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Acute versus Staged Introduction of Statins in Chronic Kidney Disease Patients.

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Abstract

Background & Aim: Chronic kidney disease is any kidney structure or function abnormalities for 3 months or more. It is progression associated with poor health outcomes, increased cardiovascular (CV) complications, early death, and kidney failure. Statins are used to treat hypercholesteremia, so they are used as a principal therapy for the prevention of atherosclerosis & cardiovascular disease. We plan to determine the impact of acute versus gradual introduction of statin doses in CKD studied cases, to improve the tolerance of these studied cases, and gain protection of kidneys and cardiovascular system.

Methodology: This prospective study was conducted between March 2023 and October 2023 and one hundred and two patients were selected. Patients were categorized into two groups (51 in each): Group (A) on high-dose statins (80 mg) from the start, and Group (B) on low introduction of statins (5 mg) then the dose increased every 4 weeks. Follow-up was 6 months from the dose of the maximum tolerated statin. The up titration of statins was increasing the dose every 1 week by 10 mg. The group of high-intensity statins was 6 months from the start. **Results:** Our analysis includes one hundred and two patients; they are 61 males (59.8%) and 41 females (40.2%) with a mean age of 58.25 ± 10.34. We found no difference among the 2groups regarding their comorbidities (hypertension, diabetes) (P-value =0.060, 0.550 respectively), and their levels of serum urea and creatinine (P-value =0.211, 0.058 respectively). We found a significant difference among the 2groups regarding liver follow-up profile (ALT, AST) (P-value = 0.007, 0.000 respectively) and creatine kinase follow-up (P-value = 0.002). **Conclusion:** Gradual introduction of statin therapy has been better tolerated than immediate high-dose statin therapy in chronic kidney disease patients. These results support starting with low-dose statins & gradually increasing the dose to improve statin tolerance and protect liver and muscle function.

Keywords: Statins, chronic kidney disease, CKD.

Introduction

The existence of anomalies in the structure or function of the kidneys that have persisted for more than three months & have an impact on health is known as chronic kidney disease. kidney damage or, regardless of the etiology, an estimated glomerular filtration rate of less than sixty ml/min/1.73mt2 that persists for 3months or more. It is a condition in which kidney function gradually declines and renal replacement therapy (dialysis or transplantation) becomes necessary) **[1].**

Global prevalence of chronic kidney disease has been a progressive condition that affects > ten percent of the general population worldwide, amounting to > 800million individuals **[2].** Risk factors of CKD are thought to be mostly hypertension and diabetes. Also, family history of kidney failure, age ≥ 60 years, smoking, obesity, kidney stones, and cardiovascular disease; however, infectious, auto-immune, genetic, obstructive, & ischemic injury have been all prevalent etiologies **[3-4].**

studied cases with chronic kidney disease experience lipid abnormalities that lead to elevated triglycerides, decreased high-density lipoprotein cholesterol, elevated levels of apolipoproteinB, & decreased levels of apolipoprotein A1. studied cases with nephrotic syndrome have higher levels of LDL-C, or low-density lipoprotein cholesterol. On the other hand, studied cases with moderate chronic kidney disease who do not have nephrotic syndrome typically have normal levels of low-density lipoprotein cholesterol, normal levels of LDL-C, & raised triglycerides **[5].**

Studied cases with CKD have been much more likely to die of cardiovascular disease than to experience kidney failure. CKD patients must be considered at increased risk for CVD. Statin medications are used in the management and treatment of hypercholesteremia so, according to several clinical research, statins are becoming a commonly used main treatment for the primary & secondary prevention of atherosclerosis & CVD **[6-7].** According to a recent investigation, atorvastatin medication decreased the relative risk of the 1st cardiovascular incident by eleven percent in individuals without CKD & twenty-eight percent in studied cases with CKD when compared to standard care **[8].**

The most frequent complication in studied cases with chronic kidney disease that advances renal damage & declines renal function is dyslipidemia brought on by renal dysfunction. It is widely acknowledged that cholesterol control therapy should be started as soon as possible in individuals with chronic kidney disease **[9].** Here, we aim to determine the effect of acute versus gradual introduction of statin doses in chronic kidney disease patients, to improve the tolerance of these patients especially the effect on the liver and muscles, to get the best protection of kidneys and cardiovascular system.

Methods

At the Aswan University Hospital in Aswan, Egypt, prospective research was carried out. The Institutional Review Board at Aswan University's Faculty of Medicine granted ethical approval for this research. Prior to the studied case's involvement in the trial, the nature, goal, & hazards were fully described to them, & each participant provided signed informed consent. All subjects' identifying information was kept private & hidden from the public. Between March 2023 and October 2023, one hundred and two studied cases had been selected from the outpatient clinics of the Internal Medicine Department at Aswan University Hospital. The calculation had been done by using Open Epi software with a confidence level of ninety five percent & power of 90%. This is based on the development of major adverse cardiac events in studied cases with chronic kidney disease receiving statins 25.2% compared to 58.1% in chronic kidney disease studied cases not receiving statins **[10].** All patients were subjected to Demographic data such as gender, age, body mass index, and history of hypertension & diabetes mellitus. Laboratory measurements such as fasting blood glucose (FBG), lipid profile, serum urea, serum creatinine, liver profile (ALT AST INR), and CK. Individuals receiving medical treatment for chronic kidney disease (Statins) were admitted to the research; those who had died throughout hospitalization, had end-stage renal disease requiring hemodialysis or peritoneal dialysis, had acute ST-segment elevation myocardial infarction, cardiogenic shock, or hemodynamic instability had not been included. Patients were categorized into two groups (51 in each): Group (A) received high-dose statin (atorvastatin 80 mg) from the start. Group (B) received a low introduction of statins (5 mg) then the dose increased every 4 weeks. According to whether they had been administered high-dose statins (atorvastatin 80mg) which is a safe dose according to the American Journal of Cardiology or a low dose (5 mg), and the increase in the dose was every 4 weeks. Follow-up was 6 months from the dose of the maximum tolerated statin. The up titration of statins was increasing the dose every 1 week by 10 mg. The group of high-intensity statins was 6 months from the start.

- Statistical Analysis:

Group differences (CKD vs CKD + CAD) had been evaluated using Wilcoxon tests for non-parametric variables & t-test for parametric variables. Continuous & categorical data had been provided as mean ± standard deviation & number (%). The Chi-square test had been utilized to compare categorical variables. Kaplan-Meier curves had been used to estimate the long-term event-free rate, & the long-rank test had been employed to see whether there had been any statistically significant differences in the survival rates of the 2groups. We employed a univariate Cox regression model to find the possible variables that could impact the frequency of cardiovascular events. To

find those independent factors, a multivariate Cox regression analysis had been also created. The degree of the risk of cardiovascular events was expressed using hazard ratios & the associated ninety five percent confidence intervals. Each statistical analysis used 2 tails. P less than 0.05 had been also regarded as statistically significant. SAS 9.1 (SAS Institute, Cary, NC, USA) had been used for all statistical analyses.

Results

This study includes one hundred and two participants, they are 61 males (59.8%) and 41 females (40.2%) with a mean age of 58.25 ± 10.34 & a mean body mass index of 25.32 ± 3.37. The participants had been separated into 2 groups; Group A, 62.7% were males the mean age was 60.92 ± 13.80 as well as the mean BMI was 24.75 ± 3.23. In Group B, 56.9% were male & the mean age was 56.22 ± 4.14 as well as the mean BMI was 25.89 ± 3.45. There has been no statistically significant difference among the2 studied groups regarding age, sex, & BMI (*P*-value = 0.086, 0.545, 0.087) respectively **(Table 1).**

As regards comorbidities, in group A, 78.4% had Hypertension and 47.1% had Diabetes mellitus, but in group B, 92.2% had Hypertension and 41.2% had Diabetes mellitus. There is no statistically significant difference among the 2studied groups regarding their comorbidities (P-value =0.060, 0.550) respectively (Table 2). In group A, the mean serum urea was 100.09 ± 32.62 and serum creatinine (mg/dL) was 2.91 ± 1.01. In group B, the mean serum urea was 94.04 ± 10.76 and serum creatinine (mg/dL) was 2.21 ± 2.42. There has been no statistically significant difference among the2 studied groups regarding S. Urea & S. Creatinine (mg/dL) (P-value =0.211, 0.058) respectively **(Table 3).**

The results of liver function tests in group A, the mean ALT was 26.58 ± 21.45 and AST was 31.67 ± 22.63. In groupB, the mean ALT had been 32.27 ± 2.73 and AST was 31.78 ± 4.83. There is no statistically significant difference among the 2studied groups regarding baseline liver function (P-value = 0.063, 0.972) respectively **(Table 4).** As regards the follow-up profile, in group A, the mean ALT was 54.59 ± 21.41 and AST was 57.83 ± 17.89. In group B, the mean ALT was 45.78 ± 7.33 and AST was 46.06 ± 7.96. There is a highly statistically significant difference among the2 studied groups regarding liver profile follow-up (P-value = 0.007, 0.000) respectively **(Table5).** The creatine kinase levels are in group A, the mean Creatine kinase level was174.76 ± 37.14. in group B, the mean Creatine kinase level was171.43 ± 12.65. There had been no statistically significant difference among the 2studied groups regarding Creatine kinase (P-value = 0.545) **(Table 6).** As regards the follow-up profile, in group A, the mean Creatine kinase level had been 223.84 ± 79.89. in groupB, the mean Creatine kinase level had been 188.53 ± 6.27. There had been a highly statistically significant difference among the2 studied groups regarding Creatine kinase follow-up (P-value = 0.002) **(Table 7).**

Discussion

It is recognized that the risk of cardiovascular disease is comparable to that of chronic kidney disease. Compared to the general population, people with CKD had a much greater incidence of CVD, which is now the main reason for death in these studied cases. The most frequent complication in individuals with chronic kidney disease is dyslipidemia brought on by renal dysfunction, which exacerbates renal damage & impairs renal function **[11].**

The cardiovascular protective impact of statins is linearly correlated with the dosage of statin medication. When compared to a moderate dose, high-intensity statin medication is more effective in lowering the risk of non-fatal events & mortality, according to a meta-analysis involving 40,000 studied cases. It is currently unknown whether studied cases with CKD may benefit from & safely take high-intensity statin medication, & this issue has drawn a lot of interest from clinical professionals around the globe **[12].** Numerous recent meta-analyses examining the impact of statins on individuals with chronic kidney disease have revealed that statin treatment may reduce mortality & cardiovascular events in CKD studied cases, but not in those receiving hemodialysis **[13].**

The results of our study -which is discussed earlier- disagree with a previous meta-analysis that examined the safety of high versus low-dose atorvastatin treatment. The authors concluded that studied cases on high-dose atorvastatin therapy had a higher likelihood of transaminase increases compared to those on low-dose atorvastatin therapy **[14].** It contradicts a systematic study & meta-analysis by Yan et al. that found no discernible difference in persistent increase of liver enzymes between high-intensity statin medication & non-intensive statin therapy or

placebo. Compared to the general population, studied cases with CKD have been thought to be more susceptible to high-dose or intense drug application. Nevertheless, they were unable to find statistically significant variations in any of the safety assessments among the high-intensity statin therapy & control groups in their investigation **[11].**

Every statin is excreted by the liver, & each statin's lipophilicity affects how quickly it is done. In comparison to low-intensity hydrophilic statins, a meta-analysis showed that the RR for elevated transaminases with high-intensity hydrophilic statins had been 3.54-fold (95%CI 1.83 - 6.85). However, there was no correlation seen between the rise of transaminases & higher-intensity lipophilic statins as opposed to low-intensity statins **[15].**

An investigation on the safety & effectiveness of high-intensity statin therapy in individuals with CVD older than sixty-five years, as this age group is both a risk factor for chronic kidney disease & a barrier to high-dose or intensive drug use **[17].**

Like a prior meta-analysis that found CK elevations were uncommon in studied cases on atorvastatin & did not appear to be dose-related, there had been no statistically significant difference among the 2groups in our trial at baseline regarding creatine kinase **[14].** According to statin therapy intensity, Davis & Weller calculated the relative risk of statin-associated musculoskeletal complaints & discovered that raised CK indicated a higher risk with greater intensity. **[18].**

Conclusion

Our study demonstrated that the gradual introduction of statin therapy has been better tolerated than immediate high-dose statin therapy in chronic kidney disease studied cases. Although baseline characteristics had been similar among the 2groups, studied cases receiving high-dose atorvastatin 80mg from the start (Group A) had significantly higher elevations in liver enzymes (ALT and AST) at follow-up compared to those receiving gradual up-titration from 5mg over 4 weeks (Group B). There had been no significant differences among groups in baseline or follow-up creatine kinase levels. Given the aim to improve statin tolerance and protect liver and muscle function in this population, these results support starting with low-dose statins and gradually increasing the dose over one month to balance cardiovascular protection with safety and tolerability. We recommend that further studies with many patients must be done to support our results for better outcomes and high satisfaction.

Ethics approval & consent to participate:

The Institutional Review Board of the Aswan University Faculty of Medicine granted ethical permission for this research, & prior to participant participation, everyone provided written informed consent. All subjects' identifying information was kept private & hidden from the public.

Conflict of interests:

The authors have disclosed no conflicts of interest.

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Tables and figures

Table (1): Comparison between both groups as regards demographic data.

	Total (n=102)	Group (A) (n=51)	Group (B) (n=51)	Test	P value
Age (years)					
Mean ± SD	58.25 ± 10.34	60.92 ± 13.80	56.22 ± 4.14	2.021	0.086
Minimum - Maximum	26 – 85	26 – 85	49 – 62		
Sex					
Male	61 (59.8%)	32 (62.7%)	29 (56.9%)	0.367	0.545

Female	41 (40.2%)	19 (37.3%)	22 (43.1%)		
BMI (kg/m^2)					
Mean ± SD	25.32 ± 3.37	24.75 ± 3.23	25.89 ± 3.45	-1.728	0.087
Minimum - Maximum	18.6 – 32.8	18.6 – 32.8	19.4 – 32.8		

X^2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.

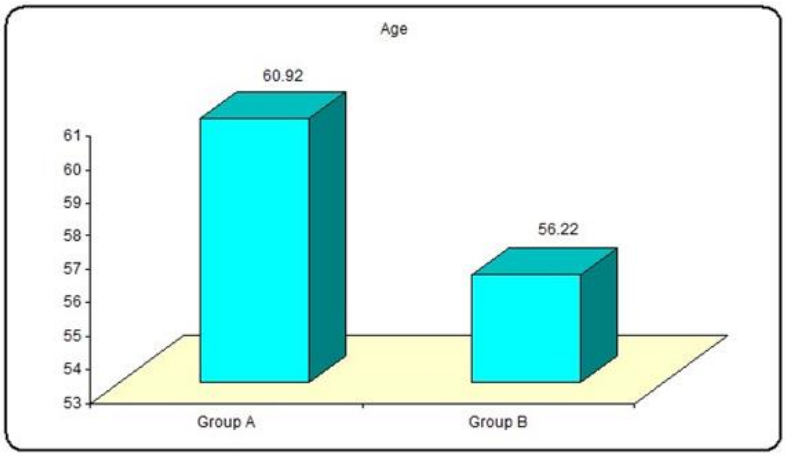

Figure (1): Comparison between both groups as regards Age.

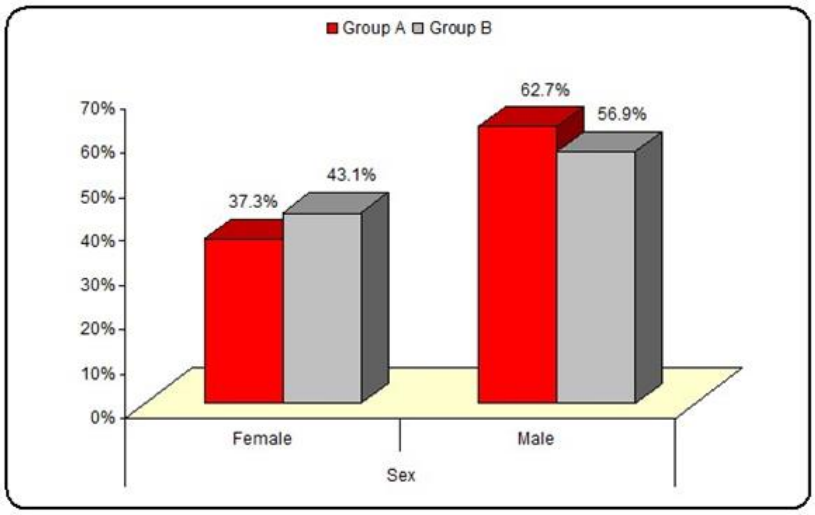

Figure (2): Comparison between both groups as regards sex.

Table (2): Comparison between both groups as regards medical data.

	Group (A) (n=51)	**Group (B) (n=51)**	**Test**	**P value**
Hypertension	40 (78.4%)	47 (92.2%)	3.830	0.060
Diabetes mellitus	24 (47.1%)	21 (41.2%)	0.358	0.550

X2: Chi-square test, p-value>0.05: nonsignificant, p-value <0.05 significant.

Table (3): Comparison between both groups as regards S. Urea and S. Creatinine (mg/dL).

	Group (A) (n=51)	Group (B) (n=51)	Test	P value
S. Urea				
Mean ± SD	100.09 ± 32.62	94.04 ± 10.76	1.259	0.211
Minimum - Maximum	35 – 187	70 – 110		
S. Creatinine (mg/dL)				
Mean ± SD	2.91 ± 1.01	2.21 ± 2.42	1.915	0.058
Minimum - Maximum	1.5 – 5.9	1.4 – 19		

X2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.

Table (4): Comparison between both groups as regards baseline liver function.

	Group (A) (n=51)	Group (B) (n=51)	Test	P value
ALT (U/L)				
Mean ± SD	26.58 ± 21.45	32.27 ± 2.73	-1.882	0.063
Minimum - Maximum	4 – 143	27 – 37		
AST (U/L)				
Mean ± SD	31.67 ± 22.63	31.78 ± 4.83	-0.035	0.972
Minimum - Maximum	8.3 – 132	22 – 41		

X2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.

Table (5): Comparison between both groups as regards follow-up liver profile.

	Group (A) (n=51)	Group (B) (n=51)	Test	P value
ALT (U/L)				
Mean ± SD	54.59 ± 21.41	45.78 ± 7.33	2.778	0.007
Minimum - Maximum	12 – 97	33 – 62		
AST (U/L)				
Mean ± SD	57.83 ± 17.89	46.06 ± 7.96	4.294	0.000
Minimum - Maximum	16 – 110	33 – 64		

X2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.

Table (6): Comparison between both groups as regards Baseline Creatine kinase level.

	Group (A) (n=51)	Group (B) (n=51)	Test value	P value
Creatine kinase level (U/L)				
Mean ± SD	174.76 ± 37.14	171.43 ± 12.65	0.607	0.545
Minimum – Maximum	66 – 308	120 – 198		

X2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.

Table (7): Comparison between both groups as regards follow-up Creatine kinase level.

	Group (A) (n=51)	Group (B) (n=51)	Test value	P value
Creatine kinase level (U/L)				
Mean ± SD	223.84 ± 79.89	188.53 ± 6.27	3.147	0.002
Minimum - Maximum	169 – 606	178 – 203		

X2: Chi-square test, T: Two-Sample Independent t-Test, p-value>0.05: nonsignificant, p-value <0.05 significant.