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Original Research Article

The effect of gluten-free diet on mean platelet volume levels as a short-term follow up biomarker in biopsy proven celiac disease patients and its comparison with IgA-tissue transglutaminase antibody levels

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ABSTRACT

Background: Celiac disease is an autoimmune disease for which there is a known environmental trigger i.e., gluten. Adherence to gluten-free diet is the mainstay of treatment.
Methods: This observational prospective study was conducted in the Department of Paediatrics, SP Medical College, Bikaner between August 2020 to August 2021. Newly diagnosed celiac disease patients below 14 years of age were included in the study excluding patients with any associated co-morbid conditions like Diabetes, Hypertension and Hypothyroidism. IgA-tTG titre and complete blood counts were performed at the time of diagnosis, and repeated after 3 months of strict gluten-free diet. The collected data were coded, tabulated and analysed. P values < 0.05 were statistically significant.
Results: The mean IgA-tTG decreased from 116.28 at the time of diagnosis to 50.98 after 3 months of the gluten-free diet (p = <0.001). Also, the mean MPV decreased from 9.58 to 9.19 and the change was statistically significant (p = 0.032). When two biomarkers i.e., MPV and IgA-tTG were compared as being better biomarkers for the gluten-free diet, a weak positive correlation was observed but was not statistically significant (p = 0.212).
Conclusions: This study showed that Mean Platelet Volume (MPV) levels can be used as a short-term biomarker to check adherence to the gluten-free diet.

Keywords: Autoimmunity, Celiac disease, Gluten-free diet, MPV

INTRODUCTION

Celiac disease (CD) is an autoimmune disease that develops in patients with a genetic predisposition. It has a multifactorial inheritance, including genetic and environmental factors with a global prevalence of around 1%.[1] A genetic factor is identified in the major histocompatibility complex region while an environmental trigger is represented by gluten in diet.[2] The reason for its under-recognition is mainly because about 50% of the affected people do not have the classic gastrointestinal symptoms, rather they present with nonspecific manifestations of nutritional deficiency or no symptoms at all. Typical cases of celiac disease are diagnosed because of obvious gastrointestinal symptoms including diarrhoea and abdominal pain, etc.[3] Those cases that usually show atypical, minimal or even absent symptoms remain undiagnosed and are represented by the submerged part of an iceberg. It's a disease known to occur in all age groups, but only in individuals with

genetic susceptibility and carrying the HLA-DQ2 and/or HLA-DQ8 alleles. It is characterized by the production of specific auto-antibodies, a wide variety of clinical signs/symptoms and a spectrum of histological changes in the duodenal mucosa. The sole presence of the predisposing HLA-DQ genes is not sufficient for disease development.[4,5] High-risk subjects include children or adults with celiac disease-associated symptoms (i.e., diarrhoea, abdominal pain and constipation), relatives of patients with already diagnosed celiac disease, children or adults with celiac disease-associated disorders and other co-existing inflammatory or genetic disorders (i.e., DM Type 1).[6]

Celiac disease is the only autoimmune condition for which there is a known environmental trigger i.e., gluten.[7] Wheat, rye and barley damage the small intestinal mucosa of a patient with celiac disease while maize and rice are harmless.[8,9] The effect of a diet containing oats is uncertain and controversial in various studies.[10,11] The elimination of gluten from the diet (gluten free diet) intake is the main therapeutic approach and usually leads to symptomatic, serologic, and histological remission.[12,13] Dietary history assessment and measurement of serum antibodies are two non-invasive means of compliance measurement while invasive ways include endoscopic and histologic criteria. The barrier to compliance includes the poor portability of gluten-free foods, confusing food labelling practices, and common co-morbid psychological burdens such as anxiety and depression. Elimination of gluten from the diet also reduces the chances of a rare but serious complication of celiac disease- Lymphoma.[14] Diagnosis of celiac disease is based on anti-tissue transglutaminase antibody levels and confirmed by endoscopic duodenal biopsy of the involved part of small intestine. Serological tests are preferred first-line tests as they are highly sensitive, cheap and easily accessible. Although biopsy is considered a gold standard test, it has many disadvantages as its an invasive, expensive and skill-oriented test with a high subjective variation.

MPV(Mean Platelet Volume) is the measure of the size of the platelets, it increases in thrombopoietic stress response. Also, inflammation induced platelet activation can be measured with MPV, thereby showing their role as an inflammatory indicator. Recently, MPV is recognised as an inflammatory biomarker in various conditions like myocardial infarction, acute pancreatitis, and ulcerative colitis.[16,17] Increased MPV levels were determined in diseases such as myocardial infarction, acute ischaemic stroke and diabetes mellitus with an association between increased MPV and disease severity. In contrast, in cases with active rheumatoid arthritis and ankylosing spondylitis, decreased MPV levels have been reported.[17,18] As MPV detects only inflammation of any cause, there is a possibility that any concomitant gastrointestinal illness or any pathogenic inflammation causing acute diarrhoea can lead to false results. MPV is a marker of inflammation, and changes when inflammation subsides, whereas tTg being an immune marker takes longer time to reach the baseline levels.

Being a cheap and easily available test in primary care setups, this study aims to assess MPV as an inflammatory biomarker for short-term follow-up in celiac disease patients. This study is intended to compare MPV with traditional tTg assay in Indian children, for monitoring dietary compliance of a gluten-free diet (GFD) in celiac disease to assess the correlation between these two biomarkers.

METHODS

This hospital-based observational and prospective study was conducted in the Department of Pediatrics, Sardar Patel Medical College and A.G. Hospitals, Bikaner, Rajasthan, from August 2020 to August 2021. Approval from the institutional ethical committee and informed consent from the subject's parents or their legal relatives were obtained.

This study included newly diagnosed biopsy-proven cases of celiac disease below 14 years of age. CD patients with oncological, haematological, autoimmune, and hepatic diseases, with accompanying acute/chronic infection, steroid use, having coexisting diabetes mellitus or hypothyroidism were excluded from the study.

Endoscopic upper gastrointestinal system examination was performed on children with clinically suspected CD and positive tissue transglutaminase values. The diagnosis was based on a pathological examination of endoscopic D2 biopsy specimens. The Celiac Disease's severity was graded histologically by the modified Marsh classification (MARSH) in newly diagnosed individuals. Detailed medical history was obtained from subjects or their parents regarding any chronic diseases, previous hospitalisation or any long-term medications such as glucocorticoids, L-thyroxine, insulin, etc. so that they can be excluded from the study. IgA- tTG titre and complete blood counts were performed in newly diagnosed patients at the time of diagnosis, and repeated after 3 months of strict gluten-free diet.

All patients were subjected to complete history taking including age, sex, symptoms, any family history of similar disease, dietary intake, endoscopic biopsy graded by MARSH classification. IgA tissue transglutaminase antibody titre was performed on a robotic Elisa Analyser through the ELISA technique considering a range of 0-7 IU/L to be normal and abnormal > 7 IU/L.

A sample size calculation (Power of study=80.00%) and Sample Size Calculation by MEDCALC 16.4 version software) showed that 18 patients were required, based on study conducted by Mohanaraj Ramachandran et al. It is round of 45 patients for present study expecting approx.30% drops out. Power of study =80%, allowable error=5% Using the formula:

$$N = [(4\sigma^2)(Z(1-(\alpha/2)) + Z(1-ß))^2] \div E^2$$

Statistical analysis

A pre-structured pre-tested proforma was used to collect the required information from eligible patients. Data were coded and recorded in MS Excel spreadsheet program. SPSS version 26 was used for data analysis. Descriptive statistics were elaborated as means/ standard deviations for continuous variables and frequencies and percentages for categorical variables. Data were presented graphically wherever appropriate for data visualization. Normally distributed continuous data were compared using the Independent Student t-test. For categorical variables, the Chi-square test was used. A value of $p<0.05$ was considered statistically significant.

RESULTS

Among 45 celiac disease patients studied, the mean age (in years) was 8.02 ± 3.72. The variable age was not normally distributed (Shapiro-Wilk Test: p = 0.003). The maximum number of patients 18 (40.0%) came under the 5- 10 years category (Table 1). Out of total 45 patients, 64.4% (29) of the participants were male and 35.6% (16) were female, 12 were < 5 years old (Table 2). 51.1% (23) patients presented with Typical Presentation (GI Symptoms), while a significant 48.9% (22) patients presented with Atypical features (other than GI Symptoms) (Figure 1).

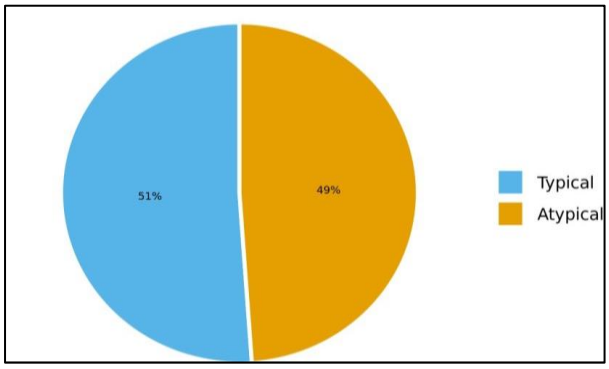

Figure 1: Distribution of type of presentation.

Out of 45 patients, abdominal pain was the most common symptom presented in 51.1% (23) of patients. Fatigue was the second most common symptom in 15 (33.3%) patients. Abdominal distension, diarrhoea and constipation were observed in an equal number of patients i.e., 9 (20.0%). Other presentations included Vomiting, Irritability, Fever and Decreased appetite which were present in 10 (22.2%), 9 (20.0%), 5 (11.1%), and 4 (8.9%) patients respectively. 34 (75.5%) patients had anaemia, 22 (50.0%) patients had short stature, and 4 (8.9%) had hepatitis (Table 3).

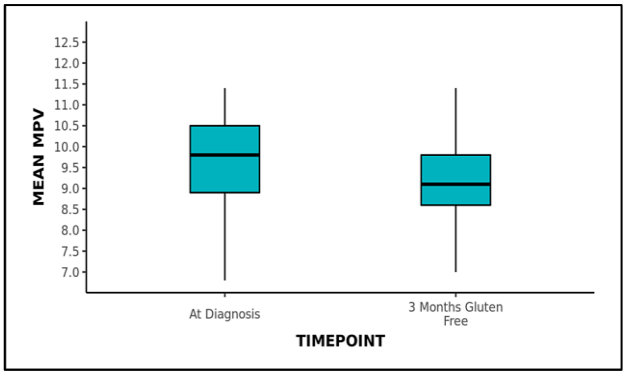

Figure 2: MPV Trend over time.

Table 1: Distribution of patients according to age.

Age	No. of Patients	Percentage
< 5 years	12	26.7%
5-10 years	18	40%
>10 years	15	33.3%

Table 2: Distribution of patients according to gender:

Gender	No. of Patients	Percentage
Male	29	64.4%
Female	16	35.6%

Table 3: Summary of presenting complaints-

Presenting complaints	No. of patients
Abdominal distension	9 (20.0%)
Abdominal pain	23 (51.1%)
Diarrhoea	9 (20.0%)
Vomiting	10 (22.2%)
Irritability	9 (20.0%)
Constipation	9 (20.0%)
Fatigue	15 (33.3%)
Fever	5 (11.1%)
Decreased appetite	4 (8.9%)

The mean IgA-tTG (at diagnosis) was 116.28±136.36 while a significant decrease in mean was noted to 50.98±69.31 after 3 months of gluten-free diet. This change was statistically significant (Wilcoxon Test: V = 913.5, p = <0.001). Parametric tests were used to make a statistical inference as data were normally distributed. Paired sample t-test was used to explore the difference in MPV at the two-time points (Table 4).

The mean MPV decreased from 9.58 at the time of diagnosis to 9.19 after 3 months of gluten- free diet. This change was statistically significant (Paired t-test: t = 2.2, p = 0.032). Box-and- Whisker plot depicts the distribution of MPV over different points of time. In each box, the middle horizontal line represents the median MPV, the upper and lower bounds of the box represent the 75th and the 25th centile of MPV respectively, and

the upper and lower extent of the whiskers represent the limits for MPV at each of the timepoints respectively (Figure 2).

Table 4: Comparison of change in IgA-tTG and change in MPV over time.

Timepont	IgA-tTG (Mean SD)	P value	MPV (Mean SD)	P- value
At diagnosis	116.28 (136.36)	<0.001	9.58 (1.10)	0.032
3 months Gluten- free	50.98 (69.31)		9.19 (1.09)	

DISCUSSION

In our study, abdominal pain was present in 51.1% (23) patients which was observed to be the most common clinical presentation, the second commonest being fatigue in 33.3% (15). There was an equal number of patients presenting with chronic diarrhoea and constipation i.e. 20% (9), thereby necessitating the need for serological testing for celiac disease in constipated patients too along with diarrhoea. In our study, out of 45 participants, 64.4% (29) of the participants were male. Poddar et al reported male to female ratio to be 3:2 which showed a similarity with our study.[19]

The mean MPV decreased from 9.58 at the time of diagnosis to 9.19 after 3 months. This change was statistically significant (p = 0.032). Therefore, MPV can be used as a surrogate biomarker for adherence to gluten-free diet. Purnak et al stated a significantly higher mean platelet volume (MPV) in the CD group compared with healthy subjects.[20] Contrary to this, Bolat et al showed no significant association between MPV and celiac disease.[21] Kapsoritakis et al in his study observed a significant decrease in MPV was noted in patients with CD compared with healthy controls (P <0.001), but a statistical difference was not found between active and inactive CD groups.[16] Hence, stated MPV as a controversial biomarker of inflammatory pathology.

In our study, the mean IgA-tTG decreased from 116.28 at the time of diagnosis to 50.98 after 3 months gluten-free time period. This change was statistically significant (p = <0.001). When two biomarkers i.e. MPV and IgA-tTG were compared as better biomarkers for the gluten-free diet, a weak positive correlation between change in MPV (3 months gluten-free) and change in IgA-tTG (3 months gluten-free) was observed, and this correlation was not statistically significant (rho = 0.19, p = 0.212). This observation was also supported by Ramachandran et al stating that pre-and post-GFD values of tTg had a good correlation of r = 0.50 (p=0.022).[22]

In addition to the above findings, the mean haemoglobin (g/dL) increased from a minimum of 7.62 at diagnosis to a maximum of 9.74 after 3 months. This change was statistically significant (p≤0.001). Annibale et al observed that 77.8% of CD patients recovered from iron deficiency anaemia after only 6 months on a gluten-free diet and 94.4% after 12 and 24 months of diet.[23] The recovery of normal haemoglobin levels was also associated with a parallel decrease in RDW, suggesting recovery in a homogeneous erythrocytes' population.

Limitation

The study sample size was small and the follow-up in this study with MPV was done for only 3 months. As this study was a prospective study, controls were not included, hence a cutoff value for MPV could not be determined. Using a control group not on GFD would have substantiated our hypothesis further, but was not ethically feasible.

CONCLUSION

This study showed that Mean Platelet Volume (MPV) levels can be used as a short-term biomarker to check adherence for GFD in biopsy-proven celiac disease patients for follow-up purposes. Change in MPV runs parallel to IgA-tTG which is a widely used test. Decreasing MPV value on follow-up, points toward appropriate dietary adherence and if there is no change or increase in MPV levels, further counselling is required. MPV is a cheap and easily available bedside test as compared to IgA-tTG, so it can be conveniently used in primary health care centres for follow-up of celiac disease patients to check dietary adherence. Constipation is not an uncommon presenting complaint in celiac disease. About 20% of patients in this study had constipation as presenting symptoms. So, there is a need for serological testing for celiac disease in patients presenting with chronic constipation too along with chronic diarrhoea. Atypical presentation of the disease is also very common nowadays, hence cannot be ignored as it's the need of the hour to diagnose every celiac patient in order to prevent long-term complications.

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