III (3, 4).



**Figure 7.** Multiple affected cousins are shown in generation IV (1, 2, 3, 4) and +ve consanguineous marriage in generation III (2, 3).

**Dental findings**

In our study we evaluated oral findings in patients diagnosed with CD and compared with a control population matched for age and gender but without CD. In the present study, 50 patients with celiac disease consisted of 32 (64.0%) females and 18 (36.0%) males, compared to 50 controls consisted of 34 (68.0%) females and 16 (32.0%) males. The mean age in CD group was 14.16 years versus 14.43 in the control group. No statistical difference was found between the 2 groups regarding age and gender (Table 1).

**Oral findings**

The most frequent lesions were oral ulcers (32%) and enamel hypoplasia (36%).

The patients with CD had more often clinical oral ulcers compared with the control group ( $p < 0.001$ ). Sixteen patients (32%) with celiac disease had mucosal oral ulcers compared with only three (6%) controls. Angular cheilitis, median rhomboid glossitis (MRG) were present in both groups but with no significant differences (Table 2).

**Enamel defects**

Defects of the enamel were found in 18 (36%) of the 50 celiac patients and in 3 (6%) of the 50 controls. Therefore, the enamel defects occurred significantly ( $p = 0.001$ ) more frequently in celiac patients than controls. We observed a greater prevalence of enamel defects on permanent teeth in patients with celiac disease and only one case in primary teeth. In control group, all enamel defects were in the permanent dentition. The location of enamel defects in cases and controls are shown in Table 3.

Regarding silent cases of celiac disease presenting only with oral and dental manifestations without gastrointestinal (GI) symptoms, 5 patients presented only with oral ulcerations, their age range from 10 to 13 years, while one patient with enamel hypoplasia with no GI manifestations, presented at age of 10 years. All the above cases were subsequently confirmed as having celiac disease with positive serology and evidence of villous atrophy in small bowel histology.

**Table 1.** Distribution of sample according to gender and age.

Celiac Disease Patient		Control	
Age	Mean	Age	Mean
From (10-18yrs)	14.16 ± 2.23	From (10-18yrs)	14.43 ± 2.23
Number	Percent	Number	Percent
Sex F 32	64.0	Sex F 34	68.0
M 17	34.0	M 16	32.0

**Table 2.** Number of oral lesions in patient and control.

Celiac Disease Patient			Control		P
<b>Oral ulcer</b>	16(32%)	10 Females 6 Males	3 (6%)	2 Females 1 Male	<0.001*
<b>Enamel defect</b>	18(36%)	8 Females 10 Males	3 (6%)	2 Females 1 Male	0.001*
<b>Angular defect</b>	6(12%)	3 Males 3 Females	2 (4%)	1 Male 1 Female	0.14
<b>Median Rhomboid Glossitis</b>	4(8%)	2 Males 2 Females	1 (2%)	1 Female	0.17

\*Significant at 5% level.

**Table 3.** Location of enamel defects in patient and control.

Location	18 CD Patients	Control
<b>Incisor</b>	13	2
<b>Canine</b>	5	0
<b>Molar</b>	4	1
<b>Primary Molar</b>	1	0

## DISCUSSION

Celiac disease is an inherited chronic inflammatory intestinal disease characterized by sensitivity to gluten (found in wheat and barley) which leads to nutrient malabsorption and improvement after withdrawal of gluten from the diet. The prevalence of CD has been reported to approach nearly 1% in the general population.<sup>22</sup> Patients with celiac disease will often have diarrhea, vomiting, abdominal distension, weight loss and pallor in response to gluten intake. The disease may also have a “silent form” in which minimal symptoms and intestinal damage are present.<sup>23</sup> At the time of diagnosis, nearly 50% of patients with CD will not have any gastrointestinal (GIT) manifestations.<sup>24</sup>

Celiac disease is known to be a multifactorial disease where elements of genetics and environment take part in

expression of the illness. Such illnesses do not follow a simple Mendelian mode of inheritance but tend to cluster in families with first- and second- degree relatives being more affected than would be expected by chance only. The inheritance of CD has been suggested to be linked to HLA genes where individuals carrying HLA-DQ2 or HLA-DQ8 have been found to be at higher risk for the disease compared to controls.<sup>10, 25</sup> HLA-DQ2 having the HLA-DQ  $\alpha 1^*0501$ ,  $\beta 1^*0201$  heterodimer has been found in more than 90% of CD patients.<sup>26, 27</sup> Studies show that CD occurs more frequently in relatives of patients compared to the general population with the risk in siblings ranging from less than 5% to more than 20%.<sup>6, 28</sup> Furthermore, about 75% of monozygotic twins are concordant for the disease.<sup>29</sup> Despite being more prevalent in females than males, in DQ2/DQ negative patients, the ratio is reversed with males being more affected.<sup>30</sup> Because of the genetic predisposition, CD has been found to coexist with other auto-immune disorders such as diabetes mellitus (type-I), thyroid and parathyroid autoimmunity, and Addison's disease.<sup>31-33</sup>

Our results show an autosomal recessive (AR) mode of inheritance in nearly half the number of cases, of which, nearly 96% show a history of consanguinity, findings which agree with available literature.<sup>34</sup> In AR type of inheritance both mutated copies of a gene pair need to be present in order for the disease to manifest. Affected children are usually born to unaffected parents, each of which is a carrier to one copy of the mutated gene. If both parents are carriers of the defective gene, each born offspring has a 25% probability of being affected and normal siblings of affected individuals have each a two thirds chance of being a carrier (heterozygote). Rare traits associated with AR inheritance are usually linked to consanguinity.<sup>35</sup>

Because CD can run a silent course or show delayed GIT manifestations, the oral cavity can be a useful tool for its early diagnosis.<sup>36</sup> This would enable a gluten-free diet treatment to begin, thereby reducing the risk of developing lymphoma or gastrointestinal carcinoma which has been known to occur with greater prevalence in CD patients.<sup>37, 38</sup> As part of the GIT system, the oral cavity may show symptoms of the illness such as recurrent Aphthous Stomatitis (RAS), dental enamel defects, atrophic glossitis, oral manifestations of dermatitis herpetiformis, Sjögren's syndrome, and oral lichen planus. The extraintestinal manifestations not only include those apparent in the mouth, but may also manifest as changes in craniofacial growth.<sup>20, 39-46</sup> As shown by Finizio *et al*<sup>47</sup> adults with CD tend to have larger foreheads compared to those without CD.

Our study included just about equal numbers of males and females ranging in age from 10-18 years. The results show that patients with CD had significantly higher prevalence of enamel defects than controls which is in accord with most literature.<sup>21, 48</sup> In their study on adult celiac patients, Aine *et al*<sup>18</sup> reported that 83% of CD patients had symmetrical chronologically distributed enamel defects compared to 4% of controls. Our study show that the defects were symmetrical and mostly on incisors and molars which is a

finding again supported by previous literature.<sup>19</sup> These findings bare clinical significance since the disease may run a silent course in some patients leading to delayed diagnosis. The presence of enamel dental defects, especially when symmetrical and affecting molars and incisors may be a useful tool in the early diagnosis of CD, therefore preventing some of the long term complications such as lymphomas and other neoplasms of the GIT system.

It is not clear why patients with CD have greater prevalence of enamel defects. We suggest that this may be due to an association with parathyroid autoimmune damage which leads to hyperparathyroidism and a disturbance in calcium metabolism.<sup>49</sup> It may also be due to the facts that individuals with CD can have the superimposed problem of lactose intolerance.<sup>50</sup> Lactose is a sugar found in dairy products and is broken down before its absorption by an enzyme (Lactase) produced by the intestinal villi. When the villi are destroyed as seen in CD patients, lactose is not absorbed normally. This will lead to patients having diarrhea, bloating, and excessive gas. Therefore, CD patients may prefer to avoid various forms of dairy products leading to deficiency in both calcium and phosphate which are necessary for enamel formation, hence enamel defects may be seen.

Recurrent aphthous stomatitis (RAS) is among the most common oral mucosal ulcerations in humans.<sup>51</sup> It is characterized by round painful ulcerations of the oral mucous membranes with necrotic centers and surrounded by erythematous halos. Recurrent aphthae can be caused by multiple factors including trauma, microbial, immunological, genetic ones.<sup>52</sup> They may also be a manifestation of certain hematological disorders such as anemia, folic acid or vitamin B12 deficiencies.<sup>53</sup> Our results show a significantly higher prevalence of RAS in patients with CD compared to controls, which is in accord with most literature where the prevalence was reported to be as high as 41% compared to nearly 20% in the general population.<sup>39</sup> Because of the ease and convenience of oral examination to most individuals, oral examination may be used as a screening tool to detect patients with CD where the typical GIT symptoms have not shown manifestations yet.

The findings of this research support previous findings on the nature of the association between CD and oral manifestations. It demonstrates the value of attentive soft and hard tissue examination in identifying cases with CD in advance of disease diagnosis and may be used as screening tools for the condition.

## CONCLUSIONS

1. An autosomal recessive mode of inheritance was evident in some of the studied cases, while others showed sporadic occurrence.
2. Pedigree analysis of families is important to identify the mode of inheritance.
3. Oral mucosal and dental clinical examinations are important in early diagnosis and monitoring cases of celiac disease.

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