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ADDING NIACIN WITH ATORVASTATIN IN PATIENTS WITH RENAL ISCHEMIA: A COMPARATIVE STUDY

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ABSTRACT: The study was aimed to compare the effect of lipid lowering only through Atorvastatin and lipid lowering combined with HDL-C raise by adding Niacin on the lipid profile and renal outcomes in renovascular disease. It was prospective, analytical hospital based study. In diagnosed patients Atorvastatin (20mg) and/or in combination with Niacin Extended Release 500mg/day was prescribed randomly distributed in two groups of equal size (n=60) for four months. 50 healthy individuals were also added to get local reference values. Pre and post treatment lipid profile and Apo A-1 were measured and analyzed using t-test at alpha 0.05. There was no difference in the baseline values. Atorvastatin induced a significant reduction in total cholesterol (p<0.05) and LDL (p<0.05), while decrease in TG and vLDL levels remained insignificant. It also causes an increase in HDL (p<0.05) and Apo A1 that was non-significant. Atorvastatin combined with NER reduced cholesterol (p<0.05), TG (p<0.05), LDL (p<0.05) enhanced HDL (p<0.0001) and Apo A1 (p<0.01). The inter-group comparison of both treatments demonstrated relatively better outcomes following Atorvastatin NER combination in terms of good cholesterol (p<0.01) for HDL and (p<0.01) for Apo A1, while in term of lipid lowering potentials, we found no difference. Addition of NER to statin has beneficial effect on lipid profile even at a comparatively low dose of 500mg and well tolerated in renovascular disease patient. This combination may be used to prevent further systemic complications in this group of patients.

INTRODUCTION: Renal ischemia is a condition of kidney hypo-perfusion beyond the level of kidney auto-regulation that brings significant decrease in glomerular filtration rate (GFR) by affecting the whole functional parenchyma and is mainly result of renal vessel occlusion¹.

It is a relatively new clinical condition that has been widely discussed and referred in literature as ischemic renal disease (IRD), chronic renal ischemic disease (cRID), azotemic renovascular disease or renal insufficiency of renovascular hypertension².

The clinical presentation includes bland urinary sediments, mild to moderate proteinuria, gradually reducing GFR that may lead to end-stage renal disease (ESRD). The progressively damaging abnormality is likely to develop in older patients (particularly over 50 years), in patients with difficult to cure hypertension usually non-

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responsive to Angiotensin-converting enzyme (ACE), diabetes mellitus, female sex, renal artery or abdominal bruit, chronic/heavy smokers, increase cholesterol level and in patients with clinically manifested atherosclerosis^{1, 3}. Among these, the most prevailed etiological findings are hypertension (97%), hypercholesterolemia (63%) and smoking (70%) as reported in multicentre GEDENI study⁴. It is potentially reversible disorder and the loss can be either prevented or slower down by treating the underlying etiological factor.

In ischemic nephropathy where elevated cholesterol is one of the principal causes, the basic disease genesis mechanism is comprised of plaque formation in the renal artery producing an obstruction in the blood flow exposing the renal tissue to ischemia. The damage to functional parenchyma that impairs the kidney physiology includes atrophied tubules, collapsed glomeruli and interstitial fibrosis⁵. The interventional approach mainly addresses to relief the renal derangements and is symptom based initially, once dyslipidemia is identified normally extended to lower the increase concentrations of cholesterol and low density lipoproteins (LDL).

Sufficient data has now been published that endorse a reduction in high density lipoprotein (HDL) is equally important contributor in the development of sclerosis artery disease, even can be sole causing factor at any level of cholesterol^{6, 7}. This is the reason current therapeutic regime is being transformed to not only aim at lowering LDL but also to enhance the levels of HDL. Statins are commonly used drugs that show a dose-dependent reduction in LDL and possess over all lipid profile beneficial effects. They also have known to bring a few percent rises in HDL level^{8,9}.

However, their primary objective is not to increase HDL so they cannot be first choice if drug administration is to improve HDL levels. To date no approved direct HDL is commonly available to be administered in human subjects as therapy but different HDL raising agents are known and in practice like fibrates and niacin and in trial phase the cholesterol ester transfer protein (CEPT) inhibitor.

Niacin would be choice HDL elevator because of severe contraindications produced by fibrates in compromised renal function used along with statins and secondly niacin provides comparatively higher percent increase in HDL level¹⁰.

The present study was designed to assess the comparative effect of two approaches on lipid profile. First in case where only LDL is aimed to lower down through Atorvastatin and second when HDL is targeted to increase using NER along with a reduction in LDL in patients with renovascular disease.

METHODOLOGY: It was a hospital based prospective, randomized, analytical research plan that was executed in collaboration with Nephrology Unit, JPMC, Karachi, Pakistan during 2007-2012. Ischemic renal changes were suspected in patients with at least 5-year diabetes mellitus and/or 10-year hypertension. Diagnosis was confirmed through renal artery Doppler scan performed by skilled technician. Existence or absence of ischemic tissue damage was sole decision of nephrology consultant.

On the basis of clinical picture and Doppler scan report, finally 135 patients were recognized as potential experimental units and were requested for consent to participate in a follow up study after explaining the purpose and answering their queries.

The exclusion criteria encompassed previous revascularization, kidney transplantation, simultaneous presence of chronic inflammatory diseases, current use of steroidal medication and statins, failure to complete 4-week statins washout period. 15 of total identified individuals did not show consent while left over were randomly (randomization by computer generated random number sequence) distributed in two treatment groups. Group 1 was prescribed Atorvastatin (20mg/day) and group 2 NER (500mg/day) in combination with same dose of Atorvastatin for 16-weeks in a 1:1 ratio.

Information regarding personal and family medical history, demographics, current medication, and other required items were taken on a structured questionnaire at day first.

To calculate baseline values of biochemical parameters, blood samples were collected from antecubital vein after 12-hour fasting in heparinized tubes, centrifuged at 3000rpm for 5-minute and plasma sample was stored at -80°C for estimation of cholesterol, LDL, HDL, triglycerides (TG), very low density lipoproteins (vLDL), creatinine and urea. Total cholesterol, HDL, TG, creatinine and urea were measured colorimetrically through research grade Randox kits while LDL and VLDL were calculated using Friedwald's formula. The same sampling & testing procedure was practiced at the end of study.

Creatine phosphokinase and liver transaminases were measured at every 30 day period while the overall patients' status concerning with dose, drug tolerance, undesired side systemic effects were also monitored. To attain the local reference values of all tested parameters, blood samples were also collected from 50 characteristic matched healthy volunteers once. The principles sketched out in the declaration of Helsinki were carefully followed throughout and the plan was approved by institutional BASR.

Collected data was tabulated and reported as Mean \pm S.D. t-Test was used to compare mean values through statistical software SPSS 17 at chosen p-value 0.05.

RESULTS: Initially 120 patients were enrolled in the follow up study. All partakers were randomly categorized in two groups of equal size (n = 60). 04 patients dropped out from the first group who failed to take medicine as prescribed or did not report back for follow up.

While 05 patients left from second group with same reasons and 04 patients discontinued combination therapy because of poor tolerance and indigestion problems, 54 patients taking statin while 51 with statin NER combination completed the protocol successfully for four months and assessed for final changes.

There was no difference in the baseline values of studied patient population at the start of plan. All lipid variables, Apo A-1, renal function analyzers and blood glucose levels were found non-significant in inter-group comparison (**Table 1**).

TABLE 1: BASELINE BIOCHEMICAL PROFILE OF RENOVASCULAR DISEASE PATIENTS TREATED WITH ATORVASTATIN ALONE OR ATORVASTATIN IN COMBINATION WITH NIACIN EXTENDED RELEASE

Parameters	Control (n=50)	Statin Group (n = 60)	Niacin + statin Group (n = 60)
TC (mg/dl)	94 \pm 13.4	180.7 \pm 35.9	178.783 \pm 38.3
LDL-C (mg/dl)	52 \pm 6.8	113.49 \pm 34.8	116.786 \pm 39.2
HDL-C (mg/dl)	35 \pm 3.6	22.933 \pm 4.7	23.1 \pm 5.4
TG (mg/dl)	80.6 \pm 9.4	223.383 \pm 28.5	215.983 \pm 34.8
VLDL (mg/dl)	18.3 \pm 2.6	46.913 \pm 12.8	44.283 \pm 11.6
Apo-A1 (mg/dl)	138.2 \pm 10.5	96.6 \pm 8.4	98.2 \pm 11.2
GFR	108.6 \pm 7.2	66.9 \pm 8.7	71.2 \pm 12.4
Pl. Creatinine (mg/dl)	0.8 \pm 0.2	4.08 \pm 0.9	3.92 \pm 1.1
Pl. Urea (mg/dl)	24.8 \pm 4.6	113.5 \pm 8.3	107.8 \pm 9.7
BUN (mg/dl)	11.6 \pm 2.4	51.1 \pm 5.2	48.6 \pm 7.3
FBG (mg/dl)	90 \pm 6	121 \pm 11	126 \pm 8

Values are shown as 'Mean \pm S.D.' No significant difference was found in Statin vs. Niacin + Statin group comparison.

Raise in lipid profile was found significant for cholesterol (p<0.01), LDL (p<0.01), TG (p<0.001), vLDL (p<0.001) while decrease in the levels of

Apo A-1(p<0.01) and HDL (p<0.01) was observed in the patient population as compared to healthy controls of similar characteristics (**Table 2**).

TABLE 2: COMPARISON BETWEEN THE LIPID PROFILE OF HEALTHY CONTROL, DISEASE CONTROL (BASELINE AVERAGE VALUES OF PATIENTS), PATIENTS GROUPS OF ISCHEMIC KIDNEY DISEASE ADMINISTERED ATORVASTATIN ALONE & ATORVASTATIN IN COMBINATION WITH NIACIN EXTENDED RELEASE

PARAMETER	GROUPS			
	Healthy Control (n=50)	Disease Control (n=107) ¹	Statin (n=56) ^{1,2}	Statin + Niacin (n=51) ^{1,2,3}
TC (mg/dl)	94 ± 13.4	179 ± 34.2 ^{**}	149.8 ± 3.8 ^{**,*}	118.5 ± 4.6 ^{N,*N}
TG (mg/dl)	80.6 ± 9.4	219.6 ± 32.4 ^{***}	195 ± 13.8 ^{**N}	168.62 ± 25.4 ^{**,*N}
LDL (mg/dl)	52 ± 6.8	114.5 ± 28.4 ^{**}	96.3 ± 16.2 ^{*,*}	88.6 ± 15.7 ^{*,*N}
HDL (mg/dl)	35 ± 3.6	24.1 ± 3.4 ^{**}	30.1 ± 2.8 ^{*,*}	37.8 ± 3.1 ^{N,***,**}
VLDL (mg/dl)	18.3 ± 2.6	44.9 ± 8.2 ^{***}	37.3 ± 4.4 ^{**N}	30.4 ± 3.5 ^{**,*}
Apo-A1 (mg/dl)	138.2 ± 10.5	96.8 ± 9.5 ^{**}	108.5 ± 12.3 ^{N,N}	133.7 ± 10.4 ^{N,**,**}

All values are Mean ± S.D. N: Non-significant, *p<0.05, ** p<0.01, ***p<0.001, 1: As compared with healthy control, 2: As compared with Disease control, 3: As compared with Statin Alone

In comparison with the disease control group comprised of patients’ baseline values, Atorvastatin induced a significant reduction in total cholesterol (p<0.05) and LDL (p<0.05), while decrease in TG and vLDL levels remained insignificant. It also causes an increase in HDL (p<0.05) and Apo A1 that was non-significant. On the other side, Atorvastatin combined with NER also showed beneficial effects on lipid not only by reducing cholesterol (p<0.05), TG (p<0.05), LDL (p<0.05) but also by enhancing HDL (p<0.0001) and Apo A1 (p<0.01). The inter-group comparison of both

treatments demonstrated relatively better outcomes following Atorvastatin NER combination in terms of good cholesterol (p<0.01) for HDL and (p<0.01) for Apo A1, while in term of lipid lowering potentials, we found no difference (Table 2).

Though the inter group comparison of overall lipid lowering protection induced by both treatments did not touch the level of significance in a statistical evaluation, still Atorvastatin NER combination provided superior useful mean percent change for almost all lipid parameters (**Figure 1**).

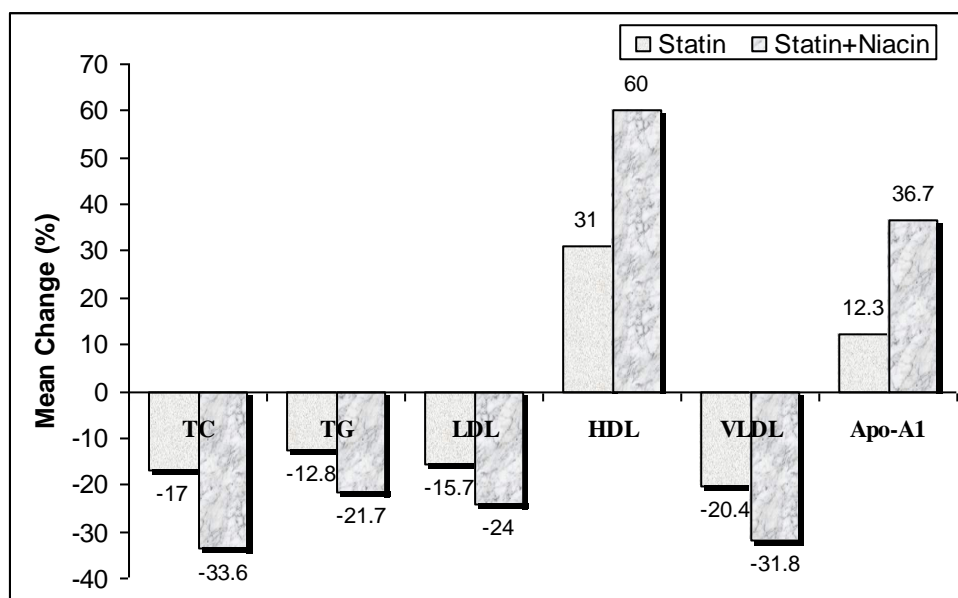


FIG. 1: MEAN PERCENT PROTECTION INDUCED BY ATORVASTATIN ALONE & ATORVASTATIN IN COMBINATION WITH NIACIN EXTENDED RELEASE IN TERMS OF MANAGING LIPID PROFILE IN PATIENTS WITH ISCHEMIC RENAL DISEASE. Negative sign indicates reduction in baseline value

As all partakers were renal patient, GFR was found significantly low (p<0.01) as compare with control. Atorvastatin alone and in combination with NER improves the GFR significantly (p<0.05, p<0.01)

respectively, though combination therapy has more sound effect as shown by Statin alone and mixed with NER group comparison (p<0.05) (**Table 3**).

TABLE 3: COMPARISON BETWEEN RENAL FUNCTION MEASURES IN HEALTHY CONTROL, DISEASE CONTROL (BASELINE AVERAGE VALUES OF PATIENTS), PATIENTS GROUPS OF ISCHEMIC KIDNEY DISEASE ADMINISTERED ATORVASTATIN ALONE & ATORVASTATIN IN COMBINATION WITH NIACIN EXTENDED RELEASE FOR FOUR MONTHS

PARAMETER	GROUPS			
	Healthy Control (n=50)	Disease Control ¹ (n=107)	Statin ^{1,2} (n=56)	Statin+NER ^{1,2,3} (n=51)
GFR	108.6 ± 7.2	69.5 ± 10.6 ^{**}	78.8 ± 7.8 ^{*,*}	85.5 ± 8.6 ^{N,***}
Creatinine (mg/dl)	0.8 ± 0.2	3.85 ± 0.72 ^{***}	3.15 ± 0.8 ^{***,N}	2.72 ± 0.4 ^{***,*}
Urea (mg/dl)	24.8 ± 4.6	109.5 ± 8.4 ^{***}	93.6 ± 6.5 ^{***,N}	82.6 ± 7.7 ^{***,*}
BUN (mg/dl)	11.6 ± 2.4	49.2 ± 6.2 ^{**}	41.1 ± 4.6 ^{***,N}	35.8 ± 6.1 ^{***,N,*}

All values are Mean ± S.D. N: Non-significant, *p<0.05, ** p<0.01, ***p<0.001.

1: As compared with healthy control

2: As compared with Disease control

3: As compared with Statin Alone

DISCUSSION: Our data showed that its not only an increase in LDL but significantly low levels of HDL is also a common finding in renovascular disease, a disease shares general atherosclerotic mechanism as in any other tissue like heart. Low HDL-cholesterol' or 'hypoalpha' syndrome is the most frequent lipoprotein abnormality in coronary patients, and found a consistent observation in most of vascular disorders¹¹ that has not received as much attention as the hyper LDL-cholesterolaemia. Raised HDL levels through NER also showed comparatively better effect on renal function with a significant decrease in creatinine level (Table 3) while this was not observed in case of statin alone.

Chiesa *et al*¹² demonstrated that an acute rise in HDL level is significant in the regression of atheromoa in experimental model while the same was also reported by Nissen *et al*¹³ in the patients of coronary artery disease; both findings are in agreement with that of we observed. In contrast, a drastic reduction in LDL levels through statins did not result in significant atheroma reduction¹⁴.

The exact mechanism through which statins increase HDL and ApoA-1 concentration is not yet well understood, though it seems unrelated to their lipid lowering mechanism. A possible explanation may be their up regulatory effect of hepatic ABC transporter A1 gene expression¹⁵ or in part their potential to reduce hepatic lipase activity¹⁶.

The lipid lowering properties of nicotinic acid have been known for 50 years. It causes significant reduction in TG levels and a remarkable increase in HDL mainly through its antilipolytic activity¹⁷, recently its interaction with a G/protein-coupled

receptor present in adipocyte has been reported¹⁸⁻²⁰. Briefly, niacin affects the hepatic holoparticle endocytosis, reduces the hepatic removal of HDL, down regulates chain adenosine triphosphate synthase cell surface expression leading to raised plasma HDL.

Secondly, on adipose tissue, it retards vLDL biosynthesis through cholesterol ester transfer protein, limits the HDL conversion to TG, vLDL, LDL, in turn further increasing plasma HDL^{21,22}. A further increase in HDL may be caused by niacin potential to inhibit ApoA1-containing HDL particles catabolism directly^{23,24}. Vajjinath²⁵ reported that niacin also significantly increases Lp(A-I); HDL particles containing apo A-1, 24% from the base line value in dose dependent fashion, the similar results we found in our study.

The study limitations are limited sample size and short time of follow up that was insufficient to assess any systemic effect associated with long term use in reno-compromised patients.

CONCLUSION: Addition of NER to statin has significant lipid lowering effect along with HDL increase even at a comparatively low dose of 500mg and well tolerated in renovascular disease patient. This combination may be used to prevent further systemic complications in this group of patients.

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CONFLICT OF INTEREST: Nil

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