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Original Article

Nutrition and stress: Two important external factors in polymyalgia rheumatica

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Abstract

Aim: Assessing the relationship between Polymyalgia Rheumatica (PMR) and nutrition and stress.

Materials and Methods: 24 patients with PMR and 24 patients without PMR (control group) were included in this pilot study. Patients' demographics, body mass index (BMI), use of tobacco and alcohol and dietary preferences were reviewed. Mean age of patient group was 65 and 59 in the control group. Both groups were composed of males and females. Patients with medication usage which might affect stress levels or appetite or weight loss, with other systemic diseases which might cause weight loss (malignancies, thyroid issues), with rheumatologic or autoimmune diseases other than PMR, and with psychiatric disorders diagnosed by psychiatrists were excluded from the study. A form was developed to assess the dietary habits of the participants in last 3 months. Objective of this form is to determine the consumption of carbohydrates, proteins, fats and processed food intake of the patients. Stress levels of patients were measured using Perceived Stress Scale (PSS).

Results: BMI was significantly higher in PMR group when compared to controls ($p<0.01$). Green vegetable daily consumption frequency was significantly higher in control group ($p<0.01$). In terms of grains, PMR group showed a significantly higher consumption of wheat instead of rice ($p=0.026$). In terms of oil choice, control group showed a significantly higher consumption of olive oil instead of margarine ($p=0.039$).No significant difference in terms of PSS scores were seen between the groups ($p=0.428$).

Conclusions: Lower BMI, consumption of green vegetables, rice and olive oil are all related with lowering the risk of PMR development and stress presence does not have a direct relationship with PMR risk.

Keywords: Nutrition; polymyalgia rheumatica; stress

INTRODUCTION

Polymyalgia rheumatica (PMR) is an autoimmune inflammatory disease frequently seen in patients over 50, which is characterized by pain in shoulder and pelvic area, morning stiffness and synovitis formations on extra-articular tissues and proximal joints. Pathogenesis of the disease is thought to be influenced by immunogenetic factors, infectious agents and endothelial dysfunctions; in addition to the response of a natural or acquired immune system response due to an unknown environmental factor (1). Diet type of the patients is one of the most important external factors. There are a number of studies that show the anti-inflammatory benefits of diets when done properly such as Mediterranean or Vegan diets, which are high in Omega-3, dietary fiber, low in carbohydrates and rich in foods such as fish, legumes, fruits and vegetables (2-4). Those diets play an important role in regulating gut microbiota and produces a synergistic effect towards anti-inflammatory action with gut homeostasis. This plays a crucial role in sustaining gut flora symbiosis and indirectly, autoimmune response (2-4). In addition, although there are no previous studies on the relationship between PMR and Body Mass Index (BMI), which is a clear result of the dietary choices (5), another study on giant-cell arteritis (GCA), which is a similar disease, showed a relationship between GCA and BMI; reporting that low BMI values are related with higher risk of GCA development (6, 7).

Another environmental factor that shows lifetime exposure is stress. Stress can develop due to a number of factors and one of those factors is wrong dietary choices

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(8). Stress is shown to be a risk factor in the pathogenesis of autoimmune and rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, juvenile chronic arthritis and fibromyalgia syndrome in previous studies (9, 10). Therefore, considering that PMR is also an autoimmune disease, we would like to assess the relationship between PMR and external risk factors of nutrition and stress.

MATERIALS and METHODS

The study was designed as a pilot study which is prospective and has a control group. Ethics approval for the study was obtained from the Ethics Committee of our institution (Decision Number: KAEK-39). All participants signed an informed consent form before participation. 24 patients diagnosed with PMR using EULAR/ACR Provisional Classification Criteria for PMR (11) treated with low-moderate dosage corticosteroids and 24 patients without PMR or other rheumatologic diseases between January and June 2019 were included in the study. Participant assessments were done using patient interviews. Patients with medication usage which might affect stress levels or appetite or weight loss, with other systemic diseases which might cause weight loss (malignancies, thyroid issues), with rheumatologic or autoimmune diseases other than PMR, and with psychiatric disorders diagnosed by psychiatrists were excluded from the study. Patients' demographics, systemic diseases, body mass index values, present medication usage, use of tobacco and alcohol and dietary preferences were reviewed in detail.

A form was developed to assess the dietary habits of the participants in last 3 months. The main objective of this form is to determine the consumption of carbohydrates, proteins, fats and processed food intake of the patients. The following questions were directed at patients under dietary preferences:

- Frequency of fruits and vegetables consumption (per week and per meal a day)
- Bread preference (White or wholegrain)
- Grains preference (wheat or rice)
- Oil preference (Olive Oil – Margarine)
- Fruit juices preference (Freshly squeezed – ready)

Stress levels of patients were measured using Perceived Stress Scale (PSS). PSS scale is a scale developed by Cohen, Kamarck and Mermelstein which consists of 14 questions. PSS is designed to measure the perception of stress of the person towards some of the situations in patient's life. Subjects choose from "Never (0)" to "Always/ Very Often (4)" on a 5-point Likert-type scale in each question. 7 of the questions with positive expressions are reverse scored. In addition to the long form of 14 questions; PSS also has 2 other forms which consist of 10 and 4 questions. PSS-14 scores vary from 0 to 56, with higher scores related with higher stress perception of the subjects. In this study, we used Turkish version of PSS (12).

Statistical Analysis

All statistical analyses were done using IBM SPSS Version 21 software. Normal spread assumptions were done using Shapiro-Wilk and normal Q-Q plots. Comparison of parametric variables between the groups was done using Student's t-test whereas categorical variables were compared using chi-square test or Fisher's exact test on some occasions. Significance level of differences was set as $p<0.05$.

RESULTS

This is a pilot study and will continue with more cases in the long run. Analysis of preliminary data supports the following findings.

The obtained study results showed no significant difference in terms of age, gender, education level, marital status, residence, chronic diseases (Diabetes Mellitus, Hypertension, Heart disease) smoking and alcohol consumption between study and control groups ($p>0.05$) (Table 1). In both groups most of the participants were female.

When BMI and PMR relationship was compared, BMI was significantly higher in PMR group when compared to controls ($p<0.01$, Table 1).

When participants were questioned about their fish, hazelnut and processed food consumption, no statistically significant difference was found between study and control groups. All 48 patients included in the study reported daily consumption of green vegetables and fruits and showed no statistical difference in fruit consumption. However, green vegetable daily consumption frequency was significantly higher in control group compared to study group ($p<0.01$, Table 2).

No statistically significant difference between the groups were detected in terms of bread choice (white – wholegrain) or fruit juice consumption (freshly squeezed – ready).

In terms of grains, PMR group showed a significantly higher consumption of wheat instead of rice ($p=0.026$).

In terms of oil choice, control group showed a significantly higher consumption of olive oil instead of margarine ($p=0.039$, Table 2).

When participants PSS scores were assessed, mean score of PMR group was found as 27.17±10.12 whereas control group mean score was 25.21±6.39. No significant difference in terms of PSS scores were seen between the groups ($p=0.428$).

Table 1. Demographics and Chronic Diseases				
	Study (n=24)	Control (n=24)	TOTAL	p-value
Age, years±SD	65.96±10.64	59.54±14.81	0.092	1.723
Gender, n (%)			0.701	
Female	21 (87.5)	19 (79.2)		
Male	3 (12.5)	5 (20.8)		
BMI, kg/cm²±SD	32.41±5.97	26.69±3.26	<0.01	4.119
Education level, n (%)			0.133	
Illiterate	11 (45.8)	5 (20.8)		
Basic Education	10 (41.7)	12 (50.0)		
High School or higher	3 (12.5)	7 (29.2)		
Residence, n (%)			0.263	
Urban	8 (33.3)	10 (41.7)		
Town	9 (37.5)	4 (16.7)		
Rural	7 (29.2)	10 (41.7)		
Marital Status, n (%)			0.533	
Married	18 (75)	15 (62.5)		
Single/Widowed	6 (25)	9 (37.5)		
Chronic Disease, n (%)			0.112	
Yes	20 (83.3)	14 (58.3)		
No	4 (16.7)	10 (41.7)		
Diabetes Mellitus, n (%)			0.330	
Yes	8 (33.3)	5 (20.8)		
No	16 (66.7)	19 (79.2)		
Hypertension, n (%)			0.248	
Yes	14 (58.3)	10 (41.7)		
No	10 (41.7)	14 (58.3)		
Heart Disease, n (%)			0.182	
Yes	8 (33.3)	4 (16.7)		
No	16 (66.7)	20 (83.3)		
Smoking, n (%)			0.666	
Yes	2 (8.3)	4 (16.7)		
No	22 (91.7)	20 (83.3)		
Alcohol consumption, n (%)			0.498	
Yes	0 (0)	2 (8.3)		
No	24 (100)	22 (91.7)		

Table 2. Dietary Preferences and Consumption			
	Study (n=24)	Controls (n=24)	p-value
Fish, n (%)			0.286
Consumed	17 (70.8)	21 (87.5)	
Not Consumed	7 (29.2)	3 (12.5)	
Hazelnuts, n (%)			0.722
Consumed	18 (75)	20 (83.3)	
Not Consumed	6 (25)	4 (16.7)	
Vegetables, n (%)			<0.01*
Daily		21 (87.5)	
Once a week	9 (37.5)	3 (12.5)	
Fruits, n (%)	15 (62.5)		1
Daily		17 (70.8)	
Once a Week	16 (66.7)	7 (29.2)	
Prepackagedfood, n (%)	8 (33.3)		0.062
Yes		11 (45.8)	
No	4 (16.7)	13 (54.2)	
BreadChoice, n (%)	20 (83.3)		0.317
White		16 (66.7)	
Wholegrain	20 (83.3)	8 (33.3)	
GrainChoice, n (%)	4 (16.7)		0.026*
Rice		9 (45.8)	
Bulghurwheat	3 (12.5)	15 (54.2)	
OilChoice, n (%)	21 (87.5)		0.039*
Margarine		2 (8.3)	
OliveOil	9 (37.5)	22 (91.7)	
Juices, n (%)	15 (62.5)		0.563
Ready		11 (45.8)	
Fresh-squeezed	14 (58.3)	13 (54.2)	

DISCUSSION

When we reviewed our study results which assessed the effect of stress and dietary habits on PMR, we found out that higher BMI is considered as a risk factor in PMR whereas consumption of olive oil, green vegetables and rice can be considered as protective factors against PMR. However, our study was written as a pilot study and our results are currently as a suggestion not statistically enough adequate.

In the literature, there is only one study that assesses BMI and PMR relationship. This study reported no significant relationship between BMI and PMR and also that BMI cannot be considered as predictive factor in the development of GCA in PMR patients (5). Other studies which assessed the relationship between BMI and GCA, which is a similar disease to PMR, reported that lower BMI is related with increased risk of GCA (6, 7). The studies where BMI is thought to be a predictor for GCA reported that the direct preventative effect of adipose tissue is due to estrogen synthesis and the effect of estrogen on anti-inflammatory pathways. Moreover, the stimulating effect of obesity over hypothalamus-pituitary axis (HPA), increasing endogenous corticosteroid levels, is thought to explain the anti-inflammatory effect (13-15). As opposed to those previous study results which contradicted our studies,

studies done on RA patients about BMI showed that increased BMI is related with increased disease activity, reduced response to treatments and increased disability in those patients (16).

Adipose tissue is thought to be an immune organ in addition to its roles as energy storage material and endocrine functions today; with obesity classified as a low-level chronic inflammatory disease (17). There is a large number of studies which show inflammatory changes in the body due to obesity, which are listed in detail below. Therefore; the studies that we mentioned above, and their results and theories are open to discussion.

It is a known fact that adipose tissue secretes a number of proteins which regulate metabolism, energy intake and fat storage. There are over 50 types of adipokines which are defined and the ones that are proven to affect adipose metabolism are leptin, adiponectin, IL-6 and TNF-alpha (17). Leptin limits food intake by directly affecting hypothalamus and other parts of the brain. In obesity, leptin concentration within circulation shows and increase and the cells develop resistance to leptin (18). Leptin, in addition to its role in CNS, plays a role in immune response as an inflammatory molecule due to its activation of adaptive immunity cells in different nutritional statuses. (17).Another major adipokine is adiponectin, with lower plasma concentrations of adiponectin seen in obese patients. Adiponectin is also shown to play a role in immunoregulation similar to leptin. It suppresses M1 macrophage response while supporting M2 macrophage proliferation, preventing pro-inflammatory status around adipose tissues (19). Adipose tissue also secretes cytokines in addition to adipokines. The main cytokines are IL-6 and TNF-alpha. Obese patients show increased levels of IL-6 and TNF-alpha. Those cytokines are inflammatory cytokines and are thought to play a role in PMR etiopathogenesis in addition to a number of other rheumatological diseases (17,20).

A current study showed that high-fat diets cause an inflammatory response within the body by triggering inflammatory activation pathways in colonic macrophages (21). The mice that were fed on a high-fat diet show an increased number of CD4+Th1 cells which secrete proinflammatory IFN-gamma, inducing inflammation stronger than Th2 and Treg cells. Although there is no clear information about the role of IFN-gamma in PMR etiopathogenesis, temporal artery biopsies of GCA patients, which are thought to be very closely related with PMR, detected IFN-gamma and can play an important role in arteritis formation (22).

When we further discuss how obesity can trigger inflammation, we saw that obesity causes B cells to aggregate within adipose tissue and those cells activate proinflammatory macrophages (M1) and T-cells, causing an inflammatory response within the body (23). Current studies showed a clear role of innate lymphoid cells (ILC) in obesity development and type-1 subunit of those cells showed an inflammatory effect by increasing proinflammatory macrophage polarization and IFN-gamma secretion (24). NK cells, which are another member of this group of cells, were shown to increase IFN-gamma and TNF-alfa secretion in addition to M1 macrophage activation in mice fed with high-fat diets, showing an inflammatory response (25).

A subtotal diet given to RA patients that show similar properties with PMR as a chronic autoimmune and inflammatory disease followingCD4+ T lymphocyte activation and numbers decreased significantly. Activation of CD4+ T lymphocyte and further differentiation of Th 1 and Th 17 were shown to play a role in RA progression. Therefore, using a specialized diet might aid in suppression of RA by causing immunosuppression due to decreased T-cell activation (4).

As the result of the detailed mechanisms explained above; it is clearly shown that obesity can trigger inflammatory response in the body. Our study results also showed a significant relationship between higher BMI and PMR, which is a chronic autoimmune inflammatory disease. Therefore, we can argue that higher BMI can be considered as a risk factor for PMR.

There are no studies that assess the effect of food groups, which is an important part of dietary preferences, over PMR development. In studies done with RA patients, a balanced diet was shown to have a positive effect on gut microbiota and dysbiosis. Proper carbohydrate consumption, especially with high-fiber foods is crucial in gut flora symbiosis sustainability and indirectly, autoimmune response. During the fermentation of dietary fiber, gut bacteria frees short-chain fatty acids (SCFAs) and produce a synergistic anti-inflammatory effect with fibers in gut homeostasis. This can be explained by the fact that short-chain fatty acids (SCFAs) are known to prevent secretion of inflammatory cytokines and chemokines such as IL-6, TNF-alpha and IFN-gamma (3). Moreover, previous studies reported that gut microbiota regulates T-cell phenotype and T-cell assisted immune response, with dysregulated gut microbiota and dysbiosis playing a role on RA etiopathogenesis (2).

Considering the fact that PMR is an autoimmune disease and PMR patients show decreased number of T-reg and Th-1 cells and increased Th-17 cells (26), disruption of gut microbiota and dysbiosis due to a diet with inadequate fiber can cause a molecular similarity between bacterial components and potential auto-antigens, so that T-cells can form a response to bacterial components and effectively causing pathogenic autoimmunity. Our study results support this argument by showing that control group had a higher daily consumption rate of green vegetables with higher fiber content, theorizing that high-fiber food consumption can be protective against PMR. However, no significant difference was found in terms of high-fiber fruit and wholegrain bread consumption between the groups. The difference green vegetables make in this aspect can be due to their additional Omega-3 content. Omega-3 polyunsaturated fatty acids are shown to suppress inflammatory signals of peroxidase proliferator activator

receptors and reduce RA-related markers (27). On the other hand, when we compared fish consumption, which is also rich in Omega-3, we did not see any significant difference between the groups. Those results showed us that using high-fiber foods with omega-3 containing foods in combination is essential for sustaining a healthy autoimmune response. An interesting finding is that we saw a higher consumption rate of rice in control group as opposed to wheat group, which has a higher fiber content. Although fiber content is higher than rice, we think that gluten plays a role and the fact that rice does not contain any gluten affects autoimmunity in a positive way and also reduces PMR risk in those patients. We based this argument on the previous studies which showed that prolonging sensitization of gluten can moderate the antigen-specific inflammatory markers such as IL-1β, IL-4, IL-15, IL-6, IFN-γ and TNF-α levels in mice, which as a result can make patients susceptible to autoimmune diseases (28).

Olive oil is rich in oleic acids and has similar anti-inflammatory effects with Omega-3 polyunsaturated fatty acids found in fish. Consumption of olive oil, which contains insoluble fibers that aid in digestion, is shown to decrease RA development risk in previous studies (4). Studies done on mice showed decreased serum levels of cartilage destruction markers such as cartilage oligomeric matrix protein (COMP) and metalloproteinase-3 (MMP-3) and reduced pro-inflammatory cytokine levels such as IL-1β, TNF-α, and IL-17 (29). Likewise, in our study we also found out that control group had a significantly higher rate of olive oil consumption compared to PMR patients. Therefore, we can say that olive oil consumption can be protective against PMR development.

Since smoking is related with lower BMI in addition to its anti-estrogenic effects, there is a study which reported smoking as a risk factor for GCA (6) yet another study did not find any relationship between those two (30). We were also unable to find a direct link between smoking and PMR.

The biggest limitation of our pilot study is the low number of participants and our results are shared currently as a suggestion not statistically enough adequate. For this reason, we think that our theory warrants further investigation in future studies with larger series of patients. Corticosteroid use is another limitation of our study. Since patients use corticosteroids, the differences between control and the patient group cannot be completely attributed to PMR. The effect of the corticosteroid cannot be excluded, albeit a low dose.

CONCLUSION

In conclusion, a balanced diet consisting of healthy foods is essential for immune system. Lower BMI, consumption of green vegetables, rice and olive oil are all related with lowering the risk of PMR development and stress presence does not have a direct relationship with PMR risk. Further studies with larger number of patients are required in the future.

Conflict of interest : The authors declare that they have no competing interest.

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