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The Effectiveness of Atorvastatin on Kidney Function in Outpatient Diabetic Nephropathy Patients

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A B S T R A C T

Introduction: *Dyslipidemia can damage the kidneys through increased oxidative stress. Statins can be used as adjunctive therapy to standard treatment with Angiotensin Converting Enzyme Inhibitor (ACEIs) or Angiotensin II Receptor Blocker (ARBs) to improve renoprotection.*

Objective: *The study is to analyze the effectiveness of atorvastatin on changes in kidney function in diabetic nephropathy patients.*

Methods: *It was observational study. Samples were taken prospectively from diabetic nephropathy patients receiving atorvastatin at the Interna Polyclinic of the Bhayangkara Hospital Surabaya namely November 2021 – January 2022. Patients aged 18 – 80 years received atorvastatin for ≤3 months before the study was conducted, with Glomerular Filtration Rate (GFR) stages 3A, 3B, and 4, with mild, moderate, and severe albuminuria degrees.*

Results: *There are several patients which receive ARBs, namely candesartan and keto acid which can affect the results of the analysis so that different tests are conducted in the three groups, the result shows a significant decrease in Blood Urea Nitrogen (BUN) values in the sample group which receives additional keto acid therapy ($p < 0.05$); besides, a decrease in parameters albuminuria in the group with additional 16 mg candesartan therapy which is not significant.*

Conclusion: *The administration of atorvastatin alone 20 mg or in combination with candesartan 16 mg and keto acid on kidney function after 3 months of use can prevent the progression of diabetic nephropathy.*

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by increased blood glucose and changes in fat and protein metabolism (1,2). This disease is the main cause of end-stage renal disease (ESRD) and predisposes to cardiovascular disease (3).

According to the World Health Organization (WHO), diabetes sufferers have increased from 108 million in 1980 to 422 million in 2014 with an increase from 4.7% to 8.5% in patients over 18 years of age. In addition, between 2000 and 2016, death from diabetes increased by 5% and it was increasing faster in low- to middle-income countries than in high-income countries (4,5).

The 2018 Basic Health Research (RISKESDAS) report by the Ministry of Health, showed an increase in the prevalence of DM to 8.5% according to the prevalence of obesity as a risk factor for diabetes, namely 14.8% in 2013 to 21.8% in 2019 (1).

Hyperglycemia induces increased levels of calcium, diacylglycerol (DAG), phosphatidylserine, hydrogen peroxide, and superoxide which activates protein kinase C (PKC) resulting in endothelial dysfunction, smooth muscle proliferation, vascular permeability, and angiogenesis and affects kidney function and structure at various levels. It is one of the main drivers of the development of diabetic nephropathy (6–8).

The three main histological changes that occur in the nephrons are glomerular sclerosis, thickening of the glomerular basement membrane (GBM), and mesangial expansion (mesangial cell hypertrophy and matrix deposition) (8,9). These structural changes lead to glomerular hyperfiltration, increased proteinuria and albumin excretion, and decreased glomerular filtration rate (3,10).

The role of intensive glycemic control in reducing the onset and development of diabetic nephropathy has been conducted in several studies with the result showing that glucose is only partially responsible for the onset of kidney damage, the rest are other factors; such as hypertension and dyslipidemia. Hyperlipidemia is a risk factor for cardiovascular disease (CVD) in patients with type 2 DM or NDDM (3,8,11).

Statins, 3-hydroxy-3 methylglutaryl CoA inhibitors, have several mechanisms; such as, activation of the endothelial nitric oxide synthesis system, reducing oxidative stress, and inhibiting fibrosis and inflammatory pathways associated with preventing renal insufficiency. Therefore, statins may be used as an adjunctive therapeutic strategy to standard treatment with ACEIs or ARBs in order to improve renoprotection (12,13).

The side effect which often occurs when using statins is SAMS (Statin Induced Muscle Symptoms). Furthermore, the PRIMO (Prediction of Muscular Risk in Observational) study, a general practice survey in France, shows that 10.5% of hyperlipidemic patients which receive high doses of statins (especially simvastatin) reported mild to moderate muscle symptoms. In addition, SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) shows the effect of dose on the development of myopathy, where the administration of simvastatin (1 x 80 mg) orally produces 10 times higher than the dose (1 x 20 mg) orally (14).

A meta-analysis trial summarizes 14 trials with 2866 participants and using several different statin class drugs, including atorvastatin 10 mg/day, atorvastatin 20 mg/day, simvastatin 10-20 mg/day, rosuvastatin 2.5-10 mg/day, and lovastatin 30 mg/day. Compared with placebo, the excretion rate of urinary albuminuria and albumin in the statin group is reduced and the effect of statins is much stronger in subjects with pathological albuminuria and the changes are greatest in patients with urinary protein excretion of 30 to 300 mg/day, and least in patients with urinary protein excretion of less than 30 mg/day. Moreover, the decrease in albuminuria is greater in type 2 DM patients with diabetic nephropathy, and the decrease is significant over a period of 1 to 3 years on statin therapy. On the other hand, statins do not significantly reduce estimates of GFR, serum creatinine, and BUN. The efficacy of statins on renal function is time dependent and it is better in type 2 diabetes patients with nephropathy (5).

This study is conducted to analyze the effectiveness of using atorvastatin on changes in kidney function (serum creatinine, BUN, GFR values, and albuminuria) in diabetic nephropathy patients at the Internal Medicine Clinic of the Bhayangkara Hospital Surabaya. Furthermore, the benefits of the results of this study are expected to be additional information for clinicians and pharmacists in the hope of improving the quality of service and optimal therapeutic results in diabetic nephropathy patients.

METHODS

This study was an observational study with prospective sampling by recording laboratory results of kidney function values (Scr, BUN, GFR, and albuminuria) in diabetic nephropathy patients and following the patient's progress regarding possible side effects. In this study, researchers did not conduct actions, treatments or interventions which were different from the protocol for using atorvastatin in the Internal Medicine Division of the Bhayangkara Hospital Surabaya. Furthermore, the research sample was all patients diagnosed with diabetic nephropathy who received statin therapy and met the inclusion criteria. Sampling was conducted by using the consecutive non-random sampling method, for each patient who met the inclusion criteria, demographic data, medical history, treatment history, evaluation of clinical data, laboratory data, and monitoring medication adherence and side effects which might arise during the study in the period November 2021 – January 2022 were collected.

Inclusion criteria were type 2 DM patients with a diagnosis of diabetic nephropathy who received statin therapy, age range 18-80 years, received atorvastatin for ≤ 3 consecutive months before the study was conducted, had GFR stages 3A, 3B, and 4; had a mild, moderate, and severe

degree of albuminuria; and willing to participate in the study by signing an informed consent.

RESULT AND DISCUSSION

During the study, 17 patients were obtained which met the inclusion and exclusion criteria, but 1 patient dropped out during the observation period due to resignation so that the final sample total was 16 patients. Statistical analysis was carried out using the SPSS for Windows version 20.0 program to see if there was an effect of statin therapy on several parameters of kidney function including serum creatinine, BUN, GFR and albuminuria. Table 1 shows the overall sample characteristics.

From demographic data, it can be seen that the number of female patients is greater than that of males, namely 62.5% and 37.5%. The higher the age the higher the risk of experiencing DM. The results are in accordance with the 2018 RISKESDAS research (1)

Table 1. Characteristics of the Research Sample

Patient characteristic	Total Patient (N = 16 Patient)	
	Total	%
Gender		
Male	6	37.5
Female	10	62.5
Age Range		
40-60	5	31.25
61-80	11	68.75
Average	64.25 ± 8.71 (56-73)	
Duration of Type 2 DM		
0-10 year	9	56.25
11-20 year	3	18.75
21-30 year	4	25
GFR stage		
3A (45-59 ml/min	4	25
3B (30-44 ml/min)	7	43.75
4 (15-29 ml/min)	5	31.25
Albuminuria stage		
Normal-Mild	3	18.75
Moderate	7	43.75
Severe	6	37.5
Combination of Diabetes Medication (Type)		
1	3	18.75
2	4	25
3	5	31.25
4	4	25
Type of Diabetes Medication (Patient receives more than 1 type of medication)		
A. Oral antidiabetic (OAD)		
Sulfonilurea Class (Glimepiride, Glikuidon, Gliklazid)	11	68.75
Biguanid Class (Metformin)	6	37.5
Alpha Glucosidase Class Inhibitors (Akarbose)	3	18.75
DPP-4 Class inhibitors (Vildagliptin)	10	62.5
Thiazolidinedione Class (Pioglitazon)	5	31.25
B. Insulin		
Rapid Acting	2	12.5
Long Acting	5	31.25
Use of *Angiotensin Receptor Blocker* (ARB)		
Patients With candesartan 16 mg	4	25
Patient Without candesartan 16 mg	12	75

Use of *keto acid,*		
Patients with ketoacids	3	18.75
Patients without ketoacids	13	81.25

Analysis of the Effect of Atorvastatin on Renal Function Parameters

The effect of atorvastatin administration on kidney function can be seen from the significant differences between the values of the dependent variables (BUN, serum creatinine, GFR, and albuminuria) during pre and post therapy conditions. For the BUN and Glomerular Filtration Rate (GFR) parameters the data are normally distributed ($p>0.05$) so that the analysis is conducted by using the Paired T-test. Meanwhile, for serum creatinine and albuminuria, the data are not normally distributed ($p<0.05$) so that the Wilcoxon signed ranks test is used for analysis. In addition, the test result shows that the use of atorvastatin 20 mg for 3 months has no effect on kidney function and it is not statistically significant ($p>0.05$) **(Table 2)**

Table 2. Differences in the values of pre- and post-patient renal function parameters

Treatment Group	**Parameter**												**Albuminuria**			
	BUN				**Serum Creatinine**				**Glomerular Filtration Rate (GFR)**							
	Average ± SD		**Sig. (p)**		**Average ± SD**		**Sig. (p)**		**Average ± SD**		**Sig. (p)**		**Average ± SD**		**Sig. (p)**	
	pre	***post***	***pre***	***post***	***pre***	***post***	***pre***	***post***	***pre***	***post***	***pre***	***post***	***pre***	***post***	***pre***	***post***
Atorvastatin	24.06 ± 6.61	22.08 ± 6.71	0.118	0.644	1.66 ± 0.59	1.70 ± 0.60	0.015	0.019	38.01 ± 9.79	37.30 ± 9.43	0.083	0.656	152.06 ± 127.99	154.86 ± 130.00	0.003	0.002

In addition, in this study some patients received one of the additional Angiotensin Receptor Blocker (ARB) therapies, namely candesartan 16 mg or keto acid. Therefore, it is necessary to conduct a test in order to see the effect of additional therapy with candesartan 16 mg or keto acid, compared to the group which only receives atorvastatin on differences in kidney function parameter values during pre and post therapy conditions. Table 2 shows that BUN, serum creatinine, and GFR are analyzed by using the Paired T-test (data is normally distributed ($p>0.05$)) while for albuminuria is tested by using Wilcoxon (data is not normally distributed ($p<0.05$)).

Table 3 shows that there is a statistically significant decrease in BUN values in the sample group which receives additional keto acid therapy ($p <0.05$). However, there is a decrease in the BUN parameter in the group which only receives 20 mg of atorvastatin, a decrease in the albuminuria parameter in the group with the additional 16 mg of candesartan therapy, and an increase in the GFR value in the group with the addition of keto acid therapy which is not statistically significant.

Analysis of the Effect of Atorvastatin on Renal Function Parameters Based on Type of Therapy

This study some patients got either additional ARB therapy, namely candesartan 16 mg or keto acid. Therefore, it is necessary to do a test to see the effect of additional therapy candesartan 16 mg or keto acid, compared to the only group to get atorvastatin on differences in current renal function parameters values pre n post therapy condition. **Table 3** showed that BUN, serum creatinine, GFR and albuminuria were analyzed ($p>0.05$). **Table 4** showed that there is a decrease in the BUN value statistically significant in the sample group that received addition of keto acid therapy ($p<0.05$). However, there is a decrease in parameters BUN in the group that only received atorvastatin 20mg, decreased parameters of albuminuria in the group with additional candesartan therapy 16 mg, and an increases GFR values in the group with the addition of ketocid therapy not significant/statistically significant. Angiotensin blockade with ARBs will dilate different arterioles, inhibit mesangial constriction, and increase GFR coefficient. Another opportunity to reduce kidney damage besides blood sugar control and hypertension is to reduce uremia symptoms by using a low protein diet with supplementation keto acid analogs or essential amino acids (13)

Table 3. Differences in pre- and post-renal function parameter values based on the type of treatment group

Treatment Group	Parameter												Albuminuria			
	BUN				Serum Creatinine				Glomerular Filtration Rate (GFR)							
	Average ± SD		Sig. (p)		Average ± SD		Sig. (p)		Average ± SD		Sig. (p)		Average ± SD		Sig. (p)	
	pre	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*
Only Atorvastatin 20 mg (N=9)	21.22 ± 5.63	20.61 ± 3.43	0.320	0.813	1.56 ± 0.38	1.58 ± 0.38	0.278	0.538	40.11 ± 8.42	39.36 ± 8.18	0.157	0.957	138.56 ± 127.83	143.70 ± 135.63	0.036	0.015
Atorvastatin 20 mg + Candesartan 16 mg (N=4)	26.25 ± 6.50	28.57 ± 9.19	0.717	0.147	2.09 ± 0.93	2.17 ± 0.96	0.578	0.218	31.40 ± 10.33	30.12 ± 10.05	0.932	0.190	212.25 ± 117.34	200.42 ± 127.27	0.232	0.272
Atorvastatin 20 mg + keto acid (N=3)	29.67 ± 6.65	21.50 ± 8.52	0.144	0.510	1.42 ± 0.41	1.39 ± 0.32	0.302	0.271	40.53 ± 12.54	40.70 ± 10.42	0.275	0.147	112.33 ± 162.53	127.60 ± 151.83	0.018	0.349

Table 4. Comparative analysis of changes (**Δ)** in renal function parameters based on the type of treatment group

Treatment Group	Δ BUN (mg/dl)		Δ Serum Kreatinin (mg/dl)		Δ GFR (mg/dl)		Δ Albuminuria (mg/dl)	
	Average ± SD	Sig. (*p*)	Average ± SD	Sig. (*p*)	Average ± SD	Sig. (*p*)	Average ±	Sig. (*p*)
Only Atorvastatin 20 mg (N=9)	-0.61 ± 4.29	0.041	0.02 ± 0.12	0.565	-0.75 ± 2.81	0.795	5.14 ± 41.19	0.324
Atorvastatin 20 mg + Candesartan 16 mg (N=4)	2.32 ± 6.97		0.08 ± 0.19		-1.27 ± 2.99		-11.82 ± 14.41	
Atorvastatin 20 mg + keto acid (N=3)	-0.82 ± 3.17		-0,03 ± 0.09		0.17 ± 2.25		15.27 ± 31.96	

Analysis of the Effect of Atorvastatin on Changes in GFR Values Based on Disease Stage/Degree

In this study, the samples studied have different stages/degrees of GFR. Therefore, an analysis is needed in order to see whether there is an effect of giving atorvastatin during pre and post therapy conditions at each stage. The results in **Table 5** showed that there is an increase in the GFR value at stage 3A, 3B and 4 which is not statistically significant. **Table 6** showed that administration of atorvastatin can increase the value of GFR at the stage 3A, 3B and 4 which is not statistically significant.

Another study by Sanguankeo et al in a meta-analysis stated that statins could not reduce proteinuria because the research sample criteria are different from several studies. Previously it was patients with CKD stages 3-4 (eGFR 15-59 ml/min/1.73 m2) with marked albumin excretion (>300 mg/day). Conclusion from the meta analysis suggests that statins may have an effect on decline albuminuria in early stage diabetic nephropathy patients preventing renal deterioration in diabetic nephropathy patients (5).

Table 5. Differences in pre- and post GFR values based on stage/degree of disease

GFR Stage	GFR (N=16)	
	Average **± SD**	Sig. (p)
3A (45-59 ml/min)	0.05 ± 2.00	0.963
3B (30-44 ml/min)	1.90 ± 2.62	0.104
4 (15-29 ml/min)	-0.42 ± 2.84	0.758

Table 6. Effect of atorvastatin administration on changes in GFR staging

GFR Stage	Average ± SD	Sig. (*p*)
3A (45-59 ml/min)	**Baseline Condition/*pre-***	0.705
	48.35 ± 2.33	
	Condition *post*	
	49.25 ± 4.87	
3B (30-44 ml/min)	**Baseline Condition/*pre-***	0,085
	42.26 ± 1.86	
	Condition *post*	
	39.92 ± 3.73	
4 (15-29 ml/min)	**Baseline Condition/*pre-***	0.556
	26.50 ± 4.38	
	Condition *post*	
	28.05 ± 1.76	

Analysis of the Effect of Atorvastatin on Changes in Albuminuria Values Based on Stage/Degree of Disease

The sample of this study has varying stages/degrees of albuminuria. Therefore, an analysis is needed to see whether there is an effect of atorvastatin administration during pre- and post-therapy conditions at each stage of albuminuria degree. The results in **table 7** showed that there is a decrease in the value of albuminuria at mild stage which is not statistically significant/significant ($p > 0.05$).

Table 7. Effect of atorvastatin administration on changes in albuminuria stage

Albuminuria Stage	Average ± SD	Sig. (*p*)
Mild (0-30 mg/L)	**Baseline condition /*pre-***	0.655
	6.5 ± 3.53	
	Condition *post*	
	6.0 ± 2.82	
Moderate (30-300 mg/L)	**Baseline condition /*pre-***	0.465
	83.50 ± 42.91	
	Condition *post*	
	95.32 ± 94.15	
Severe (>300 mg/L)	**Baseline condition /*pre-***	1.00
	300 ± 0.00	
	Condition *post*	
	300 ± 0.00	

Achievement of the therapy target in this study is that patients do not experience an increase in disease progression which can be seen from the parameters of renal function which have been studied that are BUN, serum creatinine, GFR, and albuminuria after 3 months of using atorvastatin. Furthermore, Seen from the pre- and post-results, there are several patients who experienced improvement in renal function values as listed in **table 9**. Meanwhile, several other patients, although they do not improve, do not experience an increase in the disease stage as observed from the GFR stage and albuminuria. Although not statistically significant, there were several patients who experienced improvement during the observation time as seen from a decrease in urinary excretion values and an increase in GFR, although it still did not change the patient disease stage.

Table 9. Effect of atorvastatin administration on changes in albuminuria stage

Experiencing Improvement	Number of Samples	Percentage (%)
BUN reduction	10	62.5
Serum Creatinine reduction	6	37.5
eGFR increase	8	50
Albuminuria reduction	5	31.25

During the 3-month use of atorvastatin, an assessment is conducted in the incidence of side effects in 16 samples. During the observation period, no samples are found to experience side effects in the form of myopathy due to the use of 20 mg of atorvastatin.

CONCLUSION

Based on a study conducted to see the effectiveness of atorvastatin administration on kidney function after 3 months of use in outpatient diabetic nephropathy patients conducted at the Internal Medicine Polyclinic at

Bhayangkara Hospital Surabaya for the period November 2021 to April 2022, it can be concluded that single Atorvastatin (1 x 20 mg) per oral or in combination with candesartan (1 x 16 mg) orally and keto acid can prevent the progression of diabetic nephropathy as assessed by the percentage of patients with decreased BUN values (62.5%), serum creatinine (37.5%), albuminuria (31.25%), and increased GFR (50%). In addition, the administration of combination with keto acid gives a significant difference in decreasing BUN values (18.75%).

The achievement of the therapeutic targets in this study were that the patients did not experience changes or decreased kidney function, which can be seen from the various parameters of kidney function studied, namely BUN, serum creatinine, GFR and albuminuria after 3 months of observing the use of atorvastatin. Judging from the pre- and post- results of all parameters of kidney function in each patient, all study samples (100%) did not experience a decrease in kidney function or did not experience an increase in disease stage as observed from GFR stage and albuminuria.

It is necessary to conduct strict monitoring of diet and medication adherence in patients with diabetic nephropathy. The number of research subjects and the length of the research period need to be added so that better data validity can be obtained. In addition, monitoring of kidney function for GFR parameters can be conducted every 6 months while monitoring of albuminuria can be conducted every 3-6 months. If the albuminuria value is <30 mg/24 hours, it can be re-evaluated every year.

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CONFLICT OF INTEREST

The author declares that there is no potential conflict of interest in connection with the research, writing and publication of this article.

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