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LIPID-LOWERING THERAPY IN CHRONIC KIDNEY DISEASE: EFFECTS ON LIPID PROFILES, OXIDATIVE STRESS, AND TRYPTOPHAN DEGRADATION

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive condition associated with high cardiovascular risk, oxidative stress, and inflammation. Dyslipidemia is a common comorbidity in CKD, contributing to disease progression and complications. However, the effects of different lipid-lowering therapies on lipid profiles, oxidative stress, and inflammatory markers in CKD remain unclear. ***Objectives:*** This study aimed to evaluate the effects of three lipid-lowering regimens: simvastatin monotherapy (40 mg/day) and combination therapy with ezetimibe/simvastatin (10/20 mg and 10/40 mg) on lipid profiles, oxidative stress indices, and inflammatory markers in patients with CKD stage 3-4. ***Materials and Methods:*** A 12-month prospective study was conducted on CKD patients receiving one of the three lipid-lowering regimens. Lipid parameters, oxidative stress markers (MDA, PSH, PON, TEAC), and inflammatory markers (Kyn, Kyn/Trp ratio) were measured at baseline and after treatment. Statistical analysis was performed to determine correlations between LDL-C, oxidative stress, and inflammation. ***Results:*** All three treatment regimens significantly improved lipid profiles, reduced oxidative stress (lower MDA, higher PSH, PON, TEAC), and decreased inflammation (lower Kyn, Kyn/Trp ratio). The ezetimibe/simvastatin 10/40 mg combination showed the most pronounced improvements, although differences were not statistically significant. LDL-C levels positively correlated with MDA, Kyn, and Kyn/Trp ratio, suggesting that LDL-C reduction contributes to decreased oxidative stress and inflammation. ***Conclusion:*** Lipid-lowering therapy effectively improves lipid metabolism, oxidative stress, and inflammation in CKD stage 3-4 patients. Combination therapy with higher doses of Simvastatin may offer additional benefits.

Keywords: *Chronic kidney disease, dyslipidemia, oxidative stress, inflammation, lipid-lowering therapy, ezetimibe, simvastatin.*

I. INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition characterized by a gradual decline in kidney function, diagnosed mainly through laboratory testing [1]. CKD is a growing global health concern, with a prevalence of 10–14% in the general population. In Asia, the burden is similarly high, with rate in China reaching 10.8% [2]. In Vietnam, CKD prevalence is rising alongside hypertension and diabetes, with 3.1% of the population diagnosed at stages 3–5 [3]. Due to its asymptomatic nature in early to moderate stages, CKD is often underdiagnosed, making its true incidence and prevalence difficult to determine.

Beyond its direct impact on renal function, CKD significantly increases the risk of cardiovascular disease (CVD), which is the leading cause of mortality in stages 3–4, rather than progression to end-stage renal disease (ESRD) [4]. Systemic inflammation and oxidative stress play key roles in CKD progression, leading to vascular damage and increased cardiovascular morbidity. Oxidative stress and inflammation interact in

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a cyclical relationship, where inflammatory processes attempt to repair radical-mediated damage but also generate further oxidative stress, exacerbating renal dysfunction demonstrated that these markers escalate in parallel with CKD progression, particularly during disease exacerbation [5].

Dyslipidemia is a well-recognized cardiovascular risk factor in CKD, yet it remains underemphasized in clinical management. The pathophysiology of dyslipidemia in CKD differs from that in the general population, primarily due to altered HDL and triglyceride metabolism. CKD-related dyslipidemia is characterized by increased triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) with decreased high-density lipoprotein cholesterol (HDL-C). Studies indicate that two-thirds of CKD patients exhibit mixed hyperlipidemia, with total cholesterol (TC) and LDL-C being the predominant lipid abnormalities [6]. Despite the widespread use of statins, only one-third of CKD patients on lipid-lowering therapy achieve LDL-C targets. The effectiveness of higher-dose statin monotherapy remains uncertain due to associated risks of hepatotoxicity and myopathy [7]. While lipid-lowering therapies such as statin monotherapy and statin/ezetimibe combinations have proven effective in reducing CVD risk in non-CKD populations, their impact on lipid disorders in CKD patients, particularly in later stages, requires further investigation.

Given the lack of data on lipid-lowering strategies in Vietnamese CKD patients, this study aims to (1) Evaluate the effects of lipid-lowering therapies (simvastatin monotherapy and ezetimibe/simvastatin combinations) on lipid profiles, oxidative stress, and tryptophan degradation in CKD patients. (2) Investigate the relationship between oxidative stress, tryptophan degradation, and lipid-lowering therapies.

By providing scientific evidence on the mechanisms and effectiveness of these therapies, this study seeks to improve hyperlipidemia management, enhance prescription rates of lipid-lowering medications, and ultimately optimize clinical outcomes for CKD patients.

II. MATERIALS AND METHOD

2.1. Study population

Inclusion Criteria: We enrolled patients meeting all of the following criteria: diagnosed with CKD stage 3-4 (e-GFR: 15-60 ml/min/1.73 m²), presence of proteinuria with creatinine clearance >20 ml/min/1.73 m² and urinary protein excretion >0.3 g/24 h, LDL cholesterol concentration >100 mg/dl (2.59 mmol/l), and age ≥50 or 18-49 years old with at least one of the following: diabetes mellitus, known coronary disease, prior ischemic stroke, or an estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%.[1]

Exclusion Criteria: Exclusion Criteria: Patients were not recruited into the study if they met any of the following conditions: refusal to participate, dialysis-dependent CKD, heart failure, prior or concurrent use of corticosteroids, statins, immunosuppressive agents, vitamin B6, B12, or folate, pregnancy, unwillingness to provide consent, or inability to understand the risks and provide written informed consent.

2.2. Study method

Study design: This prospective study, involving a 12-month clinical trial follow-up, was conducted in 2021-2023.

Sample size: The study recruited a total of 30 patients and 30 age- and sex-matched control participants. Patients were admitted to the Department of General Medicine - Endocrinology, HUMP, Vietnam. A convenient sampling method was used to select eligible patients who met the inclusion criteria and did not fall under the exclusion criteria.

Study contents

Treatment therapies: The 30 enrolled patients were randomized into three groups and received one of three lipid-lowering therapies at baseline, continuing for 12 months: Group 1 (10 participants): 40 mg/day simvastatin; Group 2 (10 participants): 10/20 mg/day ezetimibe/simvastatin; Group 3 (10 participants): 10/40 mg/day ezetimibe/simvastatin.

Routine Laboratory Analyses: The study collected data on clinical and demographic information, including age, gender, weight, height, body mass index (BMI), education level, systolic and diastolic blood pressure, and smoking status. Subclinical characteristics such as TC, TG, LDL-C, HDL-C, CRP, creatinine, estimated glomerular filtration rate (eGFR), MDA, PSH, kynurenine, PON, TEAC, tryptophan, and the kynurenine-to-tryptophan ratio were recorded using a structured questionnaire. Patients underwent 12 months of treatment with routine monthly clinical follow-ups and blood tests at 4, 8, and 12 months. The study process follows the diagram below:

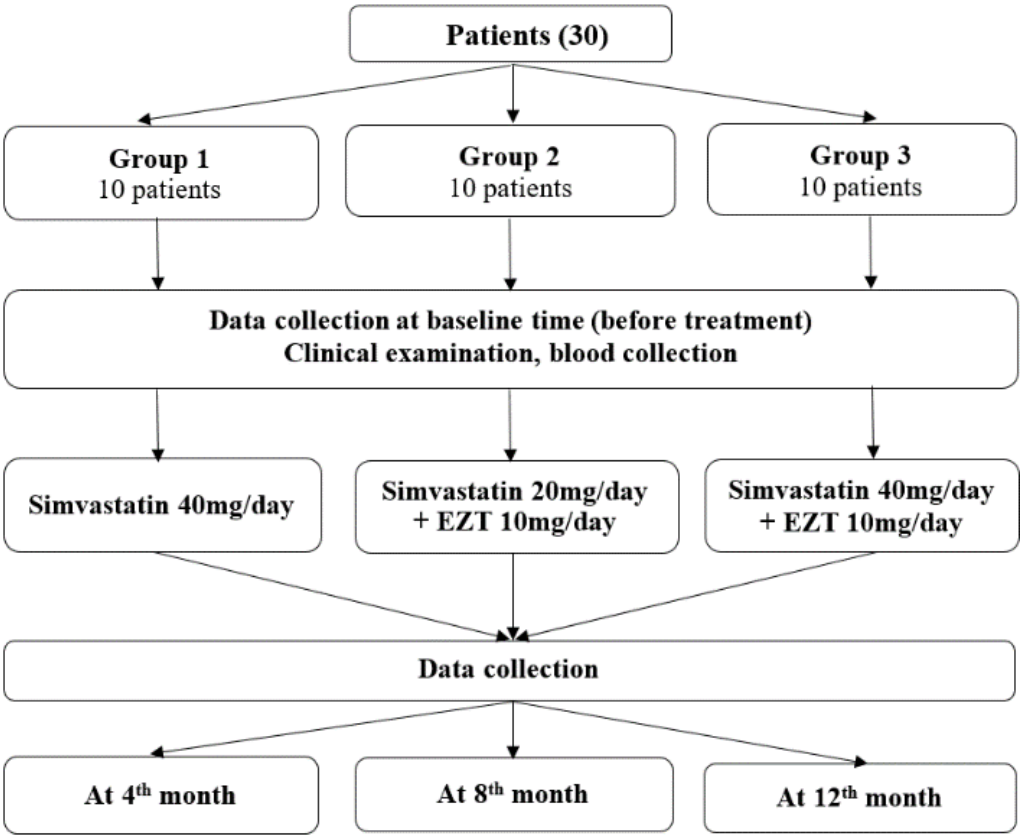

Diagram 1. Study design flow

Statistical analysis: SPSS software, version 20.0 was applied to do statistical analysis. Continuous data were expressed as mean ± standard deviation and the categorical data were expressed as percentages. One way ANOVA was used to compare the difference in 3 treatment therapies. The Levene's test was used to assess the equality of error variances and the Student-Newman-Keuls was used to access pairwise comparisons. The effect of the drug treatments on continuous variables by time was evaluated by one-way repeated measures ANOVA. Interaction between different drug therapies and time of treatment on variables were analyzed by MIX REPEAT ANOVA. Correlation analysis between the pair of variables was performed by Pearson's correlation. Statistical significance was declared if the P-value was less than 0.05.

2.3. Ethics in research

The explanation about the study and informed consent form was obtained from patients and the controllers. This study project was approved by the Ethical Committee of Hue University of Medicine and Pharmacy. The study complied with the standards of the Helsinki Declaration and was enrolled with clinical trials, gov (NCT03543774).

III. RESULTS

3.1. Demographic and clinical characteristics of patients and controls at baseline

Table 1. **Demographic and clinical characteristics of CKD groups after randomized at baseline**

Demographic and clinical characteristics	Group 1 n = 10 Simvastatin 40 mg/day Mean ± SD	Group 2 n = 10 Eze/Simva 10/20 mg/day Mean ± SD	Group 3 n = 10 Eze/Simva 10/40 mg/day Mean ± SD	p value
Male	7 (63.63%)	5 (50%)	7 (63.63%)	0.767
Female	4 (36.37%)	5 (50%)	4 (36.37%)	
Age	61.80 ± 6.6	66 ± 11.04	67.40 ± 14.07	0.505
BMI	23 ± 1.3	21 ± 0.75	23.35 ± 1.67	0.903
Systolic BP, mmHg	148.18 ± 22.28	151.5 ± 19.3	152.73 ± 19.94	0.859
Diastolic BP, mmHg	84.55 ± 12.93	85 ± 12.02	85.91 ± 10.68	0.963
Creatinine, mg/dL	1.97 ± 0.52	1.89 ± 0.39	2.29 ± 0.9	0.340
eGFR, ml/min/1.73m^2	34.46 ± 12.29	32.03 ± 7.72	30.77 ± 13.48	0.766
CRP (mg/l)	9.10 ± 5.63	13.2 ± 8.77	9.8 ± 7.10	0.415
TC, mg/dL	244.00 ± 22.3	228.80 ±16.01	255.20 ± 31.57	0.069
TG, mg/dL	232.70 ± 69.25	184.10 ± 88.54	227.80 ± 26.09	0.481
HDL-C, mg/dL	37.60 ± 9.85	38.20 ± 5.81	35.80 ± 8.15	0.790
LDL, mg/dL	159.14 ± 22.58	153.62 ± 17.75	167.86 ± 23.72	0.343
Oxidative stress indexes				
MDA (µmol/L)	3.04 ± 1.19	2.50 ± 0.98	1.78 ± 1.31	0.588
PSH (µmol/L)	4.38 ± 0.82	3.83 ± 0.61	4.65 ± 1.3	0.128
TEAC (mM)	5105.05 ± 362.43	4856.96 ± 389.42	4869.66 ± 438.16	0.307
PON (U/L)	38.13 ± 17.8	32.41 ± 21.92	31.86 ± 13.72	0.686
Tryptophan degradation indexes				
Kyn (µmol/L)	3.2 ± 1.26	3.83 ± 1.61	3.34 ± 1.68	0.685
Tryp (µmol/L)	31.81 ± 11.40	48.67 ± 12.41	43.78 ± 16.26	0.174
Kyn/Trp ratio	0.12 ± 0.10	0.09± 0.05	0.09 ± 0.06	0.554

P values for comparing between 3 groups, evaluated by one-way ANOVA with Bonferroni correction.

Thirty patients were randomly assigned to three groups, each receiving a different treatment to improve lipid concentration. No significant differences were observed between the treatment groups after randomization.

3.2. The effect of lipid-lowering regimes on lipid profile, oxidative stress indices, Tryptophan degradation during treatment.

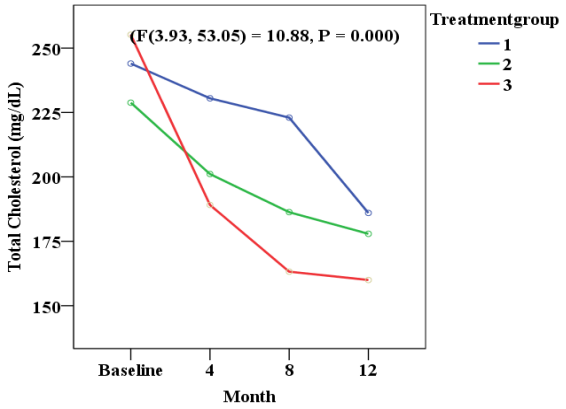

Figure 1A

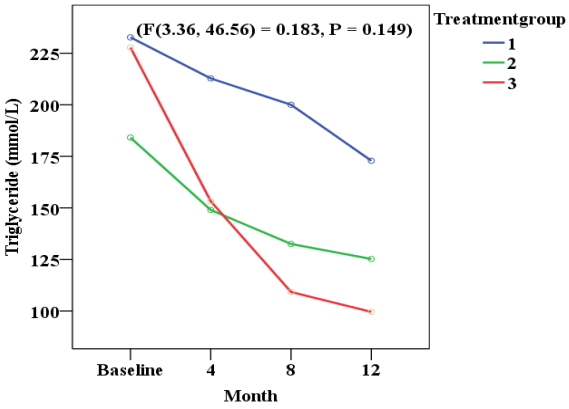

Figure 1B

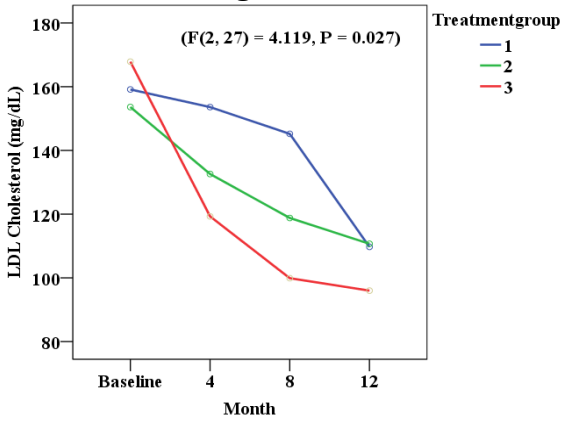

Figure 1C

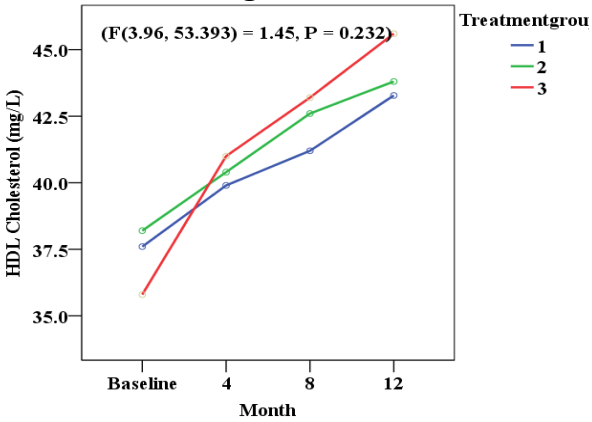

Figure 1D

Figure 1. The linear trend for TC, TG, LDL-C and HDL-C during treatment between 3 groups. The linear trend for TC (Figure 1A), TG (Figure 1B), LDL-C (Figure 1C) and HDL-C (Figure 1D)

We used repeated-measures ANOVA to analyze changes in mean scores over four time points and differences under three treatment therapies, while mixed ANOVA assessed the interaction between treatment time and type on the dependent variable. Treatment times were within-subject variables, and treatment subgroups were between-subject variables. TC gradually decreased during treatment, with significant

differences between time points in all patients and each group (p<0.05). Mixed ANOVA showed a difference between the three groups (F(3.93, 53.05) = 10.88, p=0.000) (Figure 1A), but multiple comparisons revealed significant differences only between group 1 vs. group 2 (p=0.023) and group 1 vs. group 3 (=0.003), with no difference between group 2 vs. group 3. TG also decreased significantly over time in each group, but no difference was found between the three regimens (F(3.36, 46.56) = 0.183, p=0.149) (Figure 1B). LDL-C decreased significantly in all patients, with improvements observed in each group, and the mean LDL-C concentration differed significantly between the three groups (F(2, 27) = 4.119, p=0.027) (Figure 1C), though multiple comparisons showed a significant difference only between group 1 and group 3. HDL-C increased significantly over time in all patients and within each group, but no significant difference was found between the three therapies (F(3.96, 53.393) = 1.45, p=0.232) (Figure 1C).

3.3. Correlation between lipid profiles, oxidative stress, tryptophan degradation during treatment

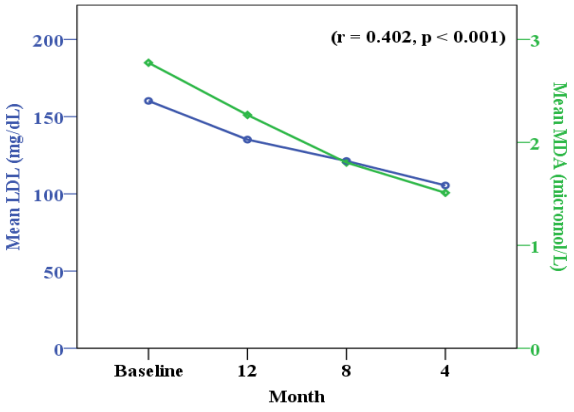

Figure 2A

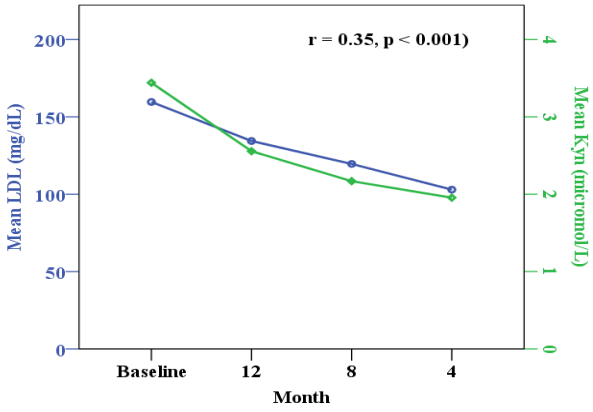

Figure 2B

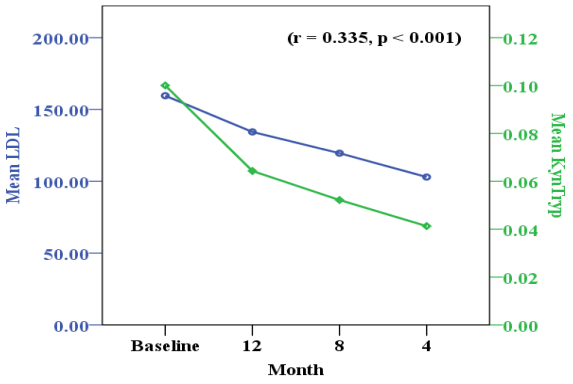

Figure 2C

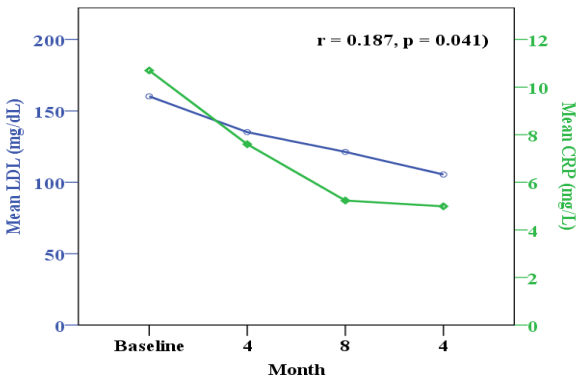

Figure 2D

Figure 2. Correlation between mean LDL-C and other variables during treatment

Correlation between mean LDL-C and mean MDA (Figure 2A); mean LDL-C and mean Kyn (Figure 2B); mean LDL-C and mean Kyn/Tryp ratio (Figure 2C); mean LDL-C and mean CRP (Figure 2D). Pearson Correlation. r is the correlation coefficient.

Figure 2 showed that during treatment with lipid-lowering drugs, a downtrend line of LDL-C leads to a decrease trend in MDA ($r = 0.402$, $p < 0.001$), as well as in inflammatory markers such as Kyn ($r = 0.35$, $p < 0.001$), Tryn / Tryp ($r = 0.335$, $p < 0.001$) and CRP ($r = 0.187$, $p < 0.041$).

IV. CONCLUSION

4.1. The effect of lipid-lowering regimes on lipid profile, oxidative stress indices, Tryptophan degradation.

CKD is frequently present with dyslipidemia, known as a risk factor for cardiovascular disease. Among that, TC, TG, and LDL-C concentrations increase while the HDL-C concentration decreases. Patients with stages 3-5 CKD are considered high or very high CV risk because of the high prevalence of the cardiovascular disease. LDL-C levels are considered a therapeutic target for hypolipidemia in CKD patients.

Single-use of statin or statin/ ezetimibe combination is indicated in CKD patients not dependent on dialysis. Based on these reasons, we have designed a study using lipid-lowering drugs to evaluate the effectiveness of the drugs on oxidative markers and inflammatory markers. We randomized patients into three different groups to receive three different treatment regimens. Group 1 was treated with 20mg of Simvastatin, group 2 was prescribed with a combination of 10 mg EZT and 20mg Simvastatin, while group 3 was given 10 mg EZT and 20mg.

Our results have demonstrated the role of lipid-lowering drugs in improving lipidemia profiles over the treatment time. TC, TG, LDL-C decreased while HDL-C gradually increased over time in all patients as well as in different treatment groups. Although there was no statistically significant difference between the 3 groups during treatment, after 12 months, the improvement in blood lipid was found to be greater in group 3 compared to the other 2 groups. As anticipated, three lipid-lowering therapies significantly improved lipid profile in all patients, in which, better results were showed in patients treated with ezetimibe/simvastatin 10/40 mg daily. Compared to all other lipid-lowering agents available, the HMG-CoA reductase inhibitor not only lowers LDL cholesterol more effectively but may also be better tolerated. The usual therapeutic dose lowers total cholesterol by 25 to 30%, LDL cholesterol by 30 to 40%, and triglycerides by 10 to 15%. HDL cholesterol increases by about 5 to 10%. Simvastatin has been reported to have a beneficial effect on cardiovascular mortality and also on coronary artery disease. In a large double-blind study in patients with coronary heart disease, simvastatin significantly reduces from 12% to 8% mortality rate and from 28% to 19% coronary events within five years [8].

Ezetimibe inhibits the cholesterol absorption from the small intestine, results in the decrease of cholesterol level in the blood. The decrease of cholesterol absorption leads to the decrease of cholesterol to the liver, therefore increased cholesterol clearance from the blood, and consequently, reduces cholesterol stores in the liver. The improvement of total cholesterol,

triglycerides, LDL-C, and HDL-C are results of the reduction in cholesterol absorption [9]. Simvastatin plus ezetimibe allows clinicians to simultaneously inhibit two cholesterol metabolisms: cholesterol biosynthesis in the liver and cholesterol absorption in the small intestine. This dual inhibitory mechanism has a substantially better performance in reducing serum low-density lipoprotein and increasing high-density lipoprotein, compared with the mechanism observed with drug alone. This combination increases an opportunity to have a successful treatment in patients with dyslipidemia [10].

Patients with CKD have high cardiovascular morbidity and mortality, as a consequence of an aggregation of cardiovascular risk factors in this population. Kidney disease increased gradually the signs of oxidative stress even in the early stages of CKD. This may be the result of an increase in reactive oxygen types as well as reduce the likelihood of anti-oxidants. This oxidative stress can accelerate the progression of kidney damage. Inflammation markers, such as C-reactive protein and cytokines increase when kidney function decline suggests that CKD is a low-grade inflammatory process. Oxidative stress is one of the factors that hat might be engaged with the activation of the inflammatory process in CKD. The utilization of statins to reduce the risk of major vascular events in CKD patients is essential because CKD is considered a high risk of the cardiovascular subject. This beneficial effect of statins is not only on lipid-lowering but especially concerning the regulation of oxidative stress and inflammation [11].

4.2. The relationship between lipid profiles, oxidative stress, tryptophan degradation during treatment.

When examining the correlation between the plasma lipid profiles, oxidative index, and inflammatory indices during treatment by lipid-lowering regimens, our results demonstrated that a decrease in LDL-C level leads to a statistically significant parallel reduction of MDA, Kyn, and Kyn/Tryp ratio. Besides, the LDL-C reduction treatment also significantly reduced the CRP concentration, although the correlation coefficient was not high ($r = 0.187$, $p = 0.041$). Moreover, the results from Fig. 2A and Fig. 2B demonstrated that, during 12 months of treatment, the reduction of MDA was accompanied by a significant reduction of Kyn/Tryp as well as a decrease of CRP. This shows the relationship between LDL-C, MDA, and Kyn, Kyn/Tryp. The improvement of inflammation in CKD patients stage 3-4 is explained by the decrease in LDL-C through improved oxidative stress. Results obtained in our study when analyzing the correlation of one antioxidant, PSH, with other variables showed that LDL-C decrease during treatment will significantly increase PSH ($r = 0.179$, $p = 0.05$) and treatment with an increase in PSH results in a marked decrease in inflammation, manifested in decreased Kyn, Kyn/Tryp. Moreover, PSH also showed a statistically significant positive correlation with other antioxidants such as PON1, TEAC. Unfortunately, the correlation coefficient between them is not high. These results suggest that 12 months of lipid-lowering therapy reduces inflammation in CKD patients possibly through an increase in antioxidants such as PSH as well as a decrease in MDA, as a result of a decrease in LDL-C. Our results are similar to our results of Angelo Zinellu, drug treatment significantly improved the lipid profile in all

patients and this was associated with a consistent reduction in Kyn and Kyn/Trp ratios regardless of treatment groups. The improvement of both oxidation and inflammation after cholesterol-lowering treatment in CKD can be mediated by restoring antioxidant taurine levels during treatment, which has been shown to improve oxidative stress status. The inflammation in CKD patients may be explained by cholesterol-lowering effects [12].

Our data are reliable with the results of another author when studying the effects of atorvastatin, a type of statins, on the inflammatory parameters of CKD [13]. This author demonstrated that, in addition to its lipid-lowering effect, atorvastatin also significantly reduces the plasma concentrations of CRP, IL-1, and TNF-a. Kyn is thought to be excreted by the kidneys, so increasing glomerular filtration rate during treatment with lipid-lowering drugs may also help improve Kyn. This is also proven in my study when there is an inverse correlation between eGFR with Kyn and with Kyn/Tryp ratio. However, all three lipid-lowering therapies in our study did not significantly improve eGFR. So the reduction of Kyn, Kyn/Tryp ratio can be explained by other factors. The significant relationship between a parallel reduction in Kyn concentration and a Kyn/Tryp ratio with a decrease in MDA suggests a close interaction between inflammation and oxidation in this context. The decrease in plasma Kyn that occurs during cholesterol-lowering therapy may be due to decreased IDO regulation as a result of reduced oxidative stress. A pre-inflammatory state is characterized in the CKD population. It is considered an important indicator of patient health and outcome. Although the exact biological mechanisms that contribute to the high rates of infection in chronic kidney disease are not well defined, ROS may have an important role to play, especially when kidney function is impaired. Tryp degradation via indoleamine (2,3) -dioxygenase (IDO), thereby increasing Kyn concentrations, has been suggested as an immune system activation marker. Inflammation is a mechanism that is sensitive to redox. Oxidative stress may contribute to a pro-inflammatory state in CKD through the activation of NF-kB, which in turn activates and recruit immune cells [11].

V. CONCLUSION

After 12 months of treatment, all three lipid-lowering therapies significantly improved lipid profiles, reduced oxidative stress (lower MDA, increased PSH, PON, and TEAC), and decreased inflammatory markers (lower Kyn concentration and Kyn/Trp ratio) in patients with CKD stage 3–4. The group receiving Simvastatin 40 mg/day + Ezetimibe 10 mg/day showed a tendency for greater improvement in inflammation and oxidative stress, though the difference was not statistically significant.

Additionally, LDL-C was positively correlated with MDA, Kyn concentration, and the Kyn/Trp ratio during treatment. The reduction in inflammation in CKD patients was primarily associated with lower LDL-C through decreased oxidative stress and may also be influenced by increased antioxidant levels, such as PSH.

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