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Consequential Effect of Gluten-Free Diet on Health-Related Quality of Life in Celiac Populace-A Meta-Analysis

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Abstract

Globally, celiac disease (CD) affects around 1-2% of the population. Gluten elimination becomes the cornerstone treatment and is also being followed by non-celiac as a healthy dietary habit. However, there is lack of sustainable evidence to understand this view. Adherence to gluten-free diet (GFD) rendered a few to reduced quality of life. Hence, a meta-analysis has been performed to determine interaction of GFD and Health-related Quality of Life (HRQoL). NCBI/MEDLINE, PubMed, Cochrane Library, Google Scholar and Science Direct were combed from date of inception to October 30, 2018 for studies assessing the effect of GFD using validated questionnaires on HRQoL a) between healthy controls and celiac patients b) dietary adherence to GFD in celiac subjects. Random effect model was used for meta-analysis. Twenty-five studies comprising 5148 CD subjects fit in the inclusion criteria. GFD had moderate significant association with HRQoL, for PGWB odds ratio's (OR) 0.613 [95% CI, 0.449-0.837], SF-36 Mental Component Score (MCS) 0.026 [95% CI, 0.011-0.060], Physical Component Score (PCS) 0.066 95% [CI, 0.032-0.138]. Partial adherence to GFD had lower quality of life when compared to strictly adherent patients for OR's SF-36 MCS 5.080 [95% CI, 1.885- 13.692], PCS 3.204 [95% CI, 1.579- 6.503] and CDQoL 2.439 [95%CI (1.724- 3.450)]. The results implied moderate significant association between GFD and HRQoL and better compliance leads to favourable HRQoL.

Article History

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Keywords

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Introduction

Celiac Disease (CD) is an autoimmune inflammatory enteropathy affecting globally around 1-2% of individuals in which women are more susceptible as compared to men,[1] distinguished by continual gluten intake intolerance in genetically predisposed populace. The gene alleles HLA DQ2 and/or HLA DQ8 and the ingested gluten interaction in CD patients provoke an abnormal mucosal immune response causing villous atrophy. A complex interplay among specific genes, environmental factors and gluten is necessary for CD to develop as not everyone who is genetically predisposed will develop the disease.[2] Of late, the world has awakened to the severity and complexities arising due to CD. Researchers have suggested that α-gliadin (component of gluten and rich in glutamine) is the main causative agent that leads to the immune response.[2,3] Owning to its chronic nature, there are histological alterations in the small bowel leading to nutrient malabsorption, psychological stress, social and family tribulation, capital strain and restrictions on different life decisions.[4,5] The dire consequences of these can be observed on the Health-related Quality of Life (HRQoL) as well. The only treatment is life-long withdrawal of gluten and a fundamental and perpetual transformation in dietetic habits.

HRQoL measures the health impact on the quality of life of people. It is a multi-dimensional concept encompassing subjective evaluation of physical, psychological and social functioning as well individual's well-being.[6,7] Analysis of HRQoL helps to measure the burden a chronic disease like CD has and provides insights between HRQoL and risk factors. Different questionnaires such as SF-36, PWGB and CDQoL are means to evaluate and quantify HRQoL in CD patients. SF-36 and PGWB are generic questionnaires which measure the functional status and psychological well-being.[8] Specific disease-related questionnaires (CDQ and CDQoL) are developed and validated for CD patients.[1,5] These questionnaires assess self-apprehended health-related welfare of the individuals. The dietary habits of celiac patients and adherence to gluten-free diet (GFD) are the main factors associated with HRQoL. Many studies have shown that complete and permanent exclusion of gluten helps to relieve the symptoms and has positive effect on HRQoL.[9–11] However, it is not surprising that strict GFD may aggravate the complexities in the patient's life and deters their quality of life. Various surveys conducted show that an extreme vigilant GFD leads to restrictive travelling, social boundaries, anxiety and fatigue.[1,12]

Thus, studying the HRQoL aspects of CD patients gives relevant knowledge about the disease's impact and its outcome can help the different food disciplines and medical services to adapt with each another. With remarkable progress in the percentage of aware consumers and increasing demand for health foods, there is a need to stress on studies that will assist to identify and set public policies, strategic plans and food standards for gluten-free products. Besides being gluten-free, products need to influence celiac patients emotional and social fears and worries, relieve economic burden and thus, elevate their quality of life. Being a rapidly growing disease and new data emerging regularly, a meta-analysis evaluating the effect of GFD and degree of adherence to diet on HRQoL of celiac patients becomes consequential.

Methodology

The present systematic review and meta-analysis were governed as per the guidelines of preferred reporting items for systematic reviews and meta-analysis (PRISMA).

Search Strategy

Varied databases including NCBI MEDLINE / PubMed, Cochrane library, google scholar and science direct were searched from their genesis until October 30, 2018 employing amalgamation of keywords: "celiac disease", "coeliac disease/ therapy", "diet, gluten-free", "glutens", "quality of life", "questionnaires" and "well-being" without any language preferences. The search was further extended with following terms: coeliac sprue, gluten sensitive enteropathy, health-related quality of life and HRQoL. The full search phrases are presented in Table 1. In addition, bibliographies were explored from the included papers to identify additional eligible articles.

Table 1: Keywords used for identification of articles for inclusion in meta- analysis[1]

1.	"Celiac Disease"
2.	"Coeliac Disease/Therapy"
3.	Diet, Gluten-Free
4.	"Glutens"
5.	"Quality of Life"
6.	"Questionnaires"
7.	"Well-Being"
8.	(#1 And #2), (#1, #2 And #3), (#1, #2, #3 And #4), (#1, #2, #3, #4 And #5), (#1, #2, #3, #4, #5 And #6), (#1, #2, #3, #4, #5, #6 And #7), (#1, #2, #3, #4, #5, #6, #7 And #8)

Selection Criteria

This meta-analysis included studies with the following criteria (1) original research work; (2) assessed HRQoL using validated questionnaires; (3) confirmation of CD using tissue sample; (4) collate HRQoL in celiac as well normal populace, prior to and subsequent introduction of GFD or among subgroups. The exclusion criteria included (1) inference devoid of GFD or; (2) absence of full-length paper; (3) studies reported without control group. The studies evaluating HRQoL using disease specific Celiac Disease Quality of Life (CDQoL)[13] or generic Short-Form 36-Item Health Survey (SF-36)[14] and Psychological General Well- Being (PGWB) Index[15] were included. The statistical summary of the included studies encompassed either mean score with standard deviation or standard error, confidence intervals or ranges, or median scores along with their ranges or interquartile ranges. Two reviewers (SR, SK) evaluated abstracts and disparities were rectified in concordance with other reviewers (SC, TJ).

Data Extraction

The included articles were rigorously examined. Extracted data included author's names, year of publication, region, age, HRQoL assessment instruments along with number of celiac patients and healthy controls (Table 2a & 2b).

Statistical Analysis

The mean and SD scores were obtained for CD patients and healthy controls along with measure for degree of adherance to GFD. Odds ratio and its 95% CI [UL, LL] has been used to sum up the difference of various identified parameters. The Z-score denoted the overall effect size obtained by odds ratio. The Z-score with a $p \leq 0.05$ was statistically significant. I2 statistics determined the heterogeneity across studies. To understand the cause of heterogeneity, a one-study remove sensitivity analysis was conducted.[34,35] Funnel plot represented the publication bias. Comprehensive Meta-analysis Version 3.3.070, USA was used for the analyses.

Results

Literature Search

The literature search retrieved 286 related citations of which 44 articles were non-human models. Two hundred eleven articles were excluded due to different reasons discussed in Fig 1. Only 31 full text articles were screened for eligibility of which 25 articles were included in the meta-analysis. The included studies were from duration 2002 to 2018.

HRQoL of CD patients and healthy controls were determined using SF-36 and PGWB questionnaire. PGWB index revealed an overall life quality whereas SF-36 questionnaire threw distinct light on both emotional and physical aspect of quality of life among CD patients. Eight studies with 2252 CD patients and 952 healthy control using Psychological General Well- Being (PGWB) Index provided prospective data on HRQoL. From the forest plot (Fig 2), it is evident that gluten free diet has moderately affected the HRQoL with ORs[95%CI] 0.613 [0.449-0.837] with p=0.002 and moderate heterogeneity (I^2) was reported i.e. 73.08%.

Table 2: (a) Characteristics of studies examining impact of gluten-free diet on health-related quality of life in celiac patients and healthy controls

S. No.	Study	Age		Continent	Case Patients			Control			Assessment Criteria
		Case	Control		N	Male	Female	N	Male	Female	
1.	Kivelä *et al.,* 2018[16]	NA	52	Europe	236	163	73	110	21	89	PGWB
2.	Paarlahti *et al.,* 2013[17]	50	52.25	Europe	596	452	144	110	21	89	PGWB
3.	Paavola *et al.,* 2012[18]	52.62	52.25	Europe	97	369	466	110	21	89	PGWB
4.	Vilppula *et al.,* 2011[19]	62.5	NA	Europe	35	15	20	110	21	89	PGWB
5.	Ukkola *et al.,* 2011[20]	50.04	51.5	Europe	698	225	473	110	21	89	PGWB
6.	Kurppa *et al.,* 2010[21]	45	49	Europe	73	58	15	110	21	89	PGWB
7.	Roos *et al.,* 2006[22]	54.5	54.5	Europe	51	30	21	182	78	104	PGWB
8.	Viljamaa *et al.,* 2005[23]	37.37	51.5	Europe	97	62	35	110	21	89	PGWB
9.	Nunes-Silva *et al.,* 2017[24]	38	36.8	South America	15	12	3	15	12	3	SF-36
10.	Paavola *et al.,* 2012[18]	52.62	49	Europe	466	97	369	2060	865	1195	SF- 36
11.	Tontini *et al.,* 2010[25]	39	39	Europe	33	23	10	66	NA	NA	SF-36
12.	Nachman *et al.,* 2010[26]	38	42	South America	53	5	48	70	15	55	SF-36
13.	Nachman et al., 2009[27]	38	42	South America	132	113	19	70	15	55	SF-36
14.	Usai *et al.,* 200728	38.7	38.4	Europe	129	101	28	526	126	400	SF-36
15.	Hauser *et al.,* 2006[29]	49.25	47.7	Europe	346	100	446	2443	1085	1358	SF-36
16.	Johnston *et al.,* 2004[30]	48.8	50.25	Europe	32	9	23	49	15	34	SF- 36
17.	Fera *et al.,* 2003[31]	40.4	41	Europe	100	75	25	100	32	62	SF-36
18.	Usai *et al.,* 2002[32]	46	47	Europe	54	15	68	136	28	112	SF-36

Table 2 (b) Characteristics of studies examining the impact of adherence to gluten-free diet on health-related quality of life in celiac patients

S. No.	Study	Age	Continent	Strict Adherence	Partial Adherence	Assessment Criteria
1.	Zysk *et al.,* 2018[4]	36.75	Europe	185	66	CDQ
2.	Pratesi *et al.,* 2018[9]	NA	South America	399	51	CDQoL
3.	Wolf *et al.,* 2018[1]	33.2	North America	19	61	CDQoL
4.	Taghdir *et al.,* 2016[5]	11.3	Asia	35	30	CDDUX
5.	Casellas *et al.,* 2015[7]	39.3	Europe	251	100	CDQoL
6.	Aksan *et al.,* 2015[11]	31.1	Asia	143	62	CDQ
7.	Nachman *et al.,* 2010[26]	38	South America	27	26	SF-36
8.	Nachman *et al.,* 2009[27]	38	South America	59	25	SF-36
9.	Hopman *et al.,* 2009[33]	40.83	Europe	33	20	SF-36
10.	Usai *et al.,* 2007[28]	38.7	Europe	80	49	SF-36
11.	Usai *et al.,* 2002[32]	46	Europe	39	27	SF-36

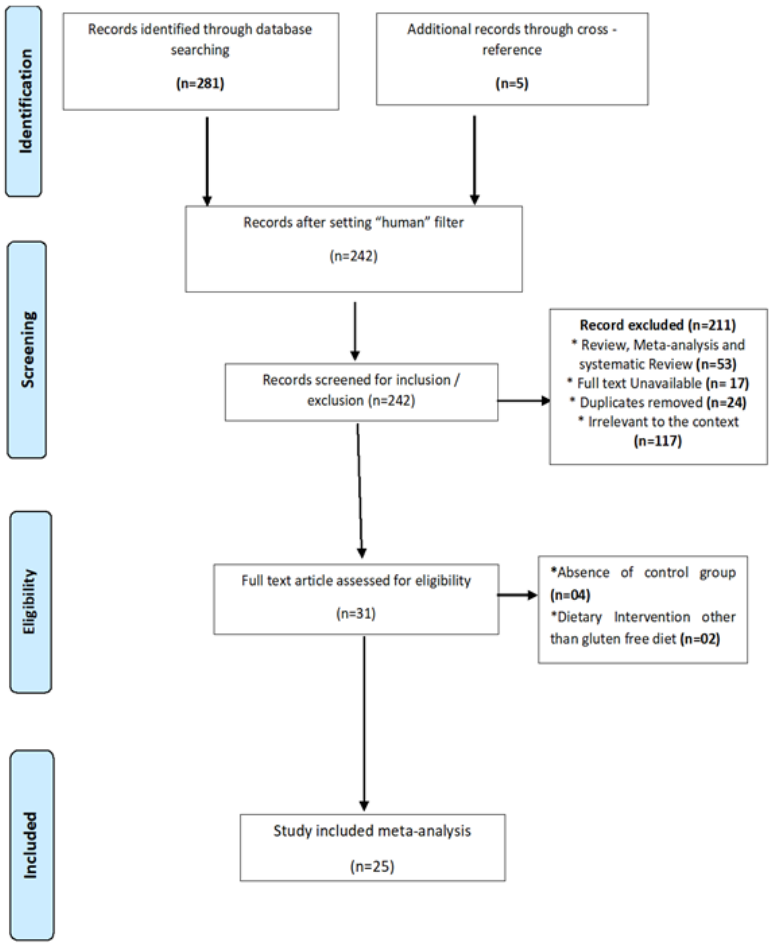

Fig. 1: Schematic representation of study selection process[3]

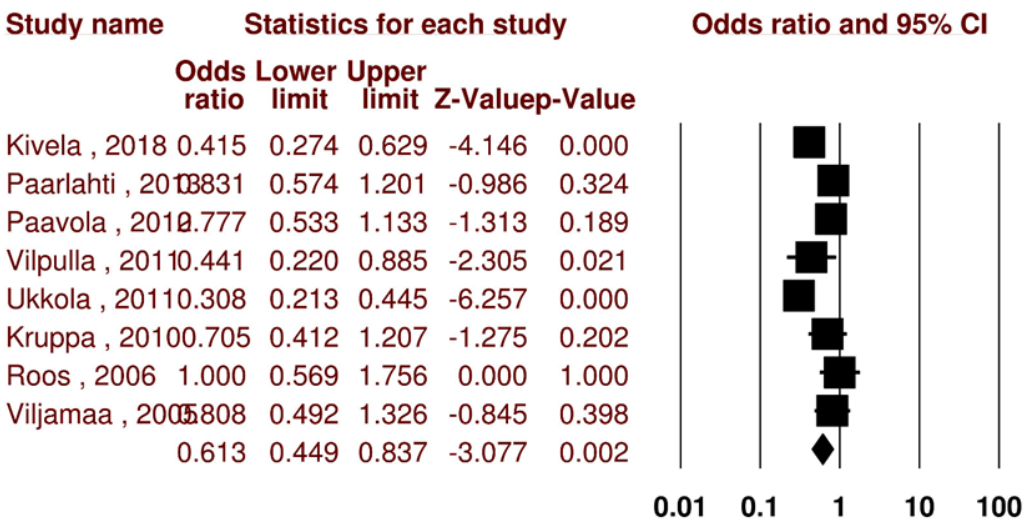

Fig. 2: Forest plot representing effect of Gluten Free Diet on HRQoL in CD Patients versus Non-celiac Controls using PGWB questionnaire[4]

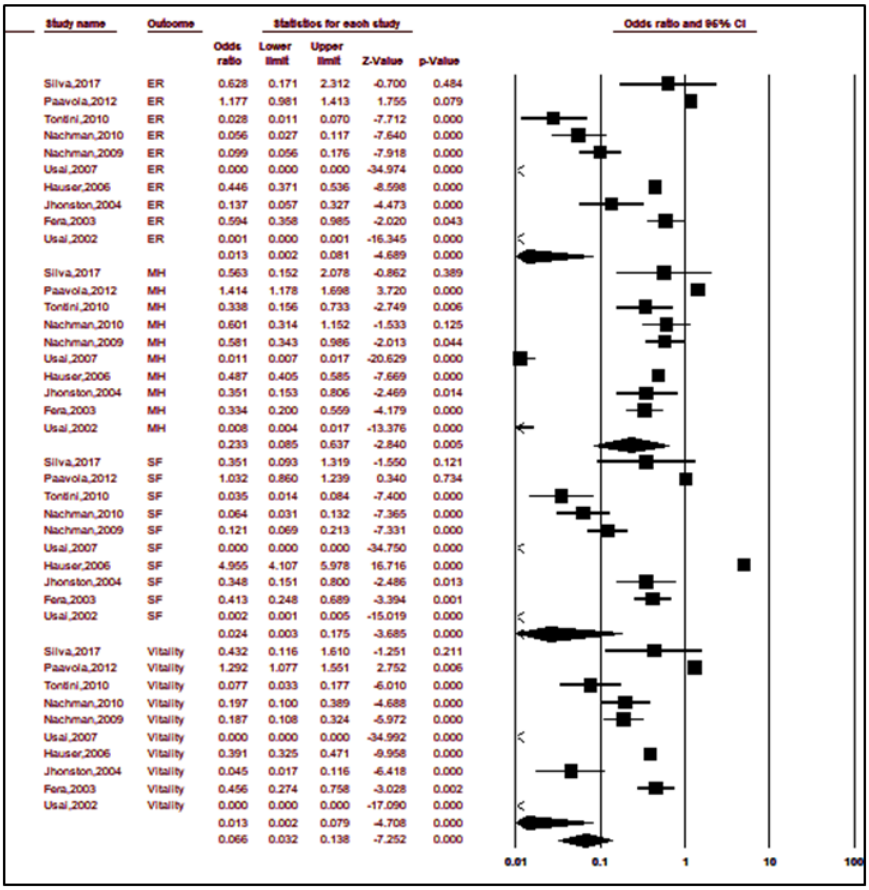

Fig. 3 (a) Forest plot representing effect of Gluten Free Diet on HRQoL (MCS) in CD Patients versus Non-celiac Controls using SF-36 questionnaire

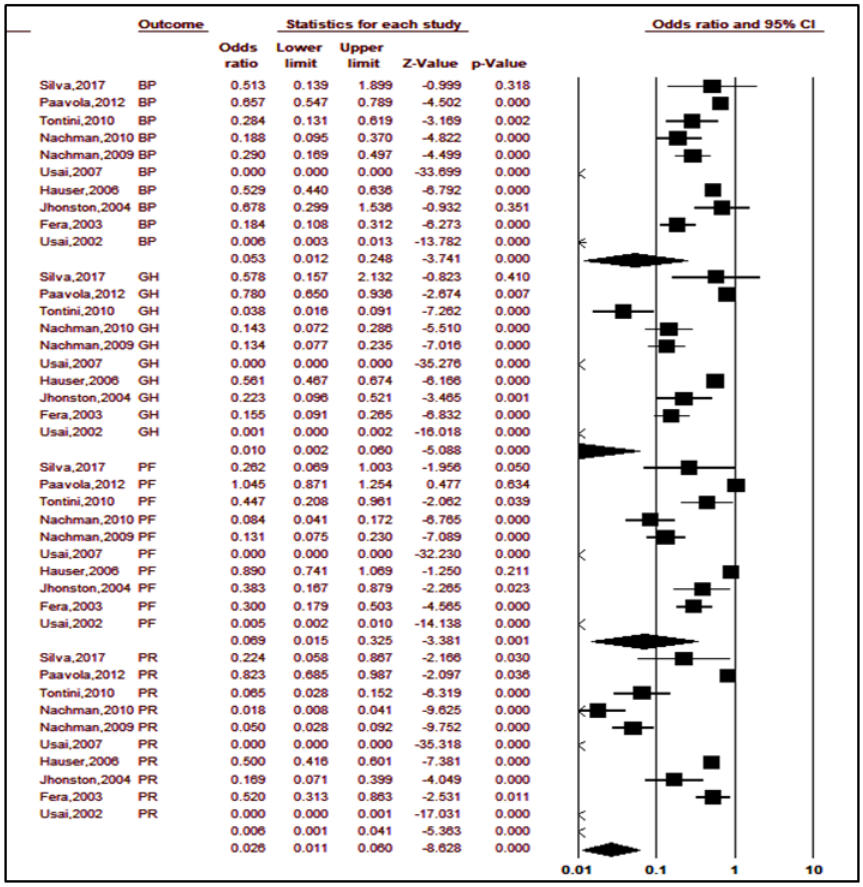

Fig. 3 (b) Forest plot representing effect of Gluten Free Diet on HRQoL (PCS) in CD Patients versus Non-celiac Controls using SF-36 questionnaire[5]

Similarly, Short-Form 36-Item Health Survey (SF-36) provided prospective data using ten studies with 1491 CD patients and 5517 non-celiac controls on HRQoL. SF-36 analyses both the physical component score (PCS) and mental component score (MCS). From the ORs, it is can be stated that gluten free diet has not affected the HRQoL. The ORs [95%CI] of emotional quality and physical quality was found to be 0.066 [0.032-0.138] and 0.026 [0.011-0.060] with p<0.001 respectively showing non-significant effect on quality of life. High heterogeneity (I2) 77.85% was reported among both the parameters (Fig 3a & Fig 3b).

Effect of Dietary Adherence on Celiac Disease Patients

Based on eleven studies, in total 1852 patients, we found that HRQoL is significantly affected based on dietary adherence. The study analysed the effect of complete and partial adherence of GFD on CD patients. Six studies using CDQ, CD-QoL and CDDUX questionnaire with 1032 patients completely adhering to GFD and 370 partially adhering to GFD were analysed together. It has been reported that strict diet adherence has more significant impact on quality of life ORs (95% CI) 2.439 (1.724 – 3.450) with p = 0.004 and heterogeneity (I^2) was reported to be 50.48% (Fig 4). However, for SF-36 questionnaire strict diet adherence has more impact on emotional well-being as compared to physical well-being. The reported ORs (95% CI) of emotional well-being was 5.080 (1.885 – 13.692) with p-value 0.001 whereas the ORs (95% CI) of physical well-being was reported to be 3.204 (1.579-6.503) with p-value 0.001 and the heterogeneity (I^2) was found to be 78%.

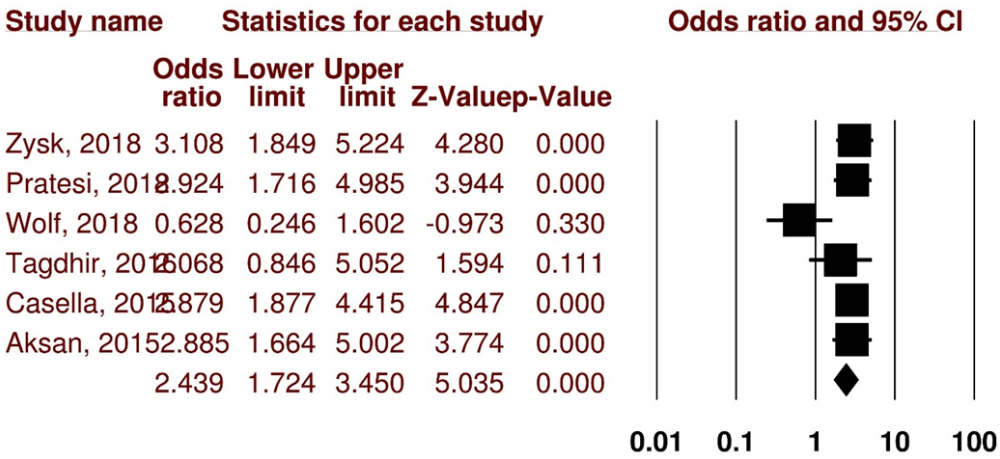

Fig. 4: Forest plot representing effect of dietary adherence on HRQoL of celiac patients[6]

Publication Bias and Sensitivity Analysis

For different studies used, publication bias was separately evaluated. Funnel plot confirmed the biasness. The illustration of publication bias in PGWB questionnaire is given in Fig 5. Egger's regression test confirmed the biasness between the studies ($p < 0.05$). The studies having greater average effects are published commonly leading to upward bias. Sensitivity analysis was done by omitting each study at a time without changing the overall statistical significance, thereby, establishing the stability and credibility of this meta-analysis.

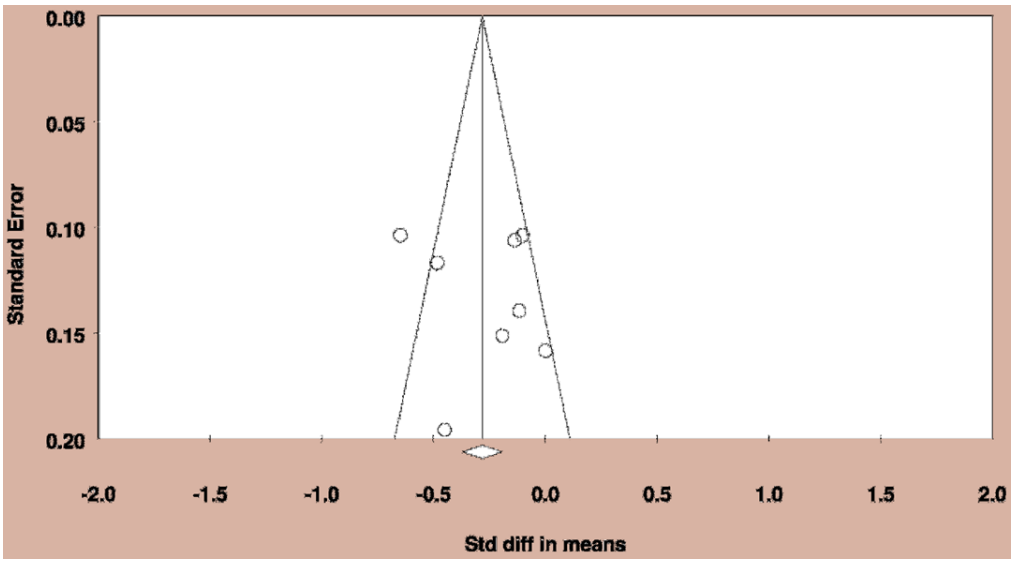

Fig. 4: Forest plot representing effect of dietary adherence on HRQoL of celiac patients[6]

Discussion

The present study highlights the effect of GFD on HRQoL in CD as well in non-celiac healthy controls. Further, we studied the HRQoL in celiac populace while adhering to GFD.

The meta-analysis involved a total of 25 studies, 15037 healthy subjects and 5144 celiac patients. The effect of GFD in healthy versus CD patients in terms of their quality of life was compared using PGWB and SF-36 questionnaires. The results for

both PGWB & SF-36 questionnaire indicates that gluten-free diet doesn't have normalizing effect on HRQoL. Our results are in agreement with previous reports[16,29,31] of GFD incompletely improving HRQoL in celiac populace. It can be attributed to the poor nutritional quality of the GF food products. They are generally high in fat and calories and deficient in important protein, vitamins, minerals, calcium and iron.[36–38] Moreover, the poor nutritional status can be attributed to the malabsorption of nutrients owed to the anomalies of the small intestinal mucosa of the patients.[39]

Indeed, the GFD alleviates the symptoms and leads to mucosal healing in patients but the socioeconomic and emotional stress counter-weights these positive effects. The profound challenges the patients face emotionally as well as psychologically cause stress to the individuals thus, disturbing their social relationships; worsening the quality of life. Accordingly, following a GFD will lead to nutritional disturbances among celiac patients as well in normal populace.

Further to this, we assessed the impact of GFD adherence on HRQoL in celiac populace using CDQoL and PGWB questionnaires. It was found that strict adherence to GFD reduces the symptoms in CD subjects helps in normalizing their quality of life. Interestingly, significant difference was observed in the odds ratio between strict compliance versus partial or no compliance [CDQoL- 2-439. 95%CI (1.724- 3.450); SF- 36 MCS- 5.080, 95% CI (1.885- 13.692), PCS- 3.204, 95% CI (1.579- 6.503)]. Previous studies and meta-analysis have consistently found an association between poorer GFD adherence and low quality of life.[4,6,7,9] Poor compliance to GFD can result in relapse of symptoms on consumption of gluten resulting in poorer quality of life.

A key importance of our study is that it bears clinical relevance. CD is a globally prevalent disease and our study indicates possible outcome of GFD on HRQoL. This outcome can aid the clinicians and researchers to devise strategic plans which will improve the quality of gluten-free foods, bear less economic and social stress on CD subjects thus ameliorate their quality of life. Additionally, we have compiled the maximum available evidence on HRQoL, thereby summarizing its current state. The study has its limitations, with lack of separately published sub-groups data it becomes difficult to interpret the effect various defining factors like gender, age, age of diagnosis on CD patients. Different risk factors that negatively affect the HRQoL needs to be further analysed.

Conclusion

GFD is a necessity for a small percentage while a choice for a wider group of people. It has become a health fad among the health enthusiasts. But further studies need to be conducted to analyse the nutritional benefits of it. In line with the present study, we can draw the conclusion that although GFD moderately improves but does not significantly harmonize the HRQoL in CD patients as compared to non-celiac. A strict compliance to the diet is an important determinant of HRQoL in CD patients. Designating a nutritionist for educating as well as support of family and friends can help to promote the quality of life.

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Conflict of Interest

The authors do not have any conflict of interest.

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