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Plasma Citrulline Levels in Patients with Celiac Disease: A Meta-analysis of Case-control Studies

Niloofar Hemati[1], Masoud Sadeghi[2, 3]*

[1]Internal Department, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran

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ABSTRACT

Celiac disease is an immune-mediated enteropathy that a few researchers have focused on the levels of some amino acids in celiac disease. Herein, we evaluated of plasma citrulline levels in patients with celiac disease in case-control studies in the meta-analysis study. Four databases of PubMed, Scopus, Web of Science, and Cochrane Library were searched on Feb 2018 without restriction of language and type of study. All studies were searched for evaluation of plasma citrulline levels in the patients with celiac disease compared with the healthy controls. Out of 101 records found in four databases, 6 studies were included and analyzed for the meta-analysis study. The citrulline level in the patients was significantly lower than the controls [MD= -10.18 µmol/l; 95%CI -17.86, -2.44; P=0.009]. Measurement of plasma citrulline levels can be as a diagnostic marker of celiac disease and also for the evaluation of the initial response to a GFD. It needs to more studies in the future with controlling age, sex, and other connected diseases.

Key words: Celiac Disease, Plasma, Citrulline, Case-control, Meta-analysis
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Corresponding author: Masoud Sadeghi
e-mail✉ sadeghi_mbrc@yahoo.com
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INTRODUCTION

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals and is one of the most frequently occurring treatable lifelong disorders [1]. Despite the increasing importance of serological methods in the diagnosis of celiac disease, the gold standard still remains the typical histological picture in intestinal biopsies such as villous atrophy, crypt cell hyperplasia, and intraepithelial lymphocytic infiltration [2]. So far few researchers have focused on the levels of some amino acids in this disease. There were some variations of plasma amino acid levels between celiac patients compared to healthy controls [3]. The small intestine is the main endogenous source of circulating citrulline. Specifically, experimental researches have shown that citrulline is synthesized in enterocytes, the small intestinal absorptive epithelial cells [4]. Citrulline is a non-protein amino acid produced by enterocytes from the conversion of glutamine [5]. It is in circulating blood, is almost exclusively contained in the enterocytes of small bowel mucosa and may represent a reliable marker of functioning enterocyte mass [6]. A few studies showed fasting plasma citrulline level to be a useful marker of intestinal failure in various small intestinal disease states [7]. The aim of this meta-analysis study was the evaluation of plasma citrulline levels in patients with celiac disease in case-control studies.

MATERIALS AND METHODS

Search strategies

A comprehensive search was used based on the terms of coeliac or celiac combined with citrulline or CIT four databases of PubMed, Scopus, Web of Science, and Cochrane Library on Feb 2018 without restriction of language and type of study.

Study selection

One author (M.S) searched the articles and then the second author (N.H) blinded to the first author. All studies were searched for evaluation of plasma citrulline levels in the patients with celiac disease compared with the healthy controls. The inclusion criteria for the studies included: I) studies reporting the mean or median of plasma citrulline level in the patients with celiac disease compared with the healthy controls, II) only studies with English-language abstract could be included; III) the human studies; IV) celiac disease was confirmed clinically and based on biopsy; V) blood sample of citrulline was taken after overnight fasting and VI) The controls without metabolic or digestive diseases. The exclusion criteria were: I) the studies didn't report mean or median of urinary or serum citrulline levels and II) the data from incomplete reports (not sufficient information), review studies and conference papers were not eligible for this study.

Data Extraction

The relevant data extracted from every study were the name of author, year of publication, country, number/age/male (%) of the patients and controls. Level of citrulline was determined by mass spectrometry or chromatography methods.

Statistical analysis

A random-effects meta-analysis was used by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using mean difference (MD) and 95% confidence intervals (CIs). Heterogeneity between the estimates was evaluated by the Q and I^2 statistic that for the Q statistic, heterogeneity was considered if P<0.1 and *p*-value (2-sided) <0.05 was considered statistically significant in this meta-analysis study. In addition to, publication bias was evaluated through funnel plot analysis with the Begg's and Egger's tests. We used the formula for estimation of mean and SD, if the study reported median plus interquartile range [8]. The unit of measurement of citrulline in this meta-analysis was µmol/l.

RESULTS

There were 101 records in four databases that after removing duplicate records, 54 records were screened. Then, 41 records were excluded with not relevant data. Thirteen articles were evaluated based on full-text that seven were excluded with reasons. At last, 6 studies were included and analyzed for the meta-analysis study (Figure 1).

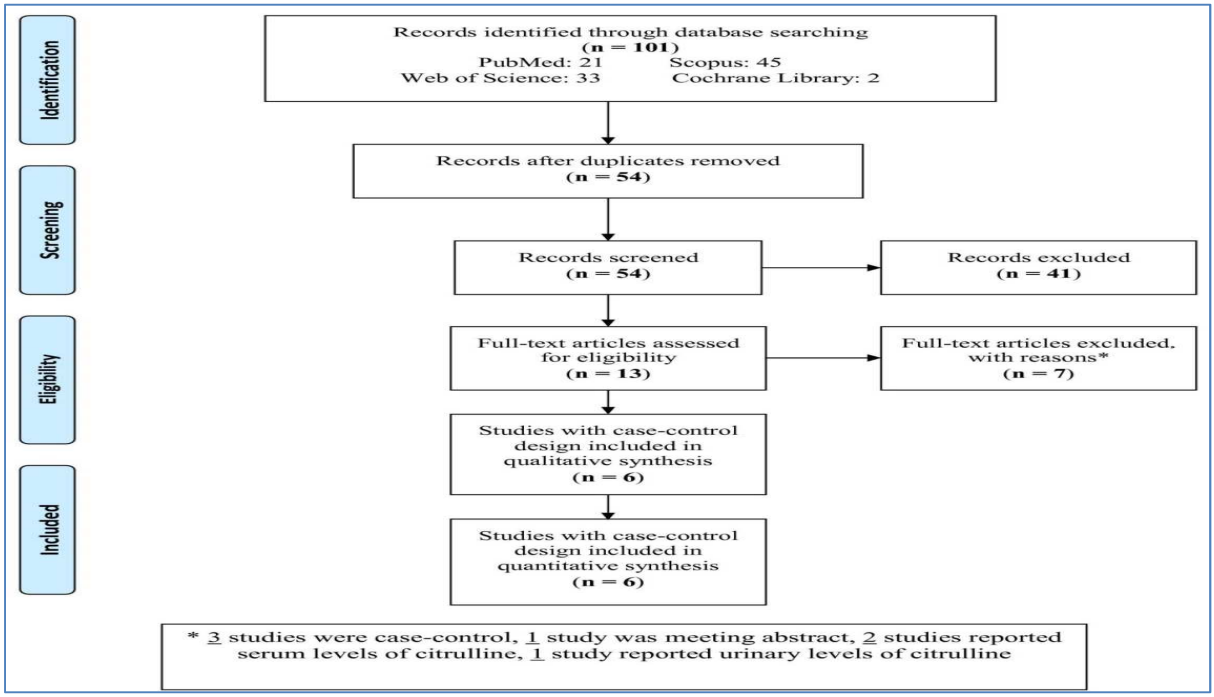

Figure 1: Flow diagram of the study

Table 1: characteristics of the studies included in meta-analysis (n=6)

First author, year	Country	Untreated patients with celiac	Controls	Untreated patients with celiac (Mean age, years/ male %)	Controls (Mean age, years/ Male %)
Crenn, 2003 [9]	France	42	51	42/73	29/47.1
Peters, 2007 [7]	Netherlands	15	21	(45.2/26.7 & 62.3/22.2)	43.7/38.1
Peters, 2008[10]	Netherlands	8	19	(36.6/25 & 64/33.3)	44/42.1
Blasco Alonso, 2011 [11]	Spain	42	46	3.3/48.5	4.9/48.5
Ioannou, 2011[12]	Greece	23	25	6.8/-	7.4/-
Sevinc, 2015 [3]	Turkey	62	62	9.5/63	8.7/50

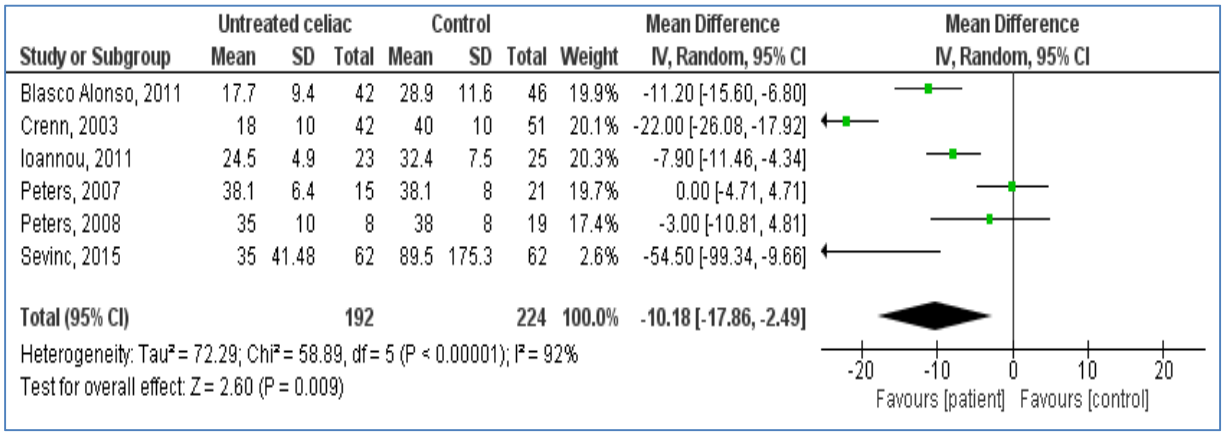

Figure 2: Forest plot of mean difference of plasma citrulline levels of the patients with untreated celiac disease compared with controls

The studies were published from 2003 to 2015 (Table 1). One study was reported from France [9], two from Netherlands [7,10], one from Spain [11], one from Greece [12], and one from Turkey [3]. The studies were included 192 untreated patients with celiac disease and 224 controls. One study [3] reported the data based on median (interquartile range) that change to mean (±SD).

Figure 2 shows the pooled MD of plasma citrulline levels of the patients with untreated celiac disease compared with controls [MD= -10.18 µmol/l; 95%CI -17.86, -2.44; P=0.009, I^2= 92% (P<0.00001)]. The citrulline level in the patients was significantly lower than the controls.

Publication bias

The Begg's and Egger's tests revealed that there was no significant bias between the studies in the subgroup analysis of the plasma citrulline levels of the patients with the untreated celiac disease compared with controls (Figure 4).

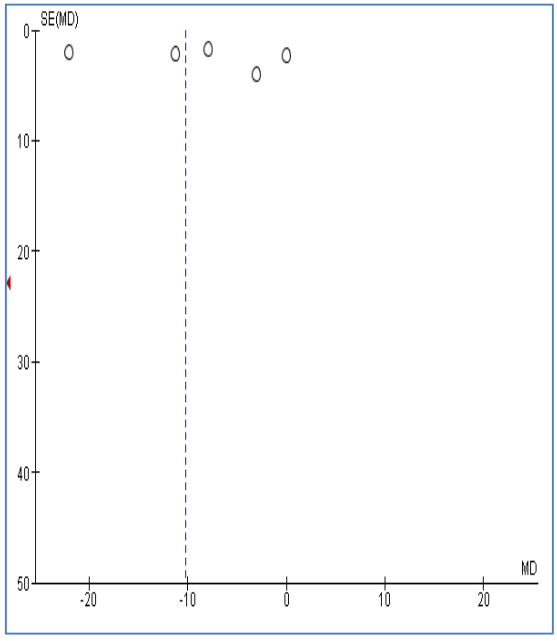

Figure 4: Funnel plot of the studies comparing mean of plasma citrulline levels of the untreated celiac disease compared with the controls

DISCUSSION

The meta-analysis showed that the plasma citrulline level in the patients with celiac was significantly less than the controls. Four studies [3, 9, 11, 12] showed that the plasma citrulline levels in the patients were significantly lower than the controls and two studies [7, 10] were not agreement. Most of these studies involved repeated measurements of fasting citrulline concentrations within the same patient, such as in patients following small intestinal transplantation [13] and patients with small intestinal toxicity following myeloablative therapy [5,14]. Fasting plasma citrulline levels have poor diagnostic accuracy for detection of a decreased intestinal absorption capacity defined by an intestinal energy absorption percentage below 85% [7]. The recent studies showed a relation between the level of plasma citrulline and mucosal damage in the celiac patients [3].

In the majority of cases, a gluten-free diet (GFD) leads to the disappearance of clinical symptoms [15]. Patients responsive to a GFD showed an increase in citrulline concentration of up to 75% of control values, whereas no change in plasma citrulline concentration was noted in unresponsive patients [16].

Papadia *et al.,* [17] reported a quadratic (nonlinear) correlation between fasting plasma citrulline concentration and remnant small bowel length, confirming the results of Crenn *et al.,*[9] Decreasing the plasma citrulline level in patients with non-celiac disease small bowel villous atrophy– associated diseases was similar to that in patients with celiac disease, with the same severity and extent of histologic mucosal lesions. This level associated with the severity and extent of villous atrophy [9]. The researchers reported an absence of correlation of citrulline values and degree of the intestinal mucosa [7,17]. But one study [9] showed that in a non-surgical clinical setting, citrulline concentration is reduced in a series of villous atrophy associated small bowel diseases in which it correlates to the severity and extent of lesions. Plasma citrulline is a theoretical marker of villous atrophy [11]. Generation of citrulline was delayed in patients with small intestinal villous atrophy from untreated celiac disease to refractory celiac disease, consistent with the assumption of a gradual decrease in enterocyte mass in these groups [10]. An oral bolus of alanine–glutamine induces a time-dependent rise on plasma citrulline level to an extent dependent on the existence of villous atrophy or enterocyte hyperplasia in celiac disease and might offer a new possibility to evaluate the functional capacity of the enterocyte [10].

Limitations

1) A low number of the studies. 2) There were different bowel diseases with celiac disease. 3) Different between age range and percentage of sex in the studies.

CONCLUSION

Measurement of plasma citrulline levels can be as a diagnostic marker of celiac disease and also for the evaluation of the initial response to a GFD. It needs to more studies in the future with controlling age, sex, and other connected diseases.

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