Arrival Date: 23.08.2023 | **Published Date:** 25.10.2023 | **Vol:** 8, **Issue:** 4 | **pp:** 1086-1091 | **Doi Number:** http://doi.org/10.5281/zenodo.10048848

EVALUATION OF IODINE DEFICIENCY STATUS OF CHILDREN DIAGNOSED WİITH CELIAC DISEASE BY SPOT URINE IODINE/CREATININE RATIO

ÇÖLYAK HASTALIĞI TANILI ÇOCUKLARDA İYOT EKSİKLİĞİ DURUMUNUN SPOT İDRAR İYOT/KREATİNİN ORANI İLE DEĞERLENDİRİLMESİ

Eren ER [1], Didem GÜLCÜ TAŞKIN [2]

[1] Health Sciences University, Tepecik Training and Research Hospital, İzmir, Türkiye
[2] Health Sciences University, Adana City Training and Research Hospital, Adana, Türkiye

ABSTRACT

Aim: Celiac disease (CD) is caused by gluten sensitivity which leads to intestinal villi damage. This damage and strict diet can cause vitamin and mineral deficiencies; such as iodine. The aim of this study is to assess the iodine deficiency status in children diagnosed with CD by measuring spot urine iodine/creatinine levels.

Material-Method: Totally 66 (42 girls, 24 boys) children with CD who were followed up in Pediatric Gastroenterology Outpatient Clinic between 18.09.2017-01.12.2022 were included in this retrospective study. Anthropometric and laboratory data were obtained from patient files. All the clinical, biochemical values and spot urine iodine/creatinine ratio were analyzed.

Results: The mean age of the patients was 9.73 ± 3.84 years, and the mean age at diagnosis was 6.57 ± 3.86 years, disease duration was 3.16 ± 2.34 years. The mean spot urinary iodine/creatinine ratio of the participants was 146.20 ± 113.59 µg/g. According to multivariate analysis results, a significant negative correlation was determined between mean patient age and urinary iodine/creatinine ratio ($p = 0.009$). No significant correlation between other parameters were found ($p > 0.05$). The patients were divided into two groups: Group 1; as the group with adequate dietary compliance, Group 2; insufficient dietary compliance. The mean spot urinary iodine/creatinine ratio of Group 1 was higher than Group 2, but this difference was not statistically significant (152.26 ± 120.51 µg/g vs. 134.65 ± 100.68 µg/g; $p=0.560$). The other parameters were also statistically insignificant ($p>0.05$).

Conclusion: This is the first study in the literature to use the spot urinary iodine/creatinine ratio in the evaluation of iodine deficiency in children and adolescents with CD. The mean spot urinary iodine/creatinine ratio of celiac patients in our study was similar in healthy populations of the same age group, regardless of dietary adherence. In this area; prospective, randomized controlled studies with more subjects are needed.

Keywords: Children, Celiac Disease, Gluten, Iodine, Urine iodine/Creatinine ratio

ÖZET

Amaç: Çölyak hastalığı (ÇH), genetik olarak duyarlı bireylerde gluten ve ilgili prolaminler tarafından ortaya çıkan immün aracılı sistemik bir hastalıktır. Gluten tarafından indüklenen intestinal mukozal hasarı, villöz atrofisine ve bunun sonucunda iyot gibi besinlerin eksikliklerine neden olabilmektedir. Bu çalışmanın amacı, çölyak hastalığı tanısı ile izlenen çocuk ve ergenlerde mevcut iyot durumunu spot idrar iyot/kreatinin düzeyleri ile değerlendirmektir.

Materyal-Metod: Bu retrospektif çalışmaya, Adana Şehir Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Poliklinik 1'de 01.10.2017-31.08.2022 tarihleri arasında çölyak hastalığı tanısı ile izlenen 66 (42 kız, 24 erkek) çocuk dahil edildi. Antropometrik ve laboratuvar verileri hasta dosyalarından elde edildi. Klinik ve biyokimyasal olan parametreler ile spot idrar iyot/kreatinin oranı arasındaki ilişki analiz edildi.

Bulgular: Çalışmaya katılan çocukların ortalama yaşı 9,73 ± 3,84 yıl, ortalama tanı yaşı 6,57 ± 3,86 yıl ve ortalama hastalık süresi 3,16 ± 2,34 yıl idi. Katılımcıların ortalama spot idrar iyot/kreatinin oranı 146,20 ± 113,59 µg/g idi. Tek değişkenli analiz sonuçlarına göre, ortalama hasta yaşı ile idrar iyot/kreatinin oranı arasında anlamlı bir negatif korelasyon gözlemlenirken ($p = 0,009$), diğer parametreler arasında anlamlı korelasyon saptanmadı ($p> 0,05$). Hastalar, diyete uyumu yeterli grup (Grup 1) ve diyete uyumu olmayan grup (Grup 2) olarak iki grupta incelendiğinde; Grup 1'in ortalama spot idrar iyot/kreatinin oranı Grup 2'ye göre daha fazla bulundu ancak bu fark istatistiksel olarak anlamlı saptanmadı (152,26 ± 120,51 µg/g'e karşı 134,65 ± 100,68 µg/g; $p=0,560$). Ek olarak; gruplar arasında diğer parametreler açısından da anlamlı fark bulunmadı ($p>0,05$).

Sonuç: Bu çalışma, çölyak hastalığı tanısı ile izlenen çocuk ve ergenlerde iyot durumunu değerlendirilmesinde spot idrar iyot/kreatinin oranın kullanıldığı literatürdeki ilk çalışmadır. Çalışmamızdaki çölyak hastalarının ortalama spot idrar iyot/kreatinin oranı diyete uyumdan bağımsız olarak, aynı yaş grubu sağlıklı popülasyonlarda benzerdi. Bu alanda; prospektif, randomize kontrollü, daha fazla hasta katılımının olduğu çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Çölyak hastalığı, Gluten, İyot, İdrar iyot/kreatinin oranı.

Sorumlu Yazar / Corresponding Author: Didem GÜLCÜ TAŞKIN, Associate Professor, Health Sciences University, Adana City Training and Research Hospital, Department of Pediatric, Pediatric Gastroenterology, Adana, Türkiye. **E-mail:** dgulcu@gmail.com

Bu makaleye atıf yapmak için / Cite this article: Er, E., & Gülcü Taşkın, D. (2023). Evaluation of Iodine Deficiency Status of Children Diagnosed with Celiac Disease by Spot Urine Iodine/Creatinine Ratio. *Gevher Nesibe Journal of Medical & Health Sciences*, 8 (4), 1086-1091. http://doi.org/10.5281/zenodo.10048848

INTRODUCTION

Celiac disease (CD) is an immune-mediated disease caused by gluten in susceptible individuals (Fasano & Catassi, 2005). Genetic predisposition, related autoantigens (tissue transglutaminase, tTG) and environmental triggers (gluten) are critical factors in the pathogenesis of the disease. After mucosal villous damage and atrophy, activation of B cells leads to autoantibody production (Green & Cellier, 2007). Due to mucosal damage, nutrients cannot be adequately absorbed, resulting in deficiencies in micronutrients such as iodine in those with CD (Delvecchio et al., 2021).

Iodine is essential for the synthesis of thyroid hormones. The absorption of iodine occurs in small intestine (Nicola et al., 2009). Iodine deficiency may occur in patients with CD, due to malabsorption, mucosal damage or insufficient iodine values of gluten-free foods (Miranda, Lasa, Bustamante, Churruca, & Simon, 2014). In CD autoimmune activation may cause the target organ dysfunction, the main endocrine organ is the thyroid tissue. The use of spot urinary iodine/creatinine ratios in the evaluation of iodine status, since it is more correlated to iodine status than spot urine iodine levels (Knudsen, Christiansen, Brandt-Christensen, Nygaard, & Perrild, 2000; Vejbjerg et al., 2009).

In this study, we aim to assess the current iodine deficiency status in pediatric CD, using spot urine iodine/creatinine ratio.

MATERIAL AND METHODS

In our study, the files of the CD patients, aged between 2-18 years were analyzed. Patients from Pediatric Gastroenterology Outpatient who were treated between 18.09.2017-01.12.2022 were analyzed retrospectively. Patients diagnosed with CD were included 8. The exclusion criteria were as follows: using drugs that would affect iodine metabolism and missing spot urine iodine/creatinine data in patients' file. Totally 66 children (24 boys and 42 girls) aged 9.73 ± 3.84 years were included. The nutritional status and serum antibody titers of the patients were perused. CD patients were divided into 2 groups by evaluating their compliance with the diet according to tissue transglutaminase IgA (tTG-IgA) levels and diet records: Group 1: patients with adequate dietary compliance, Group 2: insufficient dietary compliance. Ethics committee approval has been received from 01.12.2022 date 2288 number of ethics committee of Adana City Training and Research Hospital. All procedures were in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents of the patients. The laboratory measurements of the thyroid stimulating hormone (TSH), free thyroxine (free T4) and free triiodothyronine (free T3) assays were analysed using commercial kits (Dimension EXL integrated chemistry system LOCI Module Siemens, Erlangen, Germany). The normal levels for TSH: 0.79/5.85 mIU/L, fT4: 0.64/ 1.71 ng/dL, fT3: 2.6/6.5 ng/L. Iodine concentration was analyzed by inductively coupled mass spectrometry (ICP-MS) (Agilent 7700x, Agilent Technologies, USA). The urinary iodine/creatinine ratio: iodine concentration (µg/L) / creatinine concentration (g/L). Serum IgA concentrations, tissue transglutaminase IgA (tTG-IgA) and anti-endomysium IgA (EMA) were performed. IBM SPSS Statistics 25 program was used for all statistical analyses. The mean ± SD or median (minimum-maximum) was given for the results. Normally distributed variables were expressed as mean ± standard deviation (SD). Spearman, Pearson correlation parameters used for correlation analysis. The relationship between variables were analysed by using multivariate linear regression. Two-sided $p < 0.05$ was accepted for statistical significance.

RESULTS

The sex, age, anthropometric measurements and the laboratory characteristics of the patients are summarized in Table 1. Totally 66 CD patients, aged 9.73 ± 3.84 years, were included. The mean spot urinary iodine/creatinine ratio of the participants was 146.20 ± 113.59 µg/g. Mean TSH, fT4, and fT3 levels were 2.86 ± 1.62 mIU/L, 0.92 ± 0.13 ng/dL, and 4.08 ± 0.55 ng/L, respectively.

Table 1. The Anthropometric Measurements and Laboratory Features of the Patients

	n
Number	66
Sex (boy/girl)	24/42
	Mean ± SD
Age (years)	9.73 ± 3.84
Age at diagnosis (years)	6.57 ± 3.86

Mean duration of disease (years)	3.16 ± 2.34
Weight SDS	-1.03 ± 1.19
Height SDS	-0.87 ± 1.27
BMI SDS	-0.73 ± 1.01
Urine iodine/creatinine ratio (µg/g)	146.20 ± 113.59
Serum TSH (mIU/L)	2.86 ± 1.62
Serum Free T4 (ng/dL)	0.92 ± 0.13
Serum Free T3 (ng/L)	4.08 ± 0.55

SDS: standard deviation scores, BMI: body mass index, TSH: thyroid stimulating hormone, Free T4: free thyroxine, Free T3: free triiodothyronine.

Evaluating the relationship between clinical parameters and urinary iodine/creatinine ratio, a significant negative correlation was observed between mean patient age and urinary iodine/creatinine ratio for the unadjusted model (p = 0.009) (Figure 1). Other parameters were not correlated among themselves (p> 0.05) (Table 2).

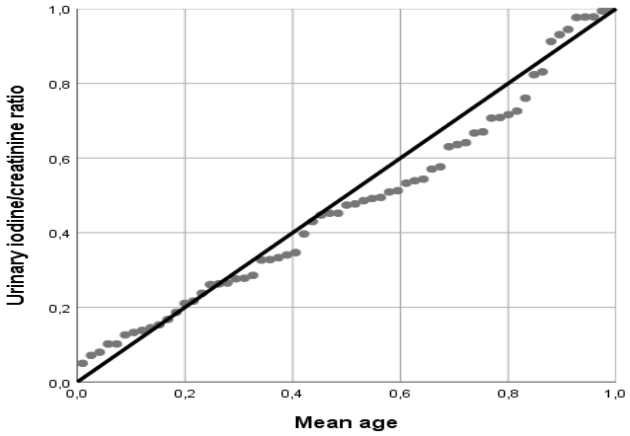

Figure 1. Linear Regression Analysis of Mean Age of The Patients and Urine Iodine/Creatinine Ratio (The line indicates the regression line)

Table 2. Multivariate Analysis of Relationships Between Clinical Parameters and Urine Iodine/Creatinine Ratio

	β	**(95% CI)**	***p***
Age (years)	-0.631	(-31.95;-4.92)	0.009
Age at diagnosis (years)	0.12	(-8.82;15.64)	0.577
Mean duration of disease (years)	-0.068	(-15.64;8.82)	0.577
Weight SDS	-1.79	(-478.71;37.37)	0.092
Height SDS	1.15	(-31.84;256.91)	0.123
BMI SDS	1.37	(-10.78;359.99)	0.064
Serum TSH (mIU/L)	0.154	(-6.13;27.74)	0.205
Serum Free T4 (ng/dL)	0.106	(-122.26;302.92)	0.396
Serum Free T3 (ng/L)	0.041	(-42.77;60.34)	0.733
Male	Reference		
Female	0.998	(0.993;1.003)	0.359

SDS: standard deviation scores, BMI: body mass index, TSH: thyroid stimulating hormone, Free T4: free thyroxine, Free T3: free triiodothyronine

Perusing the two group by mean spot urinary iodine/creatinine ratio, in Group 1 (group with adequate dietary compliance) the ratio is much higher than the Group 2 (group with insufficient dietary compliance) but the difference was statistically insignificant (152.26 ± 120.51 µg/g vs. 134.65 ± 100.68 µg/g; p=0.560). In addition; there was no significant difference between the groups in terms of other parameters (p>0.05) (Table 3).

Table 3. The Characteristics of the Group with Sufficient Dietary Compliance and the Group with Insufficient Dietary Compliance

Variables	Adequate Diet Compliance Group (n:44)	Insufficient Diet Compliance Group (n:22)	*p*
Age (years)	9.56 ± 3.65	10.05 ± 4.26	0.630
Age at diagnosis (years)	6.06 ± 3.94	7.50 ± 3.51	0.154
Mean duration of disease (years)	3.47 ± 2.37	2.55 ± 2.21	0.137
Weight SDS	-0.98 ± 1.23	-1.14 ± 1.13	0.608
Height SDS	-0.83 ± 1.19	-0.96 ± 1.46	0.715
BMI SDS	-0.67 ± 1.17	-0.85 ± 0.97	0.538
Urine iodine/creatinine ratio (µg/g)	152.26 ± 120.51	134.65 ± 100.68	0.560
TSH (mIU/L)	2.90 ± 1.64	2.48 ± 1.49	0.332
fT4 (ng/dL)	0.92 ± 0.13	0.92 ± 0.13	0.973
fT3 (ng/L)	4.16 ± 0.59	3.93 ± 0.43	0.131

SDS: standard deviation scores, BMI: body mass index, TSH: thyroid stimulating hormone, Free T4: free thyroxine, Free T3: free triiodothyronine

DISCUSSION

This is the first study in which the spot urine iodine/creatinine ratio was used in assessment of iodine status in children diagnosed with celiac disease (CD). In CD, after T-cell mediated damage, malabsorption in the villous structure and severe nutritional deficiencies develop (Abadie et al., 2020). After initiating gluten-free diet (GFD), the damage gradually regenerates and the immune response neutralizes (Monachesi et al., 2021). Patients have to consume rice, corn, etc, which are deficient for most vitamins, minerals, protein and iodine. As a result; gluten-free foods cannot meet essential nutritional requirements. After strict adherence to GFD, patients may experience persistent nutritional. Iodine deficiency may occur in patients with CD due to both malabsorption due to mucosal damage and a GFD.

For population screening, measurement of iodine concentrations in spot urine samples is recommended by UNICEF (United Nations Children's Fund), WHO (World Health Organization) and IGN (Global Iodine Network). Although 24-hour urine iodine excretion, which is used to evaluate the iodine status of individuals, is the gold standard method, spot urine samples are widely used in studies involving school-age children due to factors such as difficulty in collecting samples, storage and compliance problems (Knudsen et al., 2000). For investigating the status of iodine, urine iodine-creatinine ratio is often used (Knudsen et al., 2000; Vejbjerg et al., 2009). Urine iodine-creatinine ratio may be unreliable especially when protein intake is low, and loss of muscle mass will lead to reduced creatinine excretion in urine. However, it has also been considered a more reliable measure of iodine status, due to the day-to-day variations of iodine intake and water consumption (Nerhus et al., 2019). In our study, the mean spot urinary iodine/creatinine ratio was found to be 146.2 µg/g. This rate was similar to the study of Celmeli et al, as they evaluate iodine status in healthy population in school-age children (163.3 µg/g) (Çelmeli et al., 2020).

In our study, negative significant correlation was observed between the mean patient age and the urinary iodine/creatinine ratio. Delvecchio et al. stated that iodine deficiency is much more pronounced in school-aged children compared to preschool-aged children and reached similar results with our study in this respect (Delvecchio et al., 2021). On the other hand, in studies among school-aged children, data are conflicting with the relationship between age and iodine status. Doggui et al. found a positive correlation between age and iodine status in their study among Tunisian school children. They stated that this situation may occur as a result of socioeconomic differences, but they could not present a statistically significant evaluation (Doggui, El Ati-Hellal, Traissac, Lahmar, & El Ati, 2016). In the report published by Costa Leite et al., a negative relationship was revealed between age and iodine status, and the reason for this was stated as the higher milk consumption of the younger age group (Costa Leite et al., 2017). The studies mentioned are national-based studies in healthy children and therefore differ in our cohort. Therefore, it is difficult to explain the reason for the negative correlation between age and iodine status in a cohort with chronic disease such as CD.

Limitations

The limitations of our study were that it was a retrospective design study, we include limited number of patients followed up with a diagnosis of CD, and the absence of a control group. In addition, evaluating the iodine status of patients with a single sample was another limitation of the study.

CONCLUSION

This study is the first in the literature to use the spot urinary iodine/creatinine ratio in the assessment of iodine deficiency in CD patients. When the other parameters in the study were perused, a statistically significant relationship was observed only between the mean patient age and the urinary iodine/creatinine ratio. The mean spot urinary iodine/creatinine ratio of the participants with CD in our study was similar in healthy populations of school-aged children, regardless of dietary adherence. In this area; prospective, randomized controlled studies with the participation of more individuals are needed.

Acknowledgement

None.

Author Contributions

Plan, design: E.E, D.G.T; **Material, methods and data collection:** E.E, D.G.T; **Data analysis and comments**: E.E, D.G.T; **Writing and corrections:** E.E, D.G.T.

Conflict of interest

Authors declares no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

Abadie, V., Kim, S. M., Lejeune, T., Palanski, B. A., Ernest, J. D., Tastet, O., … Jabri, B. (2020). IL-15, gluten and HLA-DQ8 drive tissue destruction in coeliac disease. *Nature*, *578*(7796), 600–604. https://doi.org/10.1038/s41586-020-2003-8

Çelmeli, G., Çürek, Y., Özen Kücükçetin, İ., Arslan Gülten, Z., Özdem, S., Akçurin, S., & Bircan, İ. (2020). The Results of 16 Years of Iodization: Assessment of Iodine Deficiency Among School-age Children in Antalya, Turkey. *Journal of Clinical Research in Pediatric Endocrinology*, *12*(3), 256–260. https://doi.org/10.4274/jcrpe.galenos.2020.2019.0168

Costa Leite, J., Keating, E., Pestana, D., Cruz Fernandes, V., Maia, M., Norberto, S., … Calhau, C. (2017). Iodine Status and Iodised Salt Consumption in Portuguese School-Aged Children: The Iogeneration Study. *Nutrients*, *9*(5), 458. https://doi.org/10.3390/nu9050458

Delvecchio, M., Bizzoco, F., Lapolla, R., Gentile, A., Carrozza, C., Barone, M., … Francavilla, R. (2021). Iodine Absorption in Celiac Children: A Longitudinal Pilot Study. *Nutrients*, *13*(3), 808. https://doi.org/10.3390/nu13030808

Doggui, R., El Ati-Hellal, M., Traissac, P., Lahmar, L., & El Ati, J. (2016). Adequacy Assessment of a Universal Salt Iodization Program Two Decades after Its Implementation: A National Cross-Sectional Study of Iodine Status among School-Age Children in Tunisia. *Nutrients*, *9*(1), 6. https://doi.org/10.3390/nu9010006

Fasano, A., & Catassi, C. (2005). Coeliac disease in children. *Best Practice & Research. Clinical Gastroenterology*, *19*(3), 467–478. https://doi.org/10.1016/j.bpg.2005.01.008

Green, P. H. R., & Cellier, C. (2007). Celiac disease. *The New England Journal of Medicine*, *357*(17), 1731–1743. https://doi.org/10.1056/NEJMra071600

Knudsen, N., Christiansen, E., Brandt-Christensen, M., Nygaard, B., & Perrild, H. (2000). Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values. *European Journal of Clinical Nutrition*, *54*(4), 361–363. https://doi.org/10.1038/sj.ejcn.1600935

Miranda, J., Lasa, A., Bustamante, M. A., Churruca, I., & Simon, E. (2014). Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *69*(2), 182–187. https://doi.org/10.1007/s11130-014-0410-4

Monachesi, C., Verma, A. K., Catassi, G. N., Galeazzi, T., Franceschini, E., Perticaroli, V., … Catassi, C. (2021). Quantification of Accidental Gluten Contamination in the Diet of Children with Treated Celiac Disease. *Nutrients*, *13*(1), E190. https://doi.org/10.3390/nu13010190

Nerhus, I., Odland, M., Kjellevold, M., Midtbø, L. K., Markhus, M. W., Graff, I. E., … Øyen, J. (2019). Iodine status in Norwegian preschool children and associations with dietary iodine sources: The FINS-KIDS study. *European Journal of Nutrition*, *58*(6), 2219–2227. https://doi.org/10.1007/s00394-018-1768-0

Nicola, J. P., Basquin, C., Portulano, C., Reyna-Neyra, A., Paroder, M., & Carrasco, N. (2009). The Na+/I- symporter mediates active iodide uptake in the intestine. *American Journal of Physiology. Cell Physiology*, *296*(4), C654-662. https://doi.org/10.1152/ajpcell.00509.2008

Vejbjerg, P., Knudsen, N., Perrild, H., Laurberg, P., Andersen, S., Rasmussen, L. B., … Jørgensen, T. (2009). Estimation of iodine intake from various urinary iodine measurements in population studies. *Thyroid: Official Journal of the American Thyroid Association*, *19*(11), 1281–1286. https://doi.org/10.1089/thy.2009.0094