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Effect of extra virgin olive oil on inflammatory markers and intestinal microbiota in chronic kidney disease patients

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ABSTRACT

Introduction: The global prevalence of Chronic Kidney Disease (CKD) is 9.1%, with an increase of 29.3% from 1990 to 2018. A healthy diet with Extra Virgin Olive Oil (EVOO) consumption play a role in reducing inflammation and modulating gut microbiota in CKD patients. This study aims to assess the effect of extra virgin olive oil on immune system *platelet-to-lymphocyte ratio* (PLR) and *Short Chain Fatty Acids* (SCFA) in patients with Chronic Kidney Disease (CKD).

Methods: *Randomized clinical trial* at Dr. Wahidin Sudirohusodo Hospital Makassar on December 2022. The total sample was 30 and divided by two groups, each group both intervention with EVOO 40 ml / day and control group with normal diet (15 patients). Data were collected through questionnaires and direct measurements for anthropometric (Body weight and Body height). Energy intake with twenty four hours recall. *platelet-to-lymphocyte ratio* (PLR) through routine blood test and *Short chan fatty acids (*SCFA) through Pro Healthy Gut tests. Data were analyzed using SPSS version 26 with t-test analysis.

Results: EVOO administration had a significant result on inflammatory markers and gut microbiota. The intervention group had increased energy composition (1370.63±147.76 to 1690.63±147.76; p=0.000) and fat (19.93±7.25 to 57.93±7.25; p=0.000), accompanied by a decrease in *Platelet-Lymphocyte Ratio* (PLR) (210.76±80.20 to 169.89±54.22; p=0.026) and an increase in *Short Chain Fatty Acids* (SCFA) in feces (6.86±4.42 to 16.98±15.47; p=0.021) . While the control group showed no significant changes.

Conclusion: Extra virgin olive oil (EVOO) had no significant effect on the nutritional status of patients with Chronic Kidney Disease (CKD), but reduced inflammation (decreased PLR). In addition improved gut microbiota health (increased SCFA).

KEYWORDS

Nutraceutical intervention, gut microbiome, renal function, oxidative stress, kidney function, probiotic modulation, gut health, microbial diversity.

INTRODUCTION

Chronic kidney disease (CKD) is a medical condition that poses a serious challenge to global health[1,2]. As the number of cases increases in various parts of the world, CKD has become one of the chronic diseases that affect the quality of life of millions of people[3,4]. CKD is characterized by progressive deterioration in kidney function, which over time can lead to complete loss of kidney function[5-7]. Lifestyle factors such as unhealthy diet, lack of physical activity, and smoking also play an important role in the development of CKD[8,9]. In addition, genetic factors and genetic predisposition may also play a role in the emergence of CKD in an individual[10,11].

The impact of CKD on health is significant. Patients with CKD are prone to various serious complications such as heart disease, stroke, bone disorders, and anemia[12-14]. The management of CKD involves various strategies, including blood pressure control, blood sugar regulation, the use of certain medications, as well as changing to a healthier lifestyle[15]. In 2017, 1.2 million people died worldwide from CKD. The global all-age mortality rate from CKD increased by 41.5% between

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1990 and 2017. In 2017, 697.5 million cases of all-stage CKD were reported, with a global prevalence of 9.1%. The global all-age prevalence of CKD increased by 29.3% since 1990.

Based on the 2018 Basic Health Research (Riskesdas), the prevalence of non-communicable diseases has increased, for CKD there was an increase of 1.8%, from 2% to 3.8% compared to the 2013 Riskesdas. One of the largest provinces in eastern Indonesia, South Sulawesi, also has a high prevalence of CKD at 0.8% in 2018 in South Sulawesi province[16]. According to Pongsibidang, there were 858 patient visits due to CKD in 2012, 638 patient visits in 2013, and an increase to 1181 visits in 2014 at Dr. Wahidin Sudirohusodo General Hospital.

Chronic kidney disease (CKD) is characterized by immune activation that can be caused by various factors, including kidney damage, increased systemic inflammation and changes in the gut microbiota[17,18]. Some studies suggest that gut dysbiosis may be a risk factor for CKD[19]. In the early stages of CKD, there are quantitative and qualitative changes in the gut microbiota, characterized by an increase in the number of pathogenic bacteria, a decrease in the number of beneficial bacteria, and changes in the metabolic activity of the microbiota[20]. Changes in the gut microbiota in CKD may contribute to the immune activation that occurs in this disease. Pathogenic bacteria can release substances that can cause inflammation, while beneficial bacteria can help reduce inflammation[21].

Previous studies have shown that a healthy diet, characterized by a high intake of vegetables, fruit, nuts, seeds, legumes, and fish, and a low intake of saturated fat and sodium, can benefit chronic kidney disease (CKD) patients in the early stages[22]. One component of a healthy diet that has potential benefits for CKD patients is Extra Virgin Olive Oil (EVOO). EVOO, which is the main source of vegetable fat in the Mediterranean diet, has been shown to have antioxidant, anti-inflammatory, and gut microbiota modulating properties[23].

METHODOLOGY

Type of Study: This study is a randomized clinical trial with the administration of Extra Virgin Olive Oil (EVOO) and *placebo* (without EVOO). This method allows researchers to compare the effects of using EVOO with the effects of not using EVOO (placebo) to identify potential benefits or side effects of olive oil use on the parameters measured.

Place and Time of Study: This study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar on December 10-24, 2022, which is for 14 days of intervention.

Study Subjects: The population of this study were patients admitted to Dr. Wahidin Sudirohusodo with a diagnosis of Chronic Kidney Disease (CKD). Subjects were taken using the Lemeshow formula, 1998, namely:

Based on this formula, 15 research subjects were selected for each group who met the criteria, namely:

$$= \frac{\sigma^2(Z_{1-\alpha/2}+Z_{1-\beta})^2}{(\mu_0-\mu_a)^2} = \frac{23.20^2(1.96+1.65)^2}{(64.25-42.40)^2}$$

$$n = 15$$

Research Subject Criteria is participants eligible for inclusion in the study were male or female, aged between 18 and 60 years old, diagnosed as Chronic Kidney Disease (CKD) undergoing routine hemodialysis at an outpatient installation for 1-6 months and did not have more than 3 comorbidities. They had to provide written consent to participate in the study by signing the consent form. Patients were excluded from the study if they were not eligible for the study, consumed yogurt, Probiotics or similar in the last 3 months, had Gastrointestinal symptoms and disorders (Diarrhea, vomiting, IBD and gastrointestinal bleeding). Participants were considered to have dropped out of the study if they refused to adhere to the research guidelines, EVOO consumption compliance < 80% and declined to continue participating.

Data collection: Personal information such as name, age, gender, address, phone number, number of family members, occupation, monthly income, and consent to participate in the study were recorded. Anthropometric data and physical activity information were also collected, using questionnaires and direct measurements.

Research Permit and Ethical Clearance: This study was conducted after reviewing and obtaining approval from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University with ethical number No. 580/UN4.6.4.5.31/PP36/2AZ2 and obtaining permission from Dr. Wahidin Sudirohusodo Hospital.

Operational Definition:

a. **EVOO administration**: Extra Virgin Olive Oil was administered at a dose of 40 mL/day to patients in the intervention group[22].

b. ***Platelet to Lymphocyte Ratio* (PLR):** *Platelet to Lymphocyte Ratio* (PLR) is a marker of inflammation and is calculated from platelet count divided by lymphocyte count, cut off point is high PLR value ≥ 202, low < 202.

c. ***Short chain fatty acid* (SCFA):** SCFAs are short chain fatty acids (carbon atoms less than 6) derived from fermentation products of the gut microbiota from indigestible food. These products are acetate, propionate, butyrate and valerate.

Data processing and analysis: The collected data were organized based on their purpose and type, and then analyzed using appropriate statistical methods with the help of SPSS software version 26 (IBM Corp., 2019). The T-Test was used for normally distributed data, while the Mann-Whitney

test was chosen if the data were not normally distributed. To compare two or more groups on classified data, the Chi-square test was used. The relationship between the dependent and independent variables was analyzed with a scatter plot graph. Hypothesis testing decisions were made based on p values: results were not significant if $p > 0.05$, significant if $p \leq 0.05$, and highly significant if $p < 0.001$.

RESULTS

Chronic kidney disease can develop asymptomatically at first but has the potential to progress to kidney failure. Early detection is important to prevent this and obtain more effective therapy. The pathophysiology of chronic kidney disease is dependent on the underlying disease, with similar processes in subsequent progression. Reduction in renal mass causes structural and functional hypertrophy of the remaining nephrons in an attempt to compensate, triggered by vasoactive molecules such as cytokine growth factors, resulting in hyperfiltration and increased capillary pressure and glomerular blood flow[20,24].

Nutritional status assessment, monitoring and intervention are important components in the management of chronic kidney disease (CKD) patients. The changes in metabolism cause CKD stages 1 to 5 to require different nutritional management that requires specific evaluation and therapy. In addition, each individual patient has specific nutritional problems due to differences in metabolism, etiology of CKD, genetic and environmental CKD stages. Nutritional management in CKD aims to slow the progression of kidney disease, improve quality of life, and reduce cardiovascular morbidity and mortality in CKD[24].

The distribution of samples based on general characteristics can be seen in Table 1. The distribution of samples showed that the majority of respondents were over 45 years old, with almost equal numbers between the control and intervention groups (52.4% and 47.6%). Statistical test results showed a value of P=0.690, confirming the age trend of 46-65 years in CKD cases. The majority of respondents were female, with no significant difference between groups (56.3% and 43.8%). Most also had hypertension as a comorbid disease, with no significant difference between the groups (53.3% and 43.8%). The majority of respondents had been on hemodialysis for less than 3 months, with no significant difference between groups (61.1% and 38.9%). Although the majority of respondents were employed, there was no significant difference between the intervention and control groups in terms of occupation (64.7% and 35.3%).

Characteristics of Research Subjects

Table 1. Characteristics of Research Subjects

Characteristics	Intervention (n=15)	Control (n=15)	P-value
Age			
18-45 Years	5 (55.6%)	4 (44.4%)	0.690
>45 Years	10 (47.6%)	11 (52.4%)	
Gender			
Male	8 (57.1%)	6(42.9%)	0.472
Female	7 (43.8%)	9(56.3%)	
Comorbid			
Hypertension	8(53.3%)	7(46.7%)	0.394
Diabetes Mellitus	1(3.3%)	0	
Hypertension and Diabetes	4(0%)	4(50%)	
Hypertension and BSK	1(3.3%)	0	
Hypertension/Dyslipidemia	1(50%)	1(50%)	
Hypertension/BPH	0	1(3.3%)	
Hypertension/Hyperuricemia	0	1(3.3%)	
Diabetes/Obesity	0	1(3.3%)	

Independent t-test.

Table 1 continuation. Characteristics of Research Subjects

Characteristics	Intervention (n=15)	Control (n=15)	P-value
Length of HD (Months)			
<3 months	7(38.9%)	11(61.1%)	0.136
>3 months	8 (66.7%)	4 (33.3%)	
Jobs			
Work	11(64.7%)	6(35.3%)	0.065
Not Working	4(30.8%)	9(69.2%)	

Independent t-test.

Differences in Nutritional Status Pre and Post Intervention

Anthropometric measurements in this study consisted of Body Height, Body Weight (BW), and Body Mass Index (BMI). And the determination of the nutritional status of respondents using BMI calculations. Table 2 shows that the average nutritional status in the pre and post intervention group had no difference before treatment with a Mean ± SD value of 21.34 ± 3.59 and 21.34 ± 3.59 after treatment. the results of statistical tests using the t-independent test showed a p value of 0.175>0.05 which means there was no significant difference before and after in the intervention group.

Furthermore, before and after treatment in the control group showed no difference with a Mean ± SD value of 23.27 ± 4.08 and 23.27 ± 4.08 after treatment. the results of statistical tests using the *Mann Whitney test* showed a p value of 0.223>0.05 which means there is no significant difference before and after treatment in the control group.

Assessing the Pre and Post Intervention food composition of Extra Virgin Olive Oil (EVOO) diet

Based on table 3, it is known that the food composition of the energy sub variable has a difference before and after treatment with a Mean ± SD value of 1370.63 ± 147.76 be-

Table 2. Differences in Nutritional Status of the two groups Pre and Post Intervention

Group	EVOO (n=15)		P-value	Control (n=15)		P-value
	Mean±SD (Pre)	Mean±SD (Post)		Mean±SD (Pre)	Mean±SD (Post)	
Height (cm)	163.80±6.44	163.80±6.44	0.900*	156.26±8.18	156.26±8.18	0.900*
Weight (kg)	57.33±9.99	57.80±9.92	0.878*	56.76±10.02	56.70±10.08	0.766*
BMI (kg/m2)	21.34±3.59	21.52±3.57	0.175*	23.28±4.01	23.27±4.08	0.223**

Independent t-test*; *Mann Whitney test*.

Table 3. Pre and Post Intervention Dietary Composition (EVOO)

Group	EVOO (n=15)		P-value	Control (n=15)		P-value
	Mean±SD (Pre)	Mean±SD (Post)		Mean±SD (Pre)	Mean±SD (Post)	
Energy (Kcal)	1370.63±147.76	1690.63±147.76	0.000*	1235.90±160.26	1225.57±175.94	0.868*
Protein (g)	48.04±8.47	48.95±8.58	0.279*	44.99±6.47	46.59±6.66	0.408*
Carbohydrate (g)	228.34±32.58	236.88±34.77	0.154*	207.82±43.34	213.30±42.58	0.108*
Fat (g)	19.93±7.25	57.93±7.25	0.000*	15.59±4.19	17.31±4.28	0.276*

n = number of subjects; Kcal = kilocalories; g = grams; Mean ± SD. * Independent t test; ** *Mann Whitney test*.

fore and 1690.63 ± 147.76 after treatment in the intervention group with a value of p = 0.000 <0.05. This is because EVOO was given at a dose of 40 mL / day to patients in the intervention group. while in the control group there was no difference with a value of p = 0.0868> 0.05.

In the food composition of the fat sub variable, there were differences before and after treatment with a Mean ± SD value of 19.93 ± 7.25 before and 57.93 ± 7.25 after treatment in the intervention group with a value of p = 0.000 <0.05. This is because *Extra Virgin Olive Oil* was given at a dose of 40 mL / day to patients in the intervention group. while in the control group there was no difference with a value of p = 0.276> 0.05.

Assessing Platelet-Lymphocyte Ratio (PLR) levels in routine blood samples Pre and Post Intervention administration of Extra Virgin Olive Oil (EVOO)

The results of this study on pre and post examinations (EVOO group) had Platelet Mean±SD values (228.06±69.59 and 106.16±49.69) p=0.000. Lymphocytes (1.08±0.86 and 0.68±0.91) p=0.007 and PLR (210.76±80.20 and 169.89±54.22) p=0.026 and on pre-post examinations in the control group had Platelet Mean±SD values (246.66±87.41 and 214.51±69.59), with a value of p=0.550, Lymphocytes (1.45±1.26 and 1.11±0.85, with a value of p= 0.362, PLR (169.80±69.08 and 106.16±49.69) p=0.163, which means there is a significant difference between the two groups in the value of platelets, Lymphocytes and PLR with post examination in the EVOO and control groups.

Assessing Short Chain Fatty Acids (SCFA) levels in feces samples Pre and Post Intervention with Extra Virgin Olive Oil (EVOO).

The results of this study showed the value of SCFA levels in feces examination before and after in the intervention group (EVOO) obtained the results of Mean ± SD Acetate (57.74 ± 18.22 and 61.53 ± 10.70) with a value of P = 0.842. while with the control group obtained the results of Mean ± SD Acetate before and after (61.13 ± 9.32 and 61.13 ± 9.32) with a value of P = 0.413> from 0.05. Propionate in the intervention group showed a decrease from Mean±SD (27.47±34.04 to 17.33±6.15) with P=0.232 > 0.05, while in

Table 4. Platelet-Lymphocyte Ratio (PLR) levels in routine blood samples pre and post intervention with Extra Virgin Olive Oil (EVOO)

Group	EVOO (n=15)		Mean Δ	P-value	Control (n=15)		Mean Δ	P-value
	Mean±SD (Pre)	Mean±SD (Post)			Mean±SD (Pre)	Mean±SD (Post)		
PLR	210.76±80.20	169.89±54.22	40.87	0.026**	169.80±69.08	106.16±49.69	63.64	0.163**

n = number of subjects; PLR = *Platelet-Lymphocyte Ratio*, Mean ± SD. * Independent t test; ***Mann Whitney test*.

Table 5. Short Chain Fatty Acids (SCFA) levels in feces samples Pre and Post Intervention with Extra Virgin Olive Oil (EVOO)

Group	EVOO (n=15)		Mean Δ	P-value	Control (n=15)		Mean Δ	P-value
	Pre	The post			Pre	The post		
	Mean±SD				Mean±SD			
Acetate (%)	57.74±18.22	61.53±10.70	3.79	0.842**	10.458.13±1	61.13±9.32	3	0.413**
Propionate (%)	27.47±34.04	17.33±6.15	10.14	0.232**	18.73±6.08	20.47±6.81	1.74	0.469**
Butirat (%)	5.68±5.10	22.65±36.11	16.97	0.007**	7.66±5.08	21.78±36.21	14.12	0.146**
Valerat (%)	2.25±1.40	2.57±1.45	0.32	0.490*	1.78±1.63	2.46±2.12	0.68	0.334**
Absolute butyrate (mg/mL)	1.13±1.43	1.37±1.62	0.24	0.096**	1.10±0.55	1.35±1.06	0.25	0.437**
SCFA (mg/mL)	7.21±5.17	17.68±17.85	10.47	0.038*	7.86±4.68	7.87±4.80	0.01	0.127**

* Paired t test. ** Wilcoxon test.

the control group it was not significant, namely Mean±SD (18.73±6.81 to 20.47±6.81) with P=0.469 > 0.05. Butyrate in the intervention group increased significantly from Mean±SD (5.68±5.10 to 22.65±36.11) with P=0.007 < 0.05, while in the control group it was not significant, namely Mean±SD (7.66±5.08 to 21.78±36.21) with P=0.146 > 0.05. Valerate in the intervention group showed no significant change from Mean±SD (2.25±1.40 to 2.57±1.45) with P=0.490 > 0.05, while in the control group it was also not significant, namely Mean±SD (1.78±1.63 to 2.46±2.12) with P=0.334 > 0.05. Absolute butyrate in the intervention group showed no significant change from Mean±SD (1.13±1.43 to 1.37±1.62) with P=0.096 > 0.05, while in the control group it was also not significant, namely Mean±SD (1.10±0.55 to 1.35±1.06) with P=0.437 > 0.05. SCFA in the intervention group showed a significant increase from Mean± (7.21±5.17 to 17.68±17.85) with P=0.038 < 0.05, while in the control group it was not significant, namely Mean±SD (7.86±4.68 to 7.87±4.80) with P=0.127 > 0.05.

The results of this study found that there was a significant difference between the intervention group before and after treatment. and can be seen the mean value of SCFA levels which shows that there was an increase in the intervention group, this can be caused because the intervention group was given a diet of Extra Virgin Olive Oil (EVOO) for consumption at a dose of 40 ml given 4 times a day for 2 weeks.

Assessing Short Chain Fatty Acids (SCFA) levels between EVOO groups in feces samples Pre and Post Intervention of Extra Virgin Olive Oil (EVOO) administration

The results of this study showed the Mean ± SD value of SCFA in pre and post fecal examination in the intervention group obtained results on the Acetate sub variable (57.74 ± 18.21 and 61.53 ± 10.69) with a value of P = 0.492, Propionate (27.47 ± 34.04 and 17.33 ± 6.15) with P=0.266, Butyrate (10.00±8.07 and 21.78±36.21) with P=0.000, Valerate (2.25±1.40 and 2.57±1.45) with P=0.543, Absolute Butyrate (1.13±1.43 and 1.90±12.31) with P=0.280, and SCFA (6.86±4.42 and 16.98±15.47) with P=0.021.

Furthermore, the results of this study showed the Mean ± SD value of SCFA in pre and post feces examination in the control group obtained results in the Acetate sub variable (58.06 ± 10.02 and 61.13 ± 9.32) with a value of P = 0.393, Propionate (18.73 ± 6.38 and 20.47 ± 6.81) with P=0.478, Butyrate (11.66±7.61 and 8.93±5.22) with P=0.261, Valerate (1.69±1.55 and 2.46±2.12) with P=0.268, Absolute Butyrate (1.44±1.34 and 1.31±1.09) with P=0.133, and SCFA (8.53±4.50 and 8.46±4.30) with P=0.666. From the results of this study obtained differences in SCFA levels in both groups where in the EVOO group there was an increase while in the control group there was a decrease in SCFA levels.

DISCUSSION

Differences in Nutritional Status Pre and Post Intervention

This study on the administration of extra virgin olive oil to the immune system *platelet-to-lymphocyte ratio* (PLR) and *Short Chain Fatty Acids* (SCFA) in patients with *Chronic Kidney Disease* (CKD). showed that there was no difference in nutritional status before and after administration of EVOO. Nutritional and metabolic disorders in patients with *chronic kidney disease* (CKD) are characterized by the simultaneous loss of systematic body protein and energy storage, which ultimately leads to loss of muscle and fat mass and cachexia[25].

Table 6. Short Chain Fatty Acids (SCFA) levels in feces samples Pre and Post Intervention of Extra Virgin Olive Oil (EVOO) administration

Group	EVOO (n=15)		Mean Δ	P-value	Control (n=15)		Mean Δ	P-value
	Pre	The post			Pre	The post		
	Mean±SD				Mean±SD			
Acetate (%)	57.74±18.21	61.53±10.69	3.79	0.492*	58.06±10.02	61.13±9.32	3.07	0.393**
Propionate (%)	27.47±34.04	17.33±6.15	10.14	0.266*	18.73±6.38	20.47±6.81	1.74	0.478**
Butirat (%)	10.00±8.07	21.78±36.21	11.78	0.000*	11.66±7.61	8.93±5.22	2.73	0.261**
Valerat (%)	2.25±1.40	2.57±1.45	0.32	0.543*	1.69±1.55	2.46±2.12	0.77	0.268**
ButyrateAbsolute (mg/mL)	1.13±1.43	1.90±12.31	0.77	0.280*	1.44±1.34	1.31±1.09	0.13	0.133**
SCFA (mg/mL)	6.86±4.42	16.98±15.47	10.12	0.021*	8.53±4.50	8.46±4.30	0.07	0.666**

* Paired t test; ** Wilcoxon test.

Low energy and/or protein intake was found to be associated with significant reductions in nutritional parameters such as serum albumin levels and an increased risk of higher morbidity and mortality in patients with advanced CKD. Loss of appetite often leads to inadequate protein and energy intake and contributes to poor quality of life, Spontaneous decline in food intake occurs during progressive decline in renal function, and this decline correlates with accumulation of nitrogen-derived uremic toxins. Factors affecting food intake involve not only metabolic disorders but also abnormalities in the digestive system[26].

Assessing the Pre and Post Intervention food composition of Extra Virgin Olive Oil (EVOO) diet

The results of this study indicate that there are differences in food composition in energy and fat before and after in the intervention group (EVOO), which means that there is an increase before and after. while in the control group there were no changes.

Consumption pattern is a way of organizing the amount, type, and frequency of food to maintain health and prevent or help cure disease. Normal fat requirements are around 20-25% of total energy, with variations depending on the disease. Diets for heart disease, for example, recommend 20-25% fat, with 10% saturated fat and 10-15% unsaturated fat[27]. Fatty acids are distinguished by the length of the carbon tail, namely short chain (less than 6 carbons), medium (6-12 carbons), and long (more than 12 carbons). Short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate are produced from the fermentation of undigested carbohydrates in the distal gut by gut bacteria such as bacteroides and bifidobacteria. SCFAs have benefits such as maintaining gut integrity, regulating glucose and lipid metabolism, and supporting the immune system and antioxidant activity[28].

Assessing Platelet-Lymphocyte Ratio (PLR) levels in routine blood samples pre and post intervention with Extra Virgin Olive Oil (EVOO)

The results of this study found that PLR in the intervention group (EVOO) before and after treatment showed a significant difference compared to the control group. the results of this study are similar to the research of Jiaxian Liao (2022) that the inflammatory scoring system with a combination of NLR, MLR and PLR. We found an independent association between higher inflammation scores and all-cause mortality in HD patients[28]. The study by Turkmen, et al. showed that Platelet to Lymphocyte Ratio (PLR) was significantly increased in dialysis patients with chronic kidney disease (CKD). PLR was also positively correlated with inflammatory markers such as NLR, IL-6, and TNF-α. CKD patients with higher PLR had higher levels of inflammation. This study found that PLR was superior to NLR in assessing inflammation in CKD patients. The reduction in PLR in the control group was higher (63.64% difference) compared to the intervention group (40.87% difference). This may be due to the use of heparin or blood dilution in patients who have been on hemodialysis for less than 3 months. PLR is an inflammatory marker that can be used to predict inflammation and mortality in various diseases, including CKD. High PLR indicates platelet overactivation and lymphopenia, conditions associated with prothrombotic status and ischemia or reperfusion damage[29].

Assessing Short Chain Fatty Acids (SCFA) levels in feces samples Pre and Post Intervention with Extra Virgin Olive Oil (EVOO)

In this study, there was a significant difference in *Short Chain Fatty Acids* (SCFA) levels in fecal samples before and after Extra Virgin Olive Oil (EVOO) consumption. EVOO consumption increased *α-diversity*, a measure of species richness, as well as *β-diversity*, a measure of compositional differences between samples compared to controls. These results were attributed to beneficial effects on metabolic health, as reduced microbial diversity is associated with increased chronic inflammation and later development of metabolic diseases. The ability of EVOO to act as a prebiotic, stimulating the growth of beneficial bacteria, and as an antibacterial, suppressing the growth of pathogenic bacteria, is most likely due to the suite of phenolic compounds that EVOO contains. The phenolic compounds in EVOO are not consumed in isolation; rather they are consumed as part of the food matrix and may function synergistically together with other components in EVOO. In addition to the phenolic compounds and their known interactions and effects on the microbiota, other minor components in EVOO such as sterols and tocopherols may influence the composition of the gut microbiota[30].

Analyzing the comparison of Short Chain Fatty Acids (SCFA) Pre and Post Intervention of Extra Virgin Olive Oil (EVOO) in Chronic Kidney Disease (CKD)

The gut microbiota has co-existed with humans for a mutually beneficial life and plays an important role in health and disease. The normal gut microbiota influences host health by contributing to nutrition, metabolism, physiology and immune function. Disruption of the normal gut microbiota (dysbiosis) has been implicated in the pathogenesis of various diseases, such as obesity, type 2 diabetes, *inflammatory bowel disease* and cardiovascular disease. Quantitative and qualitative changes in the gut microbiota are also found in patients with CKD and ESRD[30]. The results of this study found that there were differences in SCFA levels before and after in both groups where in the EVOO group there was an increase while in the control group there was a decrease in SCFA levels. A normal kidney contains about 1 million nephrons, each of which contributes to the total glomerular filtration rate (GFR). In the face of renal injury (regardless of its etiology), the kidney has an innate ability to maintain GFR, despite progressive

nephron destruction, as the remaining healthy nephrons are capable of compensatory hyperfiltration and hypertrophy. This nephron adaptation allows for sustained normal clearance of plasma solutes.

The mechanism of hyperfiltration and residual nephron hypertrophy is beneficial, but has been hypothesized to be the main cause of progressive renal dysfunction. Disruption of the kidney due to chemical or physical causes ultimately activates inflammatory and fibrotic responses will disrupt the recovery process and lead to irreversible degeneration of renal tissue. Diseases that cause glomerular or tubular disruption eventually activate responses that damage other nephron structures and lead to a vicious cycle causing gradual nephron loss and replacement by scar tissue. Cellular damage causes inflammation and cytokine imbalance, which contributes to fibrosis, mesangial and vascular contractions leading to decreased GFR, tubular degeneration and scarring.

EVOO consumption has shown positive effects on gut microbiota and gut health in human and animal studies such as mice. However, in particular, in humans, EVOO has a prebiotic effect, promoting the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. The important role of the gut microbiota in shaping the mucosal immune system and its influence on overall inflammatory status and cardiovascular, metabolic and brain health is becoming increasingly clear[30].

Limitations

Limitations This study has several limitations, the risk of over or under reporting and memory bias in 24-hour food recall cannot be ruled out. In addition the study's sample size was relatively small.

CONCLUSION

This study evaluates the effectiveness of extra virgin olive oil (EVOO) in patients with chronic kidney disease (CKD) undergoing hemodialysis. While EVOO did not show a significant impact on the patients' nutritional status, it was proven to be beneficial in reducing inflammation (as indicated by a decrease in the Platelet-Lymphocyte Ratio (PLR)) and in improving gut microbiota health (as indicated by an increase in Short Chain Fatty Acids (SCFA)). These findings suggest the potential benefits of EVOO in helping manage CKD, although further research is needed to confirm its long-term effects.

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