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Measurement level of Dickkopf-1 as WNT signaling inhibitor, in celiac disease

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ABSTRACT

Background: Celiac disease (CD) is an autoimmune enteropathy triggered by gluten in genetically susceptible individuals. The WNT signaling pathway maintains intestinal epithelium homeostasis. This study evaluated two WNT antagonists (Dickkopf-1 and sclerostin) in CD patients with varying intestinal atrophy (Marsh scores) compared to controls. A lipid profile blood test measures the total amount of cholesterol in your blood (total cholesterol) the level of HDL-cholesterol (high-density cholesterol, often called 'good cholesterol the level of LDL-cholesterol (low-density cholesterol, often called 'bad' cholesterol triglycerides (TG, another type of fat in the body) LDL cholesterol is referred to as bad cholesterol because it can build up in the walls of your blood vessels, This increases your risk of coronary heart disease and atherosclerosis HDL cholesterol is good cholesterol because it removes excess cholesterol from your body. High triglyceride levels can also increase your risk of cardiovascular (heart and blood vessel) disease

Methods: 43 CD patients and 45 controls were enrolled. Serum levels of Dickkopf-1, sclerostin, citrulline, PTH, calcium, and vitamin D3 were measured via ELISA, spectrophotometry, and HPLC. **Results**: Dickkopf-1 ($P<0.0001$) and sclerostin ($P=0.002$) were significantly elevated in CD. PTH ($P<0.0001$) and calcium ($P=0.009$) were also higher. Citrulline correlated with sclerostin ($R=0.71$), PTH ($R=0.53$), and Dickkopf-1 ($R=0.29$). ROC analysis showed Dickkopf-1 ($AUC=0.83$), sclerostin ($AUC=0.7$), and PTH ($AUC=0.91$) differentiated CD from controls but not atrophy severity. **Conclusion**: Elevated WNT antagonists and PTH in CD correlate with enterocyte mass markers, suggesting their pathogenic role. Further studies are needed for diagnostic/therapeutic applications.

Keywords: Celiac Disease, WNT Signaling Pathway, Sclerostin, Dickkopf-1, Villus Atrophy, Parathyroid Hormone

1.Introduction

Celiac disease (CD) is type of autoimmune disorder triggered by the ingestion of gluten in genetically predisposed individuals, characterized by duodenal villous atrophy and intraepithelial lymphocytosis (IEL), leading to malabsorption and gastrointestinal as well as extra-intestinal symptoms[1]. CD occurs up to 1% globally with a higher incidence in women, however there is variation between different regions [2, 3]. For example, data reported in Iran shows a prevalence of 3% (95% CI: 0.03-0.03) according to the serology and 2% (95% CI: 0.01-0.02) based biopsy-confirmed CD [4].

The incidence of celiac disease is increasing in recent decades and the reason might be related to environmental factors that may promote loss of tolerance to dietary gluten[5]. Currently, the only available treatment for the condition is a strict, life-long gluten-free diet [6]. Early diagnosis of celiac disease is important to prevent nutritional deficiency and long-term risk of gastrointestinal malignancy. Current diagnosis of the celiac disease depends on clinicopathological correlation: history, presence of anti-transglutaminase antibodies, and disease confirmation by intestinal biopsy and duodenal tissue damage evaluation measured by MARSH score [7].

As reported previously, the intestinal stem cell (ISC) plays a critical role in epithelial regeneration after ionizing radiation induced gut injury [8]. Different mechanisms including WNT/β-catenin signaling pathway are necessary for self-renewal and maintenance of the intestinal epithelium. Much evidence supports the crucial role of WNT signaling in the regulation of ISC function, and the maintenance of epithelial architecture [9]

"The WNT/β-catenin pathway regulates intestinal epithelial homeostasis and is modulated by antagonists like Dickkopf-1 and sclerostin [9,10]."

. Dikkopf-1 is the name of a protein family in the vertebrates, consisting of 4 members, named Dikkopf-1 –4, varying in size between 255 and 350 amino acids [11]. Dikkopf-1 is an inhibitor of the WNT pathway and platelets represent a major source of Dikkopf-1 in humans [12]. Dikkopf-1 is induced by inflammatory cytokines during colitis and exacerbates tissue damage by promoting apoptosis of epithelial cells. However, little is known about the physiologic role of Dikkopf-1 in normal intestinal homeostasis and during wound repair following mucosal injury [13].

Another WNT antagonist is Sclerostin, a human bone tissue protein encoded by the SOST gene. Sclerostin belongs to the bone morphogenetic protein (BMP) family of antagonists and is involved in the anti-anabolic processes of bone formation [14]. Sclerostin inhibits the functions, differentiation and, survival rates of osteoblasts, as it promotes the apoptosis of these cells. By binding to low-density

lipoprotein receptor-related protein 5/6 receptors (LRP-5/6), this protein blocks the Wingless-type mouse mammary virus integration site (WNT) signaling pathway in osteoblasts [15]. Therefore, sclerostin has a pivotal role in bone biology and turnover. In animal model, SOST depletion not only affects B cell development in the BM relatively early but also creates an inflammatory bone marrow microenvironment that may become more severe over time[16].

The mean level of sclerostin has been reported to be decreased in Systemic autoimmune diseases (non-significant) including, Crohn's disease patients [17]. Moreover, in inflammatory bowel disease (IBD) patients with axial spondyloarthritis, the level of sclerostin (SOST) is decreased but, the level of anti-SOST-IgG is elevated compared to patients with only peripheral arthritis, IBD, and controls [18].

To our knowledge, no report is available about the changes of the sclerostin or Dickkopf-1 level in celiac patients. Regarding the pivotal role of WNT signaling in the intestinal epithelium homeostasis and crypt formation and repair, thus in this study, we postulated that the level of Dickkopf-1 or sclerostin, as WNT antagonists, may be different in CD patients regarding the score of the intestinal mucus atrophy. Indeed, considering the well-known modulatory function of WNT antagonists in bone remodeling, the biochemical factors of bone metabolism (PTH, Ca, and Vitamin D3) were also investigated in the current study.

2. Material and methods:

2.1. Sampling

This study was a case-control study and the samples (n=43 cases and n=45 controls) were provided from a previous project (IR.GOUMS.REC.1398.164). The samples were collected from the Golestan Research Center of Gastroenterology and Hepatology, Sayyad Shirazi Hospital, Gorgan, Iran. The cases were collected from patients with celiac disease, aged (20 to 65 years), diagnosed with duodenum biopsy. The control group was collected from individuals who were referred to the endoscopy center of Sayyad Shirazi Hospital in Gorgan for other reasons and the celiac was ruled out by duodenal biopsy. Individuals with IgA deficiency were excluded from the current study. Both groups were matched in terms of age and sex (table 1).

2.2.Biochemical parameters measurement

The levels of anti-Ttg antibody (table 1) and MARSH score were available from the previous study. Serum levels of the Dikkopf-1 (cat. number: ZB-10630C-H9648) and sclerostin (cat. number: ZB-RK02315-H9648) were measured using ELISA kits from ZellBio GmbH following manufacturer's

instruction. Also To measure PTH, we used an ELISA kit from ZellBio GmbH (cat number: ZB-11055C-H9648). The levels of vitamin D3 and calcium were also measured using HPLC and spectrophotometry methods, respectively in the Kavosh clinical laboratory, Gorgan, Iran.

3. Abbreviations and Acronyms:

(CD) Celiac disease , (WNT S.P) Wnt signaling pathway,(DKK-1) Dickkopf-1,(V.A) Villus Atrophy, (PTH) Parathyroid Hormone, (ISC) intestinal stem cell,(IEL)intraepithelial lymphocytosis.

3.1.Data analysis methods

All values were expressed as mean ± standard deviation (S.E.), Using SPSS software (v.17), the Shapiro-Wilk test was performed to check data distribution. The Mann–Whitney U or independent t tests were used to compare groups as indicated. The Spearman's test was performed for correlation between variables.

4.Results:

4.1. Higher Bone Remodeling Factors: PTH and Calcium in Celiac Patients

As shown in table 1, the patients were categorized according to the MARSH score of the duodenal biopsies (scores 2 and 3a: normal/mild atrophy, scores 3b, 3c: marked/complete atrophy in villi). In the current study, 39.5 % of patients showed normal/mild villus atrophy, but 60.5% were in the category of marked/complete villus atrophy. The Serum Citrulline concentration was measured as a marker of reduced enterocyte mass [19] and we observed no significant difference between celiac patients and controls. (Mann Whitney test p-value=0.6856).

Biochemical factor evaluation indicated that the lipid profile and vitamin D3 showed no significant difference between the two groups; however, the level of serum PTH was significantly (Mann Whitney test p-value< 0.0001) higher in celiac patients (396.8±7.33 pg/ml) compared to controls (300.1±13.55 pg/ml). In addition, the level of serum calcium was significantly (Mann Whitney test p-value=0.0097) higher in celiac patients (9.66±0.26 mg/dl) compared to controls (8.54±0.33 mg/dl).

"PTH was lower in severe atrophy (3b+3c: X±Y pg/mL) vs. mild (2+3a: A±B pg/mL; P=0.02)."

Table 1. demographic and clinic-pathologic parameters in celiac and control groups

Variables		Control	Celiac disease	P-Value
Age		36.02 ± 1.79	40.90 ± 1.76	>0.05*
Gender	**male**	6 (13.3%)	10 (23.2%)	0.187#
	female	39 (86.7%)	33 (0.76.8%)	
Marsh score	**2+3a**	-	17 (39.5%)	-
	3b+3c		26 (60.5%)	
tTg-IgA (Unit/ml)		-	192.60 ± 30.06	-
Citrulline (mM/ml)		11.37±0.48	11.91±0.41	0.68*
PTH (pg/ml)		300.1±13.55	396.8±7.33	**< 0.0001¶**
Ca (mg/dl)		8.54±0.33	9.66±0.26	**0.0097¶**
Vit D (ng/ml)		25.28±2.118	27.43±3.38	0.508¶
HDL (mg/dl)		30±1.74	33.53±1.9	0.48*
LDL (mg/dl)		96.93±4.88	99.54±5.19	0.65*
Cholesterol (mg/dl)		149.9±6.39	154.1±5.5	0.49*
Triglyceride (mg/dl)		135.8±13.93	112.7±11.09	0.09*

#Chi square test, *independent t test, ¶ Mann Whitney test

4.2.Elevated WNT Antagonists, Dickkopf-1 and Sclerostin in Serum of Celiac patients

We found significant (Mann Whitney U test, P-value=0.0027) up-regulation of serum sclerostin levels (figure 1A) in celiac patients (44.4±1.6 pg/ml) compared to controls (37.2±1.9 pg/ml). IN addition, the level of serum Dickkopf-1 , another WNT signaling antagonist (figure 1B) was also significantly (Mann Whitney U test, P- value<0.0001) higher in celiac patients (26.77±0.8 pg/ml) compared to controls (21.55±0.8 pg/ml).

For further evaluation, patients were categorized into two groups according to the intestinal villus atrophy (MARSH score). As indicated in figure 1 C-D, we found no difference regarding the Dickkopf-1 and sclerostin levels between patients with no or mild villus atrophy (2+3a) compared to marked and complete villus atrophy (3b+3c).

Other biochemical factors were also compared in the patients and interestingly we observed higher serum tTG-IgA antibody (Student's t-test, p-value=0.02) and lower parathyroid hormone (Student's t-test, p-value=0.02) in patients with more severe intestinal damage (marsh score 3b+3c) than those with no or mild villus atrophy (figure 1 E-F).

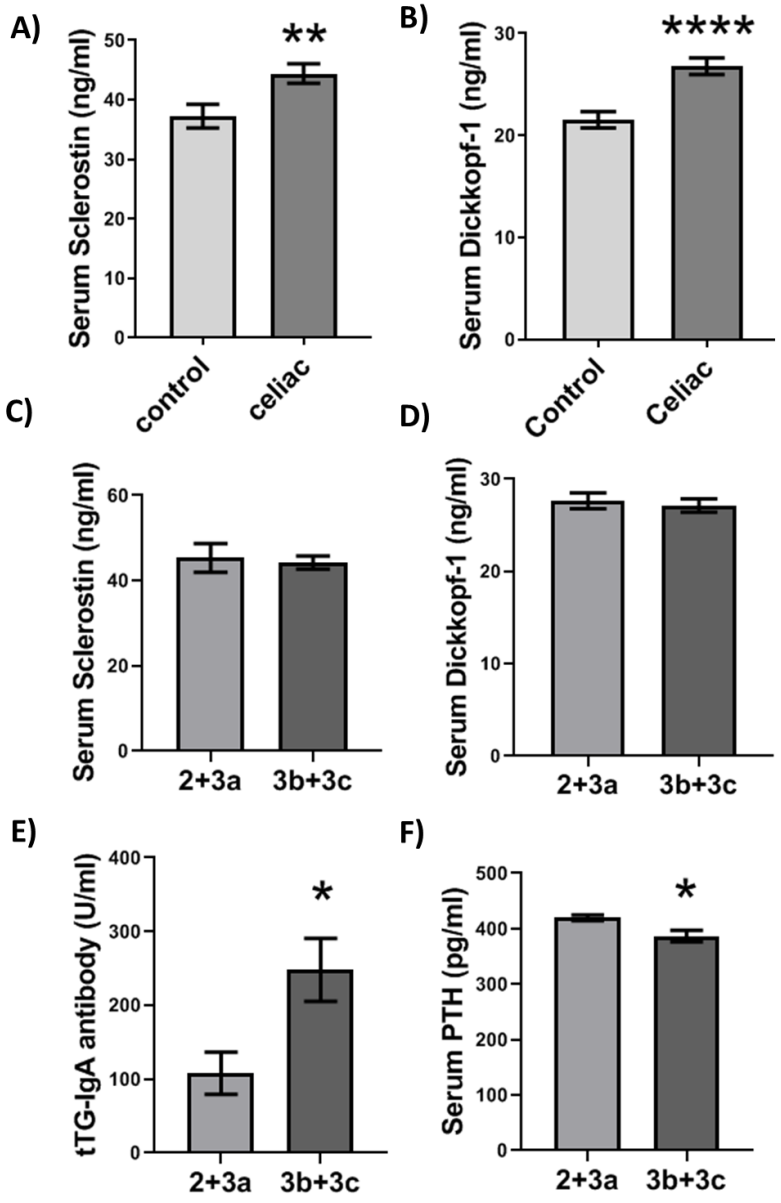

Figure 1. Serum Dikkopf-1 (ng/ml) levels of two WNT signaling antagonists; dickkopf-1 (A) and sclerostin (B) in celiac and control groups. Celiac patients categorized to two groups according the intestinal villus damage (marsh score). Marsh score 2+3a indicates patients with no/mild atrophy and 3b+3c represents patients with marked/complete atrophy. Serum sclerostin (C), dickkopf 1 (D), anti-tissue-transglutaminase IgA (tTG-IgA) (E) and parathyroid hormone (PTH) (F) were compared between patients according the intestine villus damage. Each column represents mean ± standard deviation.

4.3. Clinical significance of Dickkopf-1 and Sclerostin in Celiac Disease diagnosis and classification

To explore the importance of WNT antagonist changes in celiac disease we analyzed the correlation of biochemical and clinical characteristics. Spearman's rank correlation revealed that both Dickkopf-1 and sclerostin are correlated together (R=0.6, p-value<0.0001). Also, both showed direct correlation with PTH (R=0.69 for Dickkopf-1 and R=0.74 for sclerostin, p-value<0.0001).

Unexpectedly, there was no significant correlation between WNT antagonists and anti-tissue-transglutaminase IgA in the current study. However, the level of citrulline as a metabolite produced mainly by the enterocytes of the small intestine was also directly correlated with sclerostin (R=0.71, p-value<0.0001) and Dickkopf-1 (R=0.29, p-value=0.012). In the other hand, PTH showed direct correlation with calcium (R=0.233, p-value =0.04) and citrulline (R=0.53, p-value<0.0001). Altogether the correlation analysis underscored the direct correlation between the WNT antagonists (Dickkopf-1 and sclerostin), PTH and, citrulline as the enterocyte mass marker. For the next step, we evaluated the sensitivity and specificity of the factors correlated with enterocyte marker (citrulline) in the prediction of celiac disease and marked or complete intestinal villus atrophy (marsh score 3b+3c). As indicated in figure 2A, the area under curve (AUC) of ROC curve analysis indicated that Dickkopf-1 (AUC=0.83, P-value<0.0001), sclerostin (AUC=0.7, P-value= 0.003) and PTH (AUC=0.91, P-value<0.0001) can successfully predict the celiac disease. The cutoff points for Dickkopf-1 =24.7pg/ml with sensitivity=80% and specificity=73%, sclerostin=44.7pg/ml with sensitivity=65% and specificity=60% and PTH=362.7pg/ml with sensitivity=91% and specificity=73% could potentially predict the celiac disease compared to the gold standard of an intestinal biopsy.

However, none of them can predict the MARSH score category in celiac disease except anti-tissue-transglutaminase IgA (AUC=0.76, p-value=0.01) with cutoff=129.5 unit/ml able to discriminate patients with marked/complete intestinal atrophy from those with no/mild atrophy (sensitivity=75% and specificity=70%) (figure 2B).

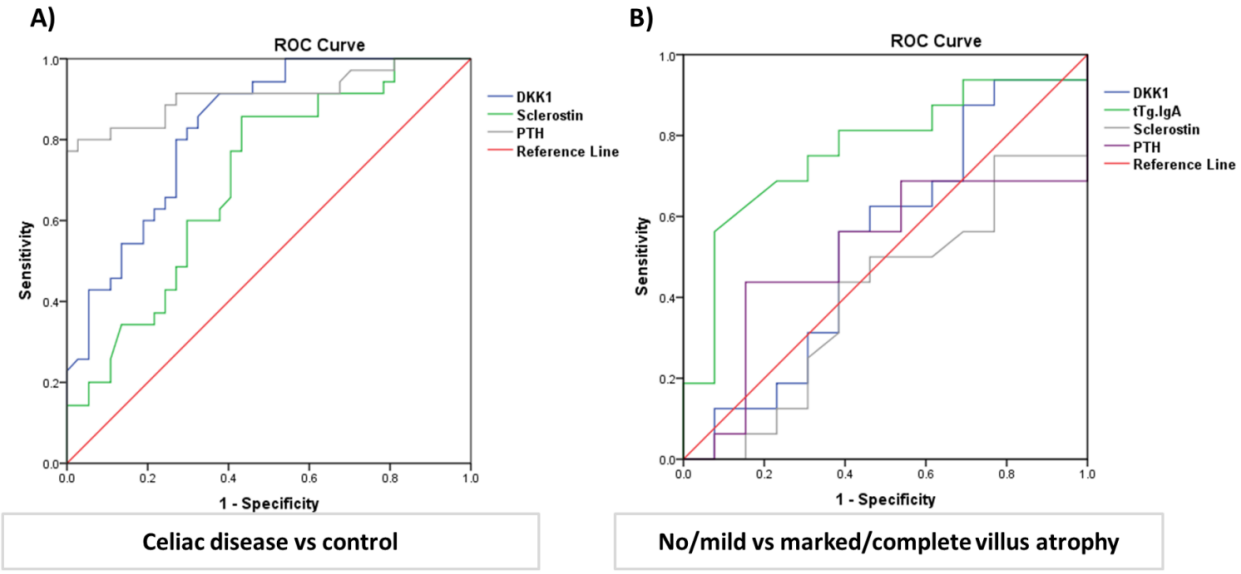

Figure 2. Specify ROC curve parameters (95% CL) analysis of Dickkopf-1 , sclerostin and PTH in celiac disease (A) and classification of intestinal atrophy (B). Reference line is colored in red color.

5.Discussion

Celiac disease is an enteropathy resulting from inappropriate adaptive immunity in response to digested gluten-derived peptides. Intestinal epithelial barrier impairment plays a role in the pathogenesis of CD and patients are usually characterized by intestinal tissue damage including decreased enterocyte height, crypt hyperplasia, and villous atrophy [20].

The obtained results in this research show that serum levels of sclerostin, Dickkopf-1as bone negative regulators and WNT antagonists, and also the two other bone modulators, PTH and Ca are significantly higher in celiac patients compared to control subjects.

The two WNT antagonists measured in the current study (sclerostin and Dickkopf-1) function as potent suppressors of bone formation. In a research conducted by Dhakad ,Ikram , Sharma ,Khan ,Pandey ,Singh., (2019) reported higher serum sclerostin was significantly higher in rheumatoid arthritis (RA) patients compared to controls (P = 0.002); however, it was not correlated with BMD or disease activity [21]. Also, Ibrahi ,Abdelsamad ,Helmy ,Farouk. reported that elevated sclerostin levels in RA patients contributed to joint damage and bone erosion in RA patients [22]. These results are in agreement with our observations of CD patients. In the other hand, Stefan Koch found that Dickkopf-1 contribute important function in intestine epithelial cell homeostasis and its depletion

can promote intestine recovery and repair in colitis, with hyper-proliferation of epithelial cells and irregular crypt structure [13]. Mi Jin Kim ,DT,MS, Jin-Soo, DDS, phD, Ji-Hwan Kim , MPH, PhD , Hae – Young Kim , Woong – Chul Kim , (2019) found elevation of serum Dickkopf-1 in patients who have Crohn's disease (P-value=0.003) correlated directly with ESR, CRP and, pediatric crohn's disease activity index [23].

Previous studies reported that the prevalence of primary hyperparathyroidism in celiac disease is higher than general population, suggesting a significant association between hyperparathyroidism and coeliac disease [24]

Ganji, A., Moghbeli, M., Moradi, Y., Babaei, N. and Baniasad, A., (2022) in a cross-sectional study reported 16.4% of celiac patients have osteoporosis and 27.7% of them had high PTH levels which was significantly associated with osteoporosis in the femoral and spine [25].

Considering their common role in bone regulation, a cross-talk between PTH and WNT antagonists has been postulated. Nagata, Y., Imanishi, Y., Tateishi, T., Miyaoka, D., Kurajoh, M., Arnold, A. and Emoto, M., (2022) reported that PTH regulates circulating levels of sclerostin and FGF-23 in a primary hyperparathyroidism model. Their results showed that patients with primary hyperparathyroidism have lower serum sclerostin levels than healthy controls, consistent with the idea of SOST down-regulation by PTH [26].

The main characteristics in celiac disease are intestinal damage and villus atrophy which can be measured with MARSH scoring. Another quantitative marker of enterocyte mass is citrulline which has been reported to be lower in celiac disease and considered as a candidate marker of histopathological severity of damage [27]. However, in contrast we observed no significant difference in citrulline levels in control and patient subjects. Similarly, research conducted by Douda, L., Hyšpler, R., Mžik, M., Vokurková, D., Drahošová, M., Řeháček, V., Čermáková, E., Douda, T., Cyrany, J., Fejfar, T. and Jirkovský, V., in 2023 reported that there were no statistically significant differences in the citrulline levels between the CD patients and the control group which is in agreement with our results [28].

Citrulline can also be produced from another mechanism through function of endothelial nitric oxide synthase (eNOS), which can catalyze the production of NO and L-citrulline from Arg. Indeed, Previous studies indicated that PTH can induce a significant increase in eNOS activity, as measured by the conversion of [(14)C]arginine to [(14)C] citrulline [29]. This is study to the citrulline level was affected by the metabolism of Arg induced by PTH stimulated increase in the eNOS activity rather

than enterocyte integrity in CD. Here in our study we also found a direct correlation between PTH and citrulline (R=0.53, p-value<0.0001).

"Elevated calcium despite malabsorption may reflect PTH-driven bone resorption, a compensatory mechanism ,Calcium malabsorption is well-known characteristics of unmanaged celiac disease[30]; however, we found elevated calcium level in CD which was positively correlated with PTH. It is widely recognized that in response to PTH, the concentration of calcium in circulation will be rised; the positive association we observed could be related to the function of PTH in the positive regulation of serum Ca.

6.Conclusion

Our study showed that elevation of the two WNT signaling antagonists, Dickkopf-1 and sclerostin, along with PTH as another bone modulator in the serum of celiac patients correlated directly with the level of citrulline, a potential marker of enterocyte mass. These findings altogether suggest the importance of Dickkopf-1 and sclerostin in the pathogenesis of celiac disease but, more studies are appealing to investigate their potential diagnostic and therapeutic application in the future.

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