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Research Article

Efficacy and Safety of Inositol Hexa Nicotinate (IHN) in Improving Serum Lipid Profile in Patients with Low HDL Levels

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Abstract

Background: *For centuries, lowering of Low-density lipoprotein (LDL) cholesterol was considered as mainstay therapy of dyslipidemia. Evidence based studies now confirm that raising High density lipoprotein (HDL) cholesterol can be equally protective, for which therapeutic options are limited. Niacin has been used clinically to this effect; serious flushing led to its discontinuation by majority of patients. Our study aims at exploring other preparations of niacin which are equally effective and tolerable as well.*

Methods: *Dyslipidemia patients ≥ 30 years attending cardiology out-patient deparment were treated with 1 gram of Inositol Hexa Nicotinate (IHN) twice daily for 12 weeks. Blood samples were collected at 0 and 12 weeks for measurement of lipid profile, liver function test (LFT), kidney function test (KFT) and blood glucose.*

Results: *At the end of study, IHN significantly decreased triglyceride (TG), very low-density lipoprotein (VLDL), Total Cholesterol and LDL levels with a significant rise in HDL levels. Fasting Blood Sugar levels were also decreased showing advantageous effect in diabetics. There was no suggestive adverse effect due to IHN, particularly incidence of flushing which was greatly averted.*

Conclusion: *IHN could be an efficacious and safe therapeutic option for raising HDL levels without causing significant side effects.*

Key Words: *Inositol Hexa Nicotinate (IHN), Dyslipidemia, Niacin, High Density Lipoprotein.*

Introduction

Coronary artery disease (CAD), primarily triggered by atherosclerosis, presents complex challenges in terms of medical and surgical interventions. While these treatments can effectively address symptomatic recovery from coronary heart disease, their ability to prevent or halt its progression is limited, given that dyslipidemia appears to be the primary underlying cause. The main risk factors in dyslipidemia are increase of total cholesterol and/or low-density lipoprotein (LDL)-cholesterol, raised triglyceride (TG) levels along with a decrease in high-density lipoprotein (HDL)-cholesterol. It may be due to dietary causes, obesity, genetic diseases, smoking or the presence of other concomitant diseases such as type 2 diabetes, hypothyroidism, cholestatic liver disease, nephrotic syndrome, and use of certain medications.

Low HDL cholesterol was considered as an essential cardiovascular risk factor as suggested by Framingham heart study in determining cardiovascular disease (CVD) risk, nonetheless blood triglyceride and LDL levels also have to be regarded along with HDL. Having high rather than low HDL is protective even when triglyceride or LDL levels are elevated **[**1**]**. It was demonstrated that persons with low HDL cholesterol had greater risks of CAD **[**2**]**. Another meta-analysis from the Asia-Pacific region acknowledged primary low HDL cholesterol as an independent risk factor for CAD **[**3**]**. Cardiovascular events were more common in patients of low HDL cholesterol levels even when LDL cholesterol levels were less than 70 mg/dl **[4]**. Even a mild increase in HDL levels can distinctly reduce cardiovascular risk. The affirmative role of HDL and its inverse association with CAD are mainly due to its crucial role in reverse cholesterol transport. In recent times clinical approaches are being researched to treat atherosclerosis through HDL-increasing therapies. These clinical studies have shown encouraging results through nutritional intervention, exercise, stress reduction, tobacco and alcohol cessation and supplemental therapies.

Though the HDL levels are influenced by genetics and lifestyle, pharmacological intervention has the plausible role in enhancing the HDL levels. This option is much less established, and the clinical endpoints are not well explored as compared to options for LDL-lowering drug therapies.

Statins used in hypercholesterolemia to reduce CVD risks has had a substantial market share since decades but still cardiovascular events continue to occur **[**5**]**.

This remaining risk may be due to low HDL-C levels and high levels of tiny, dense, and compact LDL particles [6]. Hence to decrease the medical and financial burden of CVD, a comprehensive strategy leading to modulation of lipid levels including HDL, LDL and TG will be a rational and scientific approach.

Currently the most widely used non-statin drug available to increase HDL levels is nicotinic acid or niacin. Niacin is proposed to reduce the risk of cardiovascular disease by lowering LDL cholesterol concentrations and raising HDL cholesterol. Niacin is often recommended to patients who have low HDL cholesterol concentrations. Some studies report that niacin can increase HDL levels by 25% to 35%, when given in the highest doses [7]. It also reduces TG, LDL-C, lipoprotein (a) levels and lowers the small compact dense LDL particles [8].

Niacin (vitamin B3), though available in the market mainly to raise HDL levels has been scarcely used due to high incidence of side effects particularly flushing, characterized by redness and burning sensation of face and upper part of body along with itching and tingling. Other preparations of Niacin like extended release (ER) manifests less flushing as compared to immediate release (IR) preparation and has better safety and efficacy profile. Another preparation of Niacin- Inositol Hexa Nicotinate (IHN) is a bioavailable source of niacin and can be added to food supplements to provide niacin [9]. IHN, like extended-release nicotinic acid, has been investigated for potential beneficial effects on serum lipids while minimizing the flushing effect [10]. The available data suggest that intestinal absorption of IHN varies extensively, approximately 70% of the administered dose is absorbed into the bloodstream [11]. However, the bulk of IHN that is absorbed remains intact after absorption. Metabolism of IHN to release free nicotinic acid can result in the physiological functions of nicotinic acid, depending on the dose, rate, and amount of release. Beneficial lipid-lowering effects of free nicotinic acid and extended-release nicotinic acid are well established, but the favorable effects of IHN on serum lipids would be dependent on uptake of IHN and later release of the nicotinic acid moieties from the IHN molecule.

Niacin is being currently used to raise HDL levels but due to high incidence of flushing its compliance has been found to be poor. Inositol Hexa Nicotinate also known as “no flush niacin” has less adverse effects as compared to niacin but the studies to assess effect on lipid levels by IHN are limited. We decided to assess the safety, efficacy and tolerability of IHN on serum lipid levels in patients with low HDL levels and evaluate its clinical outcome.

Materials and Methods

We enrolled patients attending Cardiology OPD at Sanjay Gandhi PGIMS over a period of 6 months. Patients with age ≥30 years with dyslipidemia, females with HDL <50mg/dl, males with HDL <40mg/dl either statin naïve or on statin therapy, were included in the study. Patients with familial dyslipidemias, pregnancy and any acute or chronic illness including malignancy, infection, renal dysfunction, liver disease and hematological diseases were excluded from the study. Study protocol was approved by Institutional Ethics Committee. Written informed consent was obtained from all participants.

Patients were treated with 1 gram of IHN twice daily for 12 weeks. All patients were initiated with 500 mg per day and up titrated to the maximum dose of 1 gram twice daily over a period of 3 weeks. Titration of dose was done on a weekly basis.

Fasting blood samples were collected for measurement of Lipid profile, LFT, KFT and Blood Glucose at the beginning of the study and at the end of the 12 weeks.

Results

Total of 50 patients were recruited but data from 43 patients were available for final analysis as 5 patients were lost to follow up and 2 patients had non-drug related medical issues requiring discontinuation of the drug. A comparison of the pre and post levels of measured biochemical parameters were made along with a record of reported adverse events, if any.

The results were analyzed using descriptive statistics and making comparisons before and after treatment for various lipid parameters. Data was summarized as in Mean ± SD (standard deviation). Students paired t-test was used to compare before and after treatment values. P-value < 0.05 was considered significant. SPSS version 18 software was used for analysis.

Table – 1: Demographic Characteristics of Subjects

Variable		Value
Age - Mean ± SD		58.30 ± 11.82
SEX	Female - No. (%)	7 (16.3)
	Male - No. (%)	36 (83.7)

Table 1 shows the demographic characteristics of subjects

Table – 2: Comparison of Lipid Profile Before & After Treatment

Parameter	Time	Mean (mg/dl)	SD	t-value	p-value
T. CHOL	Before	126.69	40.837	2.236	**.031***
	After	116.60	33.970		
TG	Before	146.10	88.343	3.924	**<0.001***
	After	119.08	64.266		
HDL	Before	34.02	6.046	-5.195	**<0.001***
	After	37.37	6.123		
LDL	Before	70.84	35.617	2.693	**.010***
	After	62.00	26.903		
VLDL	Before	29.18	17.704	3.397	**.002***
	After	25.76	17.259		
CREAT	Before	1.08	.295	.220	.827
	After	1.07	.289		
SGPT	Before	31.68	11.602	-.589	.559
	After	33.05	14.175		
BS(F)	Before	118.93	30.889	2.023	.049
	After	111.12	20.401		

Table 2 shows on comparing the lipid profile before and after treatment it was found that after treatment a highly significant reduction ($p<0.005$) was found in TG (146.10±88.34 mg/dl to 119.08±64.27 mg/dl) and VLDL (29.18±17.70 mg/dl to 25.76±17.26 mg/dl). A significant reduction ($p<0.05$) was also found in Total Cholesterol levels (126.69±40.84 mg/dl to 116.60±33.97 mg/dl), LDL (70.84±35.62 mg/dl to 62.00±26.90 mg/dl) and BS (F)- Blood Sugar (Fasting) (118.93±30.89 mg/dl to 111.12±20.40 mg/dl). A highly significant increase ($p<0.001$) was found in HDL (34.02±6.05 mg/dl to 37.37±6.12 mg/dl)

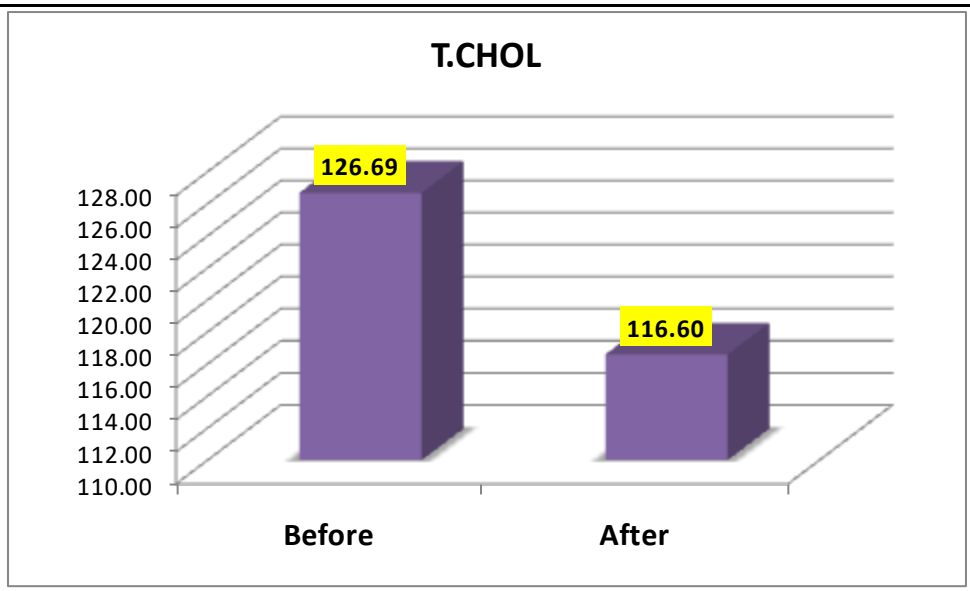

Fig 1: shows the decrease in Total cholesterol (T.CHOL) levels

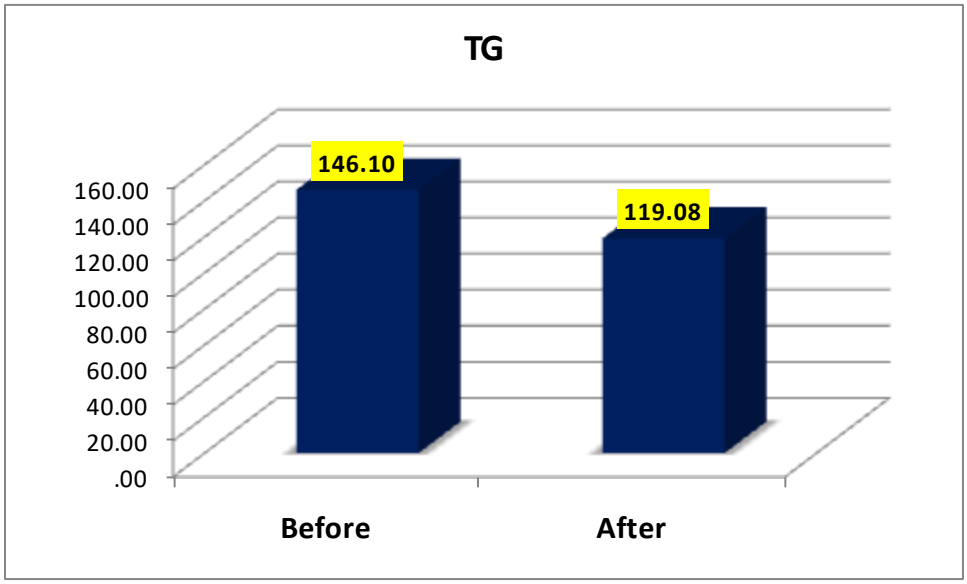

Fig 2: shows the decrease in Triglyceride levels (TG: Triglyceride)

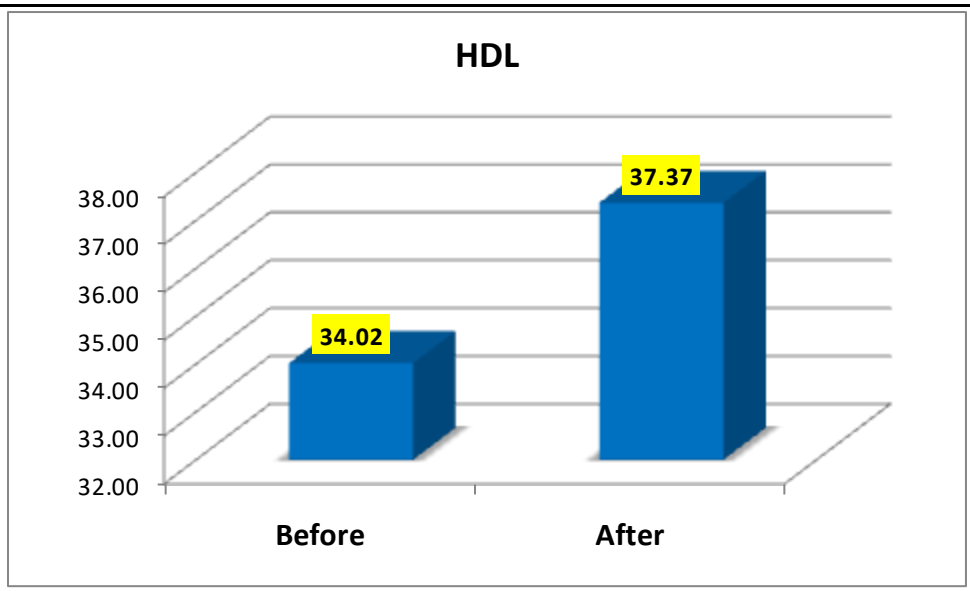

Fig 3: shows the increase in HDL-cholesterol levels

HDL: High density lipoprotein

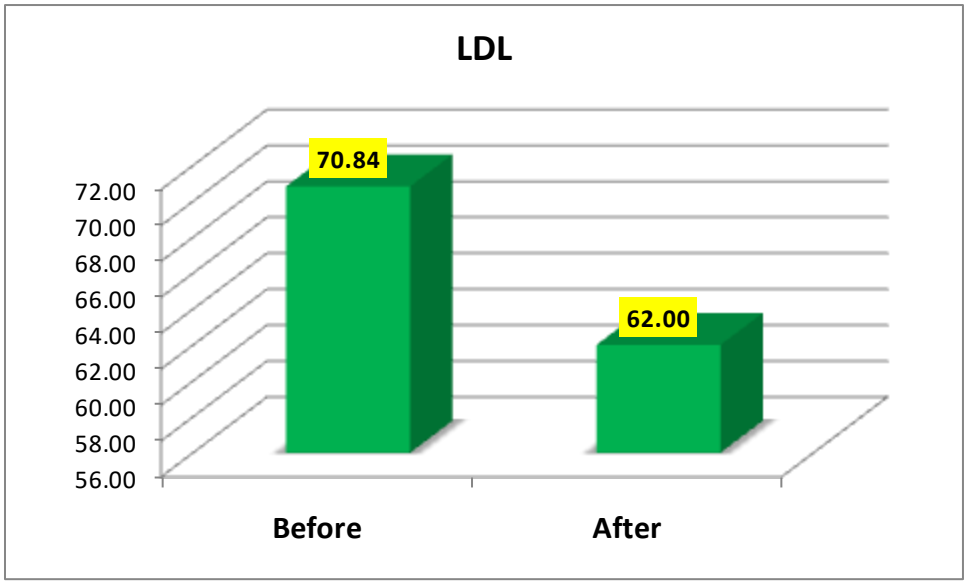

Fig 4: shows the decrease in LDL-cholesterol levels

LDL: Low density lipoprotein

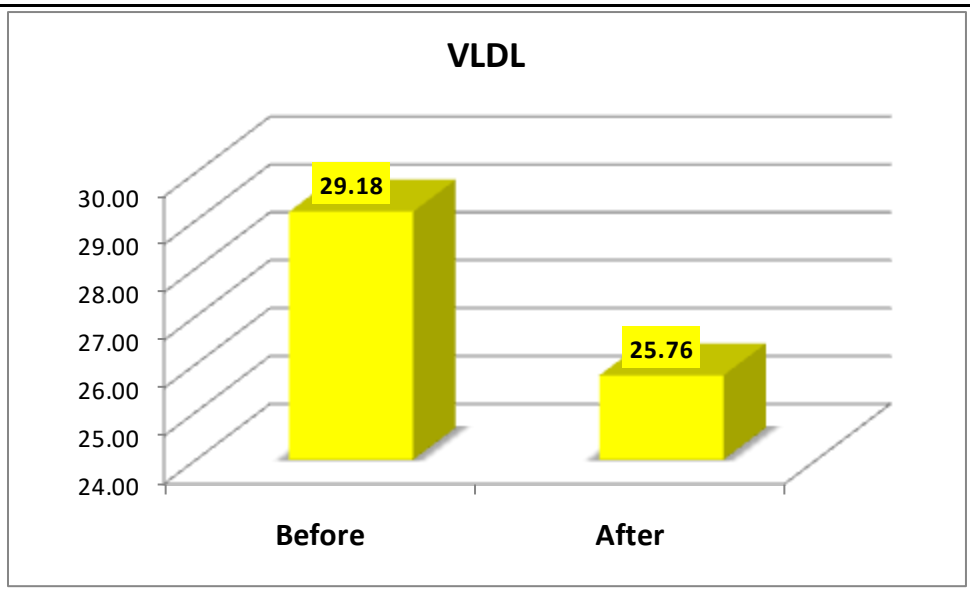

Fig 5: shows the decrease in VLDL- cholesterol levels

VLDL: Very Low-density lipoprotein

Adverse Drug Reaction

ADR	No of patients
Flushing	0
Skin rashes	1
Headache	2
Others-myalgia	1

Table 3 shows the occurrence of Adverse drug reaction in study population.

Discussion

Hypolipidemic action of niacin is unrelated to its vitamin activity. Several mechanisms for these favorable effects have been postulated. Niacin decreases lipolysis in peripheral adipose tissue, which leads to less transport of fatty acids to the liver. It reduces VLDL production in liver by inhibiting Cholesterol synthesis and thus VLDL degradation products IDL and LDL are also decreased [12].

It also raises HDL level by inhibiting hepatic uptake of HDL and decreasing triglyceride levels. Reduced triglyceride levels produce HDL particles that have fewer supplements of triglyceride, which decreases HDL break down by slowing down the catabolism of Apo A1 in the liver [13]. Effects of niacin are mediated through a cell surface Gi protein coupled receptor called as Niacin receptor or Hydroxycarboxylic acid receptor-2 (HCAR-2) or GPR109A receptor [14].

Since high-density lipoprotein cholesterol is a strong and independent epidemiologic risk factor and is a proven anti-atherogenic moiety, many efforts have been made to enhance HDL levels as a therapeutic approach for patients with atherosclerosis [15]. In an epidemiologic study it was observed that every 1-mg/dL increase in HDL is associated with a 2% to 3% decrease in coronary artery disease risk, independent of low-density lipoprotein (LDL) cholesterol and triglyceride levels [16].

The forms of "niacin" which are marketed include - nicotinic acid (unmodified, immediate release-IR), slow-release or extended release (ER) forms that contains an acid and an agent to slow the release, nicotinamide, Inositol hexa-nicotinate (IHN) described as "no flush niacin" [9]. Nicotinic acid is a cutaneous vasodilator causing marked flushing after every dose.

There are two pathways by which niacin is metabolized. First, niacin undergoes an oxidation-reduction reaction to form nicotinamide and eventually forms pyramidine metabolites which further leads to formation of few hepatotoxic metabolites. Second, there is metabolism by a conjugation reaction with glycine to form nicotinuric acid, which is excreted in the urine. This pathway also releases prostaglandin D2 by dermal macrophage cells in skin, which probably causes flushing (and is often preventable by pretreatment with aspirin or other prostaglandin inhibitors or minimized by starting with a low dose or taken with meals and gradually increasing the dose). The Immediate Release (IR) niacin is mainly metabolized by the conjugation pathway and sustained-release (SR) niacin is predominantly metabolized by the oxidation-reduction reaction. Thus, IR niacin predisposes to flushing and SR niacin has more potential for liver toxicity and less flushing. Extended release (ER) niacin has lipid effects like IR niacin and utilizes both metabolic pathways, but has a comparatively lesser incidence of flushing than with IR niacin and a much lower frequency of hepatic adverse effects than with SR preparations.

Inositol hexa-nicotinate (IHN) is an ester of two compounds - Niacin and Inositol. After oral absorption it is further hydrolyzed to yield two products - free nicotinic acid and Inositol. The release of free nicotinic acid occurs in a sustained and slow-release manner, taking more than 10 hours on an average, which is then utilized by the body. Because of this sustained slow release of nicotinic acid, the incidence of flushing is almost nil, hence known as "no flush" niacin.

In our study we evaluated the efficacy and safety of Inositol hexa-nicotinate in improving serum lipid profile with special emphasis on HDL cholesterol levels. There was a significant reduction in TG, VLDL, Total Cholesterol and LDL levels. A significant rise was found in HDL levels. Blood Sugar (Fasting) levels were also significantly decreased. Hence, we can advocate its use in diabetic dyslipidemia patients also.

A randomized placebo-controlled trial of Over the Counter (OTC) 500 mg IR Niacin in healthy individuals demonstrated that 100% volunteers on niacin flushed with mean time being 18.2 min and mean duration was 75.4 min hence patient awareness before prescribing this drug is essential [17]. Similarly, a pooled analysis from eight studies using ER Niacin showed 66.6% patients experienced flushing but discontinuation rate was only 5-6% as patient were educated about flushing and its management [18]. Hence Inositol Hexa Nicotinate or no flush niacin may be a safer option as used in our study along with significant lowering of LDL cholesterol and increase of HDL-Cholesterol.

A study by Alsheikh-Ali AA et al showed that though lowering of LDL-cholesterol contributes in decreasing CAD risk, but increase in HDL-cholesterol may be a better predictive factor and of more benefit [19].

HDL shows several protective antiatherogenic effects, like modulating macrophage cholesterol efflux, shielding against LDL oxidation, preserving endothelial function, reducing inflammation, and blocking thrombosis [20]. Thus, increasing the serum HDL level may be an important therapeutic target for reducing risk of CAD.

A study by Harsha KP et al demonstrates that increase in HDL was significant & comparable by both IHN and Extended Release niacin (ER niacin) groups, but IHN showed significantly lesser adverse effects and better tolerability hence IHN can be regarded as a better niacin formulation. Our study also ascertained the same [21].

In a double blind placebo controlled clinical trial, Simvastatin plus niacin group showed better clinical and angiographically measurable benefits in patients with coronary disease as compared to statins alone. LDL-C levels decreased by 42% and HDL levels increased by 26% thereby confirming the role of niacin in modulating the lipid levels [22]. Our study also corroborated the same finding.

Our study was in conformity to another randomized, double-blind, placebo-controlled clinical trial conducted in military retirees which proved that combination regimen aimed at increasing HDL cholesterol levels by gemfibrozil, niacin and cholestyramine improves cholesterol profiles, helps prevent angiographic progression of coronary stenosis and may avert cardiovascular events [23].

Our study demonstrated the beneficial effects of niacin on lipid levels with no significant adverse effects. The dyslipidemia seen in atherosclerotic patients is considered to have small dense LDL particles which is not significantly affected by Statins [24]. Niacin has various additional effects like decreasing cholesterol efflux, decreasing inflammation and suggestively decreases these small compact lipoproteins which predisposes to atherogenesis, thereby decreasing the cardiovascular risk [25]. This has been proven in several trials correlating with significant clinical and arteriographic improvement in patients independent of lipid values [26].

On evaluating the ADRs only two patients experienced mild headache and one patient had myalgia and one had skin rashes. These side effects may not be directly attributed to use of IHN. It may be due to other concomitant drug, statins, being used in our study population. None of the patients experienced flushing reactions. Hence INH is a much safer niacin preparation to be used in dyslipidemia.

Conclusion

Our study confirmed that Inositol Hexa Nicotinate (IHN) substantially improves serum lipid profile with considerable decrease in TG, VLDL, Total cholesterol and LDL levels and a significant rise in HDL levels. Fasting Blood Sugar levels were also decreased. There was no significant adverse effect which could be directly accredited to IHN. Hence, we can conclude that IHN is an effective and safe alternative to niacin which helps in controlling dyslipidemia without causing side effects.

Limitations: The biochemical effects of increasing HDL levels by using INH does not necessarily transform to clinical benefit and whether this intervention will provide any mortality benefit in primary prevention or established CAD is a matter of research which will require large interventional trials and longer follow-up. Further studies are required in other concomitant diseases like diabetes as preliminary results show beneficial effect in diabetes also.

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