Citrulline level as a marker of adherence to diet free of gluten and clinical status in children with celiac disease

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Abstract

Aim of the study: The assessment of serum citrulline level as a marker of clinical status of celiac disease (CD) children and its relation with their degree of adherence to gluten free diet (GFD). **Patients and Methods:** This is a cross-sectional study that was conducted on 60 randomly selected children (mean age 6 ± 3.21 years), diagnosed with CD within 6 months before study initiation, the patients attended the gastroenterology outpatient clinic at children hospital at Cairo University in the period from December 2019 to March 2020. After their recruitment, subjects were grouped according to their adherence to GFD into 4 groups: excellent, good, poor and no adherence. Serum citrulline levels was measured using enzyme linked immunosorbent assay and its levels compared between groups. **Results:** Statistically significant differences were found in serum citrulline levels between different groups with variable degrees of adherence to GFD (p=0.000). Its levels showed positive correlations with WHO weight and height z-score, hemoglobin, serum Sodium and albumin levels. **Conclusion:** Serum citrulline is a good indicator for the degree of adherence of CD children to GFD.

Keywords: celiac disease; citrulline; gluten free diet.

Introduction

Celiac disease is an enteropathy mediated by an immune response caused by a reaction to glutens found in cereal grains. Antibodies against gluten and tissue transglutaminase (tTG) enzyme are produced in CD patients, which attack the intestinal villi that results in malabsorption of different nutrients ***(Plenge RM., 2010).***

Lifelong GFD is the key treatment in CD patients and adherence to GFD is key in prevention of nutritional complications and improving the quality of life, which is achieved through a suitable nutritional education program involving continuous counselling and support ***(Rashid M., 2005).***

Citrulline is an amino acid found watermelon juice ***(Fragkos KC and Forbes A, 2011)*** and in humans, that is produced from metabolism of glutamine and/or proline ***(Wu G, 1995).***

The main source of circulating serum citrulline is the small intestinal epithelium ***(Schoknecht PA and Pond WG, 1993; Wu G and Morris SM, 2004).*** Thus, it can be regarded as a marker for the functional cell mass of the small intestinal epithelium under steady-state conditions ***(Pita AM et al., 2003; Gondolesi GE et al., 2004; Osowska S et al., 2004; Jianfeng G et al., 2005; Rhoads JM et al., 2005 and Gondolesi G et al., 2006).***

Several studies have focused on the relation between serum citrulline and gut health in celiac disease. Many have compared the citrulline level in celiac patients against healthy controls. Others have compared citrulline level in celiac patients who received GFD to those who had not. In other studies, the relation between citrulline levels and disease severity was assessed ***(Hozyasz KK et al., 2006; Crenn P, 2008; Miceli E et al., 2008; Ioannou HP et al., 2011).***

Aim of the study

The present study aimed to evaluate the usefulness of the measurement of serum citrulline levels in a group of CD children to assess their adherence degree to GFD and their clinical status. Application of this non-invasive marker will allow the physicians to easily follow up CD patients and subsequently provide the appropriate nutrition support programs. Early intervention and correction of any minimal deviation will give a good chance for better growth and quality of life for those patients.

Patients and methods

Patients:

This cross-sectional study was conducted on sixty children, aged 1.5-12 years, who attended the gastroenterology department at children hospital at Cairo University and were diagnosed with CD within the six months preceding their enrollment in the study through upper endoscopy and duodenal biopsy. Subjects were recruited over a period of 4 months, starting from December 2019 and ending in March 2020.

Sample size:

Our sample size was calculated according to the results of the previous study by ***Ioannou et al, 2011,*** using Epi-info™ statistical package program version 7.2, with 80% proposed power of the study and a two-sided confidence interval of 95%, the total sample size was 58.

Ethical considerations:

The study was approved by the Scientific Research Ethics Committee of Pediatrics Department, Faculty of Medicine, Cairo University on 24/11/2019 (approval code: MS-304-2019). A scanned copy of the approval is available upon request.

Before enrollment in the study, an informed consent was obtained from each participant's parents.

Patients' data confidentiality was preserved during all study procedures.

The patient and parents have the right to withdraw from the study at any time.

There was no conflict of interest regarding the study or its publication.

There is no financial support or sponsorship.

Inclusion criteria:

- Patients diagnosed with CD with or without GFD of less than 6 months duration.
- Both genders (males and females).
- Age below 13 years.

Exclusion criteria:

- Patients diagnosed with CD on GFD of more than 6 months duration.
- Patient having chronic kidney disease.
- Patients diagnosed with celiac disease concomitant with other chronic disease like diabetes mellitus that affect nutritional status

Study procedure:

All the studied patients were subjected to the following:

Full history taking including:

Demographic data, consanguinity, age at diagnosis, gastrointestinal symptoms, history of unexplained anemia, faltering growth/unexplained short stature, history of other food allergies and history of celiac disease or other allergies in other family members, detailed nutritional history including twenty-four hours dietary recall and full history about the start and adherence to GFD in the six months preceding the patient's recruitment in the study was obtained.

Thorough clinical examination including:

General examination, systemic examination and anthropometric measurements including length (subjects below 2 years old), height (subjects more than 2 years), weight and mid-upper arm circumference (MUAC) and triceps skinfold (TSF). Body mass index (BMI) and anthropometric parameters' standard deviation (z) scores were calculated using *WHO Anthro Plus 3.2* and macros for children aged up to 5 years and *Medscape z-score calculator (Medscape references)* for children older than 5 years.

Laboratory workup:

Sample collection

Venous blood (5 milliliters) were collected from each participant where 3 milliliters were collected on serum tube and allowed to clot for 30 min for chemistry analysis and 2 milliliters were collected on EDTA for blood count. Centrifugation is done for serum tubes at the speed of 2000-3000 rpm for 15 minutes followed by serum separation and storage at -20'C till analysis.

Routine laboratory investigations including

Complete blood picture (CBC) was done on Sysmex XT1800. Assessment of kidney functions (blood urea nitrogen, BUN and creatinine), electrolytes in the form of sodium (Na), potassium (K), albumin (Alb), serum iron (Fe) and total iron-binding capacity (TIBC) were done on Beckman coulter AU480.

Specific laboratory investigations including

- **Serum citrulline level:** measured using quantitative sandwich enzyme immunoassay using enzyme linked immunosorbent assay technique (ELISA) using *(Sinogeneclon Biotech Co., Ltd, China)* kit. The assay was performed according to manufacturer's instructions.
- Anti-tissue transglutaminase IgA (Anti-TTG) levels were retrieved from patients' files at the gastroenterology clinic.

After the recruitment of all study subjects, they were grouped according to their adherence to GFD into 4 groups, where groups were defined according to ***Rajpoot P et al., 2015*** as follows:

Excellent adherence: the intake of gluten by the patients only once during the six months period.

Good adherence: the intake of gluten from zero to one time per month.

Poor adherence: the intake of gluten from two to three times per month.

No adherence: those who were not following GFD at all.

Patients with excellent, good and poor adherence degrees were considered adherent to GFD.

Statistical analysis

Statistical Package for Social Science (IBM SPSS) version 23 was used to process data. Chi-square test and/or Fisher exact test were used for comparison of qualitative data between groups when the expected count in any cell was found less than 5. Paired t-test was used to compare quantitative data with parametric distribution between two paired groups, while One Way ANOVA test was used for comparison between more than two independent groups. To correlate two quantitative parameters in the same group, Pearson correlation coefficients test was used. The confidence interval (CI) was set to 95%. The margin of error accepted was set to 5%. The p-value was non-significant (NS) when p-value was > 0.05, significant when p-value was < 0.05 and highly significant (HS) when p-value was < 0.001.

Results:

Our results will be demonstrated in the following tables and figures:

Table 1 Demographic and clinical characteristics of CD patients in relation to adherence to GFD

		Adherent (n=43)	**Non adherent (n=17)**	**P-Value**
Age* (years)		6.08±3.21 (1.5-12)		
Gender#	Male	32 (53.3%)		
	Female	28 (46.7%)		
Persistent diarrhea#	Yes	22 (51.2%)	13 (76.5%)	0.073
	No	21 (48.8%)	4 (23.5%)	
Abdominal pain#	Yes	35 (81.4%)	16 (94.1%)	0.214

	No	8 (18.6%)	1 (5.9%)	
Abdominal distension[#]	Yes	37 (86.0%)	16 (94.1%)	0.380
	No	6 (14.0%)	1 (5.9%)	
Constipation[#]	Yes	4 (9.3%)	1 (5.9%)	0.666
	No	39 (90.7%)	16 (94.1%)	
Short stature[#]	Yes	31 (72.1%)	16 (94.1%)	0.062
	No	12 (27.9%)	1 (5.9%)	
Weight Z-score•		-1.34 (-2.8 – -0.84) -3 – 1.34	-2.73 (-3 – -1.63) -3 – -0.58	**0.020**
Height/Length Z-score•		-2.55 (-3.52 – -1.41) -6.46 – 1.26	-2.65 (-3.35 – -2.56) -7.59 – -1.19	0.215
Weight for height/Length•		-0.05 (-1.07 – 1.06) -3– 3	-0.46 (-1.37 – 0.78) -3 – 1.29	0.364
BMI*, kg/m^2		15.58 ± 3.62 (7-25)	15.03 ± 2.05 (10.6 – 18.3)	0.558

[#]Data presented as n (%); *data presented as mean±SD (range); •data presented as median (IQR) range. P-value >0.05 (non-significant); <0.05 (significant); <0.001 (highly significant).

This table shows the demographic data of the studied cases.

Table 2 Laboratory data of CD patients in relation to adherence to GFD

	Adherent (n=43)	**Non adherent (n=17)**	**P-Value**
Hemoglobin*, g/dl	10.97 ± 1.27 (8 – 13.8)	10.09 ± 1.57 (7.5 – 13)	**0.029**
Iron*, ug/dl	40.53 ± 17.83 (10 – 73)	25.47 ± 10 (11 – 44)	**0.002**
TIBC*, ug/dl	359.84 ± 53.38 (290 – 495)	394.82 ± 52.65 (313 – 502)	**0.025**
Sodium*, mmol/l	139.53 ± 1.76 (135 – 143)	139.71 ± 1.49 (137 – 143)	0.726
Potassium*, mmol/l	4.07 ± 0.17 (3.7 – 4.6)	3.92 ± 0.35 (3 – 4.3)	**0.022**
BUN*, mg/dl	12.41 ± 4.14 (3 – 20)	13.12 ± 3.79 (5 – 18)	0.545
Creatinine*, mg/dl	0.41 ± 0.08 (0.3 – 0.6)	0.4 ± 0.07 (0.3 – 0.5)	0.576
Albumin*, g/dl	4.1 ± 0.38 (3.2 – 5.1)	3.86 ± 0.5 (2.5 – 4.7)	0.052

Anti-TTG•, U/ml	22 (8 – 182) 2 – 410	130 (8 – 250) 5 – 640	0.218

*Data presented as mean±SD (range); •data presented as median (IQR) range. P-value >0.05 (non-significant); <0.05 (significant); <0.001 (highly significant).

There were statistically significant differences between adherent and non-adherent patients' groups regarding weight Z-score, hemoglobin, serum iron, TIBC and serum Potassium levels **(Table 1 and 2).**

Table 3 Serum citrulline level in relation to degree of adherence of CD patients to GFD

	Excellent adherence (n=9)	**Good adherence (n=13)**	**Poor adherence (n=21)**	**No adherence (n=17)**	**P-Value**
Serum Citrulline*, pg/ml	1483.28±212.99 (1190-1803)	836.23±41.23 (570-1148)	542.07±88.57 (372-689)	678±350.33 (287-1530)	**0.000**[a,b,c,d,e] 0.137[f] 0.095[g]

*Data presented as mean±SD (range). P-value >0.05 (non-significant); <0.05 (significant); <0.001 (highly significant). [a] all groups comparison; [b] Excellent compared to good adherence; [c] Excellent compared to poor adherence; [d] Excellent compared to no adherence; [e] Good compared to poor adherence; [f] Good compared to no adherence; [g] Poor compared to no adherence

Serum citrulline levels showed statistically significant differences in relation to different degrees of adherence to GFD and better degrees of adherence showed increasing citrulline levels **(Table 3 and figure 1).**

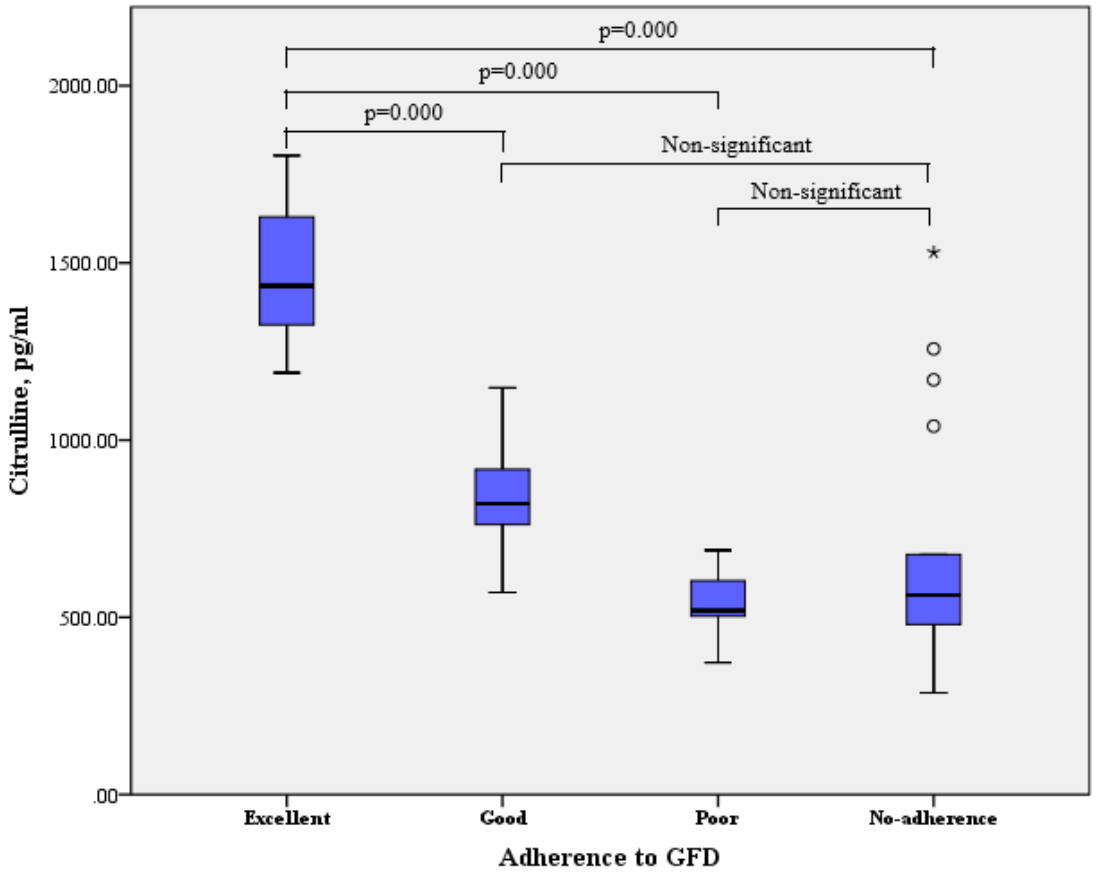

Figure 1 Relation of serum citrulline levels and degree of adherence to GF

Table 4 Relation of demographic, clinic-pathologic characteristics with serum citrulline levels in CD patients

		n (%)	Serum citrulline level, pg/ml Mean ± SD (Range)	P-value
Sex	Female	28 (46.7%)	799.52±405.28 (388.5-1803)	0.793
	Male	32 (53.3%)	773.24±365.19 (287-1750)	
History of celiac in family	No	52 (86.7%)	774.34±374.22 (287-1750)	0.568
	Yes	8 (13.3%)	858.06±445.42 (510-1803)	
History of other food allergies in family	No	53 (88.3%)	745.55±374.49 (287 – 1803)	**0.024**
	Yes	7 (11.7%)	1088.01±305.99 (762-1531.6)	
Consanguinity	No	28 (46.7%)	904.7±400.52	**0.022**

			(388.5-1750)	
	Yes	32 (53.3%)	681.2±336.12 (287-1803)	
Persistent diarrhea	No	25 (41.7%)	699.5±269.32 (287-1435.5)	0.141
	Yes	35 (58.3%)	846.93±437.97 (388.5-1803)	
Abdominal pain	No	9 (15%)	640.28±257.37 (287-948)	0.218
	Yes	51 (85%)	811.13±395.63 (388.5-1803)	
Abdominal distention	No	7 (11.7%)	779.21±414.37 (287-1435.5)	0.963
	Yes	53 (88.3%)	786.33±381.01 (372-1803)	
Constipation	No	55 (91.7%)	790.12±392.22 (287-1803)	0.759
	Yes	5 (8.3%)	734.7±254.04 (372-948)	
Short stature	No	13 (21.7%)	997.04±387.88 (503-1750)	**0.023**
	Yes	47 (78.3%)	726.99±362.1 (287-1803)	
Duodenal biopsy (Grade of villous atrophy)	Mild	13 (21.7%)	864.78±451.73 (287-1750)	0.402
	Moderate to severe	47 (78.3%)	763.57±361.95 (372-1803)	

P-value >0.05 (non-significant); <0.05 (significant); <0.001 (highly significant).

Mean serum citrulline level decreased significantly in patients with positive consanguinity (p=0.022), while it increased significantly in patients with positive history of other food allergies in family (p= 0.024). Its levels did not show statistically significant differences with the presence of clinical manifestations except for short stature where its levels showed significantly lower values with short stature (p=0.023) **(table 4).**

Table 5 Correlation of serum citrulline levels with anthropometric measurements and laboratory findings

	Serum citrulline level (pg/ml)	
	Correlation coefficient, r	**P-value**
Age of gluten introduction (months)	0.324	**0.011**
GFD initiation interval (weeks)	0.155	0.237
Weight z-score	0.277	**0.032**
Height/length z-score	0.284	**0.028**
Weight for height or weight for length	0.042	0.768
BMI	-0.042	0.752
TSF	0.095	0.468
MUAC	0.049	0.709
Hemoglobin	0.301	**0.019**
Platelets	0.048	0.713
White Blood Cells	-0.066	0.617
Fe	0.190	0.147
TIBC	-0.151	0.249
Na	0.301	**0.019**
K	0.113	0.388
BUN	-0.015	0.910
Creatinine	-0.050	0.704
Albumin	0.288	**0.026**
Anti TTG	0.027	0.838

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.001: Highly significant.

Serum citrulline levels showed statistically significant weak positive correlations with age of gluten introduction, patient's weight and height for age z-score, sodium, hemoglobin and albumin levels **(Table 5).**

Discussion

Celiac disease is an immune disorder in genetic predisposed individuals characterized by injury of the small intestine by auto-antibodies produced against the small intestinal mucosa following the intake of gluten protein, which is found in some grains among which wheat is the most famous ***(Rahmani P et al., 2022).***

Citrulline is a non-protein amino acid produced by the small intestinal enterocytes and its level therefore represents enterocytes' functional synthetic capacity ***(Mir BA et al., 2022).***

To prevent small intestinal mucosal cells from damage and allow small intestinal healing, celiac disease patients should avoid consuming gluten containing foods and stick to GFD regimens ***(Fragkos KC and Forbes A, 2018).***

Studies have showed that serum citrulline may be a suitable biomarker for

the assessment of the severity of small intestinal dysfunction of different etiologies (surgical, radiological intervention or medical condition), ***(Maric S et al., 2021; Martín-Masot R et al., 2023)*** and also for the follow-up of nutritional, surgical or pharmacological small intestine treatment protocols ***(Martín-Masot R et al., 2023).***

The current study aimed to assess the usefullness of the measurement of serum citrulline as a biomarker assessment of adherence to GFD in CD patients and their clinical status.

Objective detailed 24-hours dietary recall of the caregivers of the patients included in the current study revealed variable degrees of adherence to GFD. Among all CD patients who were on GFD for a period of 4.35±1.17 months, only 36.6% of the patients achieved excellent or good adherence degree. A study by **Rajpoot et al.** revealed that 53% of the patients who were on GFD maintained an excellent or good level of adherence and at 6 months with repeated counselling they increased to 92.4% (***Rajpoot et al., 2015)***.

The discrepancy in numbers of the aforementioned results between the current study and those by ***Rajpoot et al., 2015*** is probably because of low socioeconomic level of the patients enrolled in the present study leading to low affordability and accessibility to gluten-free foods.

Results of the present study showed that patient weight Z-score and hemoglobin levels were significantly better in GFD adherent than non-adherent CD patients which were also in agreement with those by **Rajpoot et al.** who found that patient weight, hemoglobin levels significantly improved in patients with improved adherence level to GFD through repeated nutritional counselling ***(Rajpoot et al., 2015).***

In the current study, serum citrulline levels showed statistically significant differences in relation to different degrees of adherence to GFD (p=0.000) and better degrees of adherence showed increasing citrulline levels. This was in agreement with the results of the studies by **Crenn P et al., Miceli E et al. Ioannou HP et al. and Lomash A et al.,** which revealed that there was an increasing pattern of serum citrulline levels over time with significant differences of serum citrulline levels at the start and at the end of the enrollment period, as they all studied serum citrulline levels in children with CD over a period that varied from 12 to 24 months, with serial measurement of citrulline level at baseline before gluten introduction and at different time intervals after GFD initiation ***(Crenn P et al., 2003; Miceli E et al.,2008; Ioannou HP et al., 2011 and Lomash A et al., 2021).*** In addition, **Ioannou et al.** studied serum citrulline levels in a group of diagnosed CD children before GFD initiation and compared them to their levels in another group of CD patients who were on GFD

for 2 years and found that there is a statistically increased levels of citrulline in the latter group **(*Ioannou HP et al., 2011*)**, which is also in agreement to the results of the current study.

Serum citrulline level showed statistically significant weak positive correlations with patients' weight (r= 0.277, p= 0.032) in the present study which were contradictory with **Douda L el al.'** results, where serum citrulline showed a weak negative correlation with patients' weight (r = -0.066) ***(Douda L el al., 2022).***

The results of the correlation of serum citrulline levels with hemoglobin level (r=0.301) in the present study were in line with those by **Douda L el al.** (r=0.111) ***(Douda L el al., 2022).***

Conclusion

Serum citrulline can be used as a rapid affordable marker for the assessment of adherence degree of CD patients to GFD. This will help endorsing the counseling and family support for those who are not compliant to GFD.

Recommendations

Longitudinal studies for the assessment of serum citrulline and comparison of its levels at different time intervals are needed along with consistent nutritional counseling for the endorsement of serum citrulline as a follow up marker for the degree of adherence of CD patients to GFD.

More studies are required to assess the relationship between serum citrulline and different clinical characteristics and other laboratory tests to evaluate the role of serum citrulline as a marker of the clinical status of CD patients.

Follow up studies are needed to investigate citrulline role in predicting long term complications of celiac disease.

Limitations

In addition to GFD, history of other food allergies in the families of patients, consanguinity and short stature were found to affect citrulline level in the present study.

The absence of significant differences in citrulline levels between some of the studied groups limited the derivation of cutoffs to differentiate between the different degrees of adherence to GFD

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