

## Clinical Study of Primary Hyperlipidaemia and the Role of Kalonji (*Nigella sativa*) and Saboos-e-Asapghol (*Plantago ovata*) in its Management

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Lipid disorders comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations. The growing prevalence of obesity, type 2 diabetes mellitus, hyperlipidaemia and metabolic disorders are important risk factors for atherosclerosis. To cure the hyperlipidaemia several synthetic drugs of better efficacy are being introduced in the modern system of medicine. But most of the medications induce adverse side effects. Therefore search for safe and effective lipid lowering drugs was the main motivating factor behind this study. In Unani System of Medicine many drugs (single drugs as well as compound formulations) are used for the purpose of reducing body weight and treating the obesity. Saboos-e-Asapghol (*Plantago ovata*) and kalonji (*Nigella sativa*) are among these medicines. Their efficacy has also been proved pharmacologically and documented as good hypolipidemic. A clinical study was carried out in Ajmal Khan Tibbiya College Hospital on 60 patients of primary hyperlipidaemia. The diagnosis was made on inclusion and exclusion criteria. The Unani formulation Sufoof-e-Kalonji (*Nigella sativa*) 2 gm and Saboos-e-Asapghol (*Plantago ovata*) 4 gm twice daily before meal were given for 90 days.

The combination of drugs was found to be significant in lowering the lipid level and in increasing the level of serum HDL-cholesterol, in patients of primary hyperlipidaemia. Therapeutic responses were evaluated through follow up observations at 45th day interval. The results were analyzed statistically and results were encouraging.

**Keywords:** Atherosclerosis, Kalonji, Saboos-e-Asapghol, Primary hyperlipidaemia.

## Introduction

Cardiovascular disease (CVD) is the number one leading cause of mortality in the United States. Each year 900,000 Americans have an acute myocardial infarction; of them, 225,000 die<sup>1</sup>. WHO has also declared that CVDs are leading cause of mortality globally e.g. an estimated 17.5 million died from CVDs in 2005, representing 30% of all global deaths<sup>2</sup>. With regard to cardiovascular diseases, a key element of dietary change is an increase in intake of saturated animal fats and hydrogenated vegetable fats. The increase mechanization that accompanies the economic transition leads to a shift from physically demanding, agriculture-based work to largely sedentary industry and office-based work that is part of urbanisation. When the decision is made to treat hyperlipidaemia dietary measures are always initiated first and may obviate the need for drugs. Decision to use drug therapy for hyperlipidaemia must be based on the specific metabolic defects and potential for causing atherosclerosis or pancreatitis.

As countries move through the epidemiologic transition, mean population plasma cholesterol levels tend to rise. Social and individual changes that accompany urbanization clearly play a role because plasma cholesterol levels tend to be higher among urban residents than rural residents. This shift is largely driven greater consumption of dietary fats—primarily from animal products and processed vegetable oils and decreased physical activity. In high income countries, mean population cholesterol levels are generally falling but low and middle income countries, there is wide variations in these levels<sup>3</sup>.

In ancient Unani literature there is no description of any disease by the name of Hyperlipidaemia (*Fart-e-Tadassum-Fid-Dam*), because in that time the facility of biochemical analysis of blood was not available. But many of Unani physicians and scholars have briefly described the condition of obesity under the name of *Saman-e-Mufrat* which is almost similar to Hyperlipidaemia in all aspects as in etiology, clinical features, complications and management. Thus we can get valuable informations regarding Hyperlipidaemia in the context of *Saman-e-Mufrat* (obesity). The first physician Hippocrates (460 B.C.) the father of medicine, who described the obesity as a disease in detail in his famous Unani books *Fusool-Buqrat*, *Abzemiya*, *Tabiyatul-Insaan* and *Hifzul-Sehat*. Galen writes in reference to Hippocrates in *Fusool-Buqrat mai Talkhees Jaleenoos*. “An obese person dies earlier in comparison to lean or thin individuals”<sup>4</sup>. The second Unani physician Rofas (98-117) wrote a book *Kitab Tahzeelul Saman* and describe the clinical presentation, complications and management of obesity<sup>5</sup>. Galen (130-200 A.D.), the

Roman pioneer of Unani system of medicine told ‘when a person attains extreme of obesity then his death can occur suddenly due to the rupture of any major blood vessels of his body’. He also told the importance of evacuation (*Istifragh*) in the treatment of obesity<sup>4</sup>. The most famous physician of Arabian period Abu Bakar Mohammad bin Zakariya Razi (885-925 A.D.) described the obesity in about sixty pages in his famous book *Al-Havi Fit-Tib* in Vol. 6. He explained the importance of dietotherapy in the management of obesity. He also contributed the experiences regarding obesity and told “pulses and vegetables reduce obesity because of their low calorific value. Further he told that diuretics, vinegar and intake of small quantity of alcohol reduce body fat” and also wrote in reference to Galen in his book “when excess of fat get deposited in the body then stroke, paralysis and sudden death may occur”<sup>6</sup>. Both *shaham* and *sameen* are formed by that blood which has the property of *Dasoomat* (meaning oily substance). Ali Ibn Abbas Majoosi (930 A.D.) in his book *Kamil-us-Sana’a* told that obesity is very dangerous for a person specially when it is primary (Ibtedai). Further he told that *Hararat-e-Ghareezi* of such person is low and blood vessels of his body are narrow and compressed<sup>7</sup>. Sheikh Ibn Sina (980-1030 A.D.) in his famous book *Al-Qanoon fit-Tib* has described the etiology, clinical features, complications and management of obesity in detail. According to him, when there is excess deposit of fat in the body then it causes narrowing of blood vessels and as a result sufficient amount of blood and oxygen can’t flow in these affected blood vessels, and also told that these blood vessels can be ruptured and as a result massive hemorrhage and death can occur suddenly<sup>8</sup>.

At the end of 19th century, there was no existence of any disease by the name of ‘Hyperlipidaemia’. But it is the 20th century when work has been done in a very systematic way in the light of science and technologies and as a result there is presence of lipids, their metabolism and functions have been discovered. Thereafter, obesity and hyperlipidaemia were accepted as two different diseases. Hyperlipidaemia has received the most recent attention and in last four or five decades, many work has been done on this disease, because of its major role in pathogenesis of atherosclerosis and complications such as coronary artery disease, essential hypertension and cerebral stroke etc.<sup>9</sup>. In Modern medicine ‘Hyperlipidaemia’ is characterized by abnormally increased concentrations of lipids (triglyceride, cholesterol) levels of any or both or all lipids and/or lipoproteins in the blood<sup>10-11</sup>. Normally blood contains 0.6 to 0.7 percent of fat but in hyperlipidaemia, the value may rise to 26 percent<sup>12</sup>. Harrison defines the hyperlipidaemia “In a practice hyperlipidaemia is considered whenever the plasma cholesterol level exceeds 5.2 mmol/l (200 mg/dl) and/or the triglycerides level exceeds

2.2 mmol/l (200 mg/dl), but the risk increase as cholesterol level increase<sup>13</sup>. The hyperlipidaemia theory is based on the biochemical changes in the blood, i.e. disturbed lipid metabolism and as a consequence of increased concentration of lipids in the blood circulation. Hyperlipidaemia is divided into two major groups; Primary Hyperlipidaemia: is usually due to genetic causes (such as a mutation in a receptor protein) either single gene disorders (monogenic) or may be due to multiple genetic and environmental factors (polygenic). It is classified into Familial hypercholesterolemia, Familial hypertriglyceridemia, Familial combined hyperlipidaemia.<sup>11</sup> Secondary hyperlipidaemia is complications of more generalized metabolic disturbances such as hypothyroidism, hepatic syndrome, metabolic disease, cholestasis and chronic renal failure etc. on the treatment of underlying disease the lipid levels come to normal levels. In these conditions, the genetic defect is absent. Genetic defect if present may aggravate the condition.

Various clinical studies and clinical trials has been carried out as well as going on at few reputed centres of Unani medicines in India, likewise Ajmal Khan Tibbiya College (AMU), Aligarh, National Institute of Unani Medicine (NIUM) Bangalore, and Central Council of Research in Unani Medicine (CCRUM), New Delhi that may be documented and compiled to understand the complexes of lipoprotein disorders under Unani ideology and concepts. There is a hope to develop a safe, effective and well tolerated pharmacologic agent in the therapeutics of Unani medicine to treat this ailment. But the studies are lacking with several technical aspects of research and not as per the GCP-ICMR guidelines. It is also a matter of worry that we have no standard operative procedures (SOPs) for clinical studies and research as per the Unani concepts and parameters. Although Unani pharmacopeia is rich in therapeutics but it needs evidence based, reverse pharmacological, multicentric and collaborative studies to put forward the datas before the medical fraternity with confidence and satisfaction. The medical use of Unani drugs in their natural and unprocessed form undoubtedly began when the first intelligent animals (human beings) noticed that certain plants altered particular functions e.g. bowel activity, moods etc. The human civilizations and cultures institutionalized these observations show that consumptions of botanicals often serve important cultural traditions, and such traditions are now known as folk medicine. *Nigella sativa* seeds and *Plantago ovata* husk are used for various therapeutic purposes as well as for dietary purposes since ancient time with all safety and efficacy, and their effects are mentioned in Unani classic literature.

Apart from this the Islamic literatures and *Tibb-e-Nabwi* are rich regarding a therapeutic benefit of *Nigella sativa*. Various pharmacological studies are there in support of these drugs<sup>14-15</sup>. Keeping in mind the

efficacy mentioned in our Unani therapeutics, a study was designed for primary hyperlipidaemia with following aims and objectives:

- 1) To explore the concept of hyperlipidaemia in Unani medicine with reference to ancient and modern literature.
- 2) To observe the effect of *Nigella sativa* and *Plantago ovata* husk in cases of primary hyperlipidaemia.
- 3) If it is found effective then it may be proposed for the ailments like primary hyperlipidaemia.
- 4) Also to observe any concomitant effect and apparent toxicity.

### Methodology

The present study is a single blind control clinical trial on primary hyperlipidaemia. During the study all G.C.P–ICMR guidelines were followed. The study was conducted on 60 patients comprising 30 patients in each group i.e. test group and control group respectively, and the grouping was made on the basis of lottery system. All the patients were randomly selected from Moalejat and Modern Medicine OPD, Ajmal Khan Tibbiya College Hospital, AMU, Aligarh, during the period extending from the year 2010 to 2012. The patients were selected on the basis of inclusion and exclusion criteria mentioned as below:

Those cases having deranged lipid profile without any clinical illness related with secondary hyperlipidaemia were selected for the study. The patients selected for study were thoroughly examined and investigated as per proforma mentioned elsewhere. Before initiation of treatment, all the clinical and haematological changes were noted regularly at 0 day, 45th day and 90th day. The patients below 21 years and above 60 years, patients who fail to follow up and suffering from diabetes mellitus, hypothyroidism, acromegaly, Cushing's syndrome, nephrotic syndrome or any other clinical illness were not included in the study, similarly those taking oestrogen containing oral contraceptive, alcohol, or any hypolipidaemic drugs or any system of medicine were excluded in the study.

Patients selected for lipid profile were asked the P.G Laboratory, Department of Moalejat AKTC, AMU in a 12-14 hrs fasting state (water permitted) The samples were obtained in plain vials and centrifuged to obtain serum lipid profile to estimate serum lipid and lipoproteins. Serum total cholesterol triglycerides, and high density lipoproteins (HDL-C) were estimated. Very Low Density lipoprotein (VLDL-C) was also estimated using following calculation<sup>16</sup>.

$$\text{VLDL Cholesterol} = \frac{\text{Triglycerides (in mg per dl)}}{5}$$

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Low Density lipoprotein (VLDL-C) was estimated by the following calculation:

$$\text{LDL-Cholesterol (mg/dl)} = \text{Total Cholesterol} - \text{HDL Cholesterol} - \frac{\text{Triglycerides}}{5}$$

Patients having increased concentration of plasma lipids, serum amylase or abnormalities in liver function, renal function and blood sugar (random) conducted at the beginning of the study were excluded. Renal function and liver function tests were also repeated at the end of the study to assess a safety profile of test drugs. Saboos-e-Aspaghool (*Plantago ovata*) and Sufoof-e-Kalonji (*Nigella sativa*) 4 gm twice daily 2 gm twice daily respectively before meal for 90 days. Atorlip-10 (Atorvastatin 10 mg) 1 OD for 90 days as a standard drug. The patients were informed about the expected advantages and disadvantages of the drugs which were used in the treatment of hyperlipidaemia. The follow up of all the cases was done at 0 day, 45th day, 90th day in the study duration of 90 days, No concomitant treatment was allowed. The individual assessment was carried out on the basis of physical examination and investigation. Observations were noted in the case report form, all the data were tabulated and statistically analyzed with the help of a statistician by calculating mean and standard deviation followed by paired and unpaired t-test.

As far as the age of the patients is concerned most of the patients in both the groups were between 31-40 years of age (middle age group) which is the most prevalent age group for primary hyperlipidaemia and more prone for subsequent CAD and other vascular problems (Table 1). When the gender distribution is concerned females were outnumbered which is

**TABLE 1**  
**Distribution of Patients According to Age n=60**

| Age groups | No. of patients | %     |
|------------|-----------------|-------|
| 21-30      | 10              | 16.66 |
| 31-40      | 21              | 35    |
| 41-50      | 18              | 30    |
| 51-60      | 11              | 18.33 |

a contradiction with other observations and findings in respect with hyperlipidaemia versus oestrogenaemia, the most probable reason is that females attendance was more in OPDs for their general clinical problems than males (Table 2). As far as religious distribution is concerned Muslims were pre-dominant in both the group and it is mainly due to locality of our hospital but its obvious that Muslims have more non-vegetarian habits and comparatively frequently consume more red meat than others<sup>17-19</sup> (Tables 3-5). In middle income group the incident was noted as maximum, most probably their dietary habit and less calorie consciousness in these groups, while as in low income group, there is low calorie diet and in high income group the calorie conscious diet along with awareness on health subjects are the key factors for the low incidence (Table 4). The *mizaj* is the key factor for phenotypic and genotypic presentation of the patients and in accordingly their disease acquiring tendency. In our study the phlegmatic individual were more than others probably due to the morphology, character and habit of a phlegmatic personality as mentioned by Unani scholars in their descriptions to be associated with clinical illnesses like CAD, CVA, hypertension etc. Hence phlegmatic personality and temperament may be considered as one of the risk factor for hyperlipidaemia and related disorders (Table 6).

**TABLE 2**  
**Distribution of Patients According to Gender n=60**

| Gender | No. of patients | %     |
|--------|-----------------|-------|
| Male   | 26              | 43.33 |
| Female | 34              | 56.66 |

**TABLE 3**  
**Distribution of Patients According to Religion n=60**

| Religion | No. of Patients | %  |
|----------|-----------------|----|
| Muslim   | 51              | 85 |
| Hindu    | 6               | 10 |
| Sikh     | 3               | 5  |

**TABLE 4**  
**Distribution of Patients According to Occupation n=60**

| <b>Occupation</b> | <b>No. of Patients</b> | <b>%</b> |
|-------------------|------------------------|----------|
| Business          | 10                     | 16.66    |
| Employee          | 17                     | 28.33    |
| Student           | 6                      | 10       |
| Housewife         | 27                     | 45       |

**TABLE 5**  
**Distribution of Patients According to Dietary Habits n=60**

| <b>Dietary Habits</b> | <b>No. of Patients</b> | <b>%</b> |
|-----------------------|------------------------|----------|
| Vegetarian            | 11                     | 18.33    |
| Non-vegetarian        | 49                     | 81.66    |

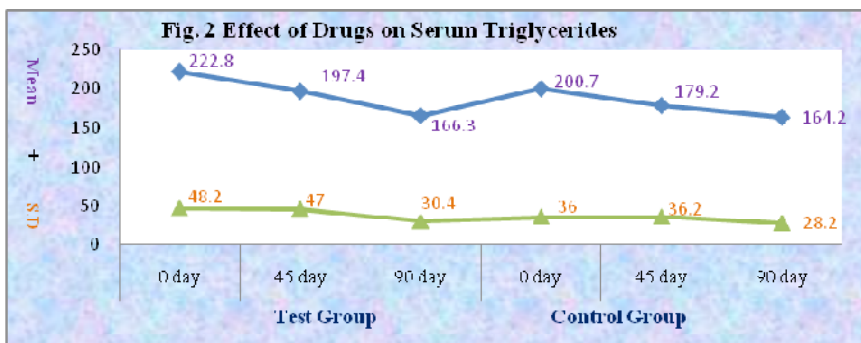
**TABLE 6**  
**Distribution of Patients according to**  
***Mizaj* (Temperament) n=60**

| <b>Mizaj</b>                   | <b>No. of Patients</b> | <b>%</b> |
|--------------------------------|------------------------|----------|
| Sanguinous ( <i>Damvi</i> )    | 4                      | 6.66     |
| Bilious ( <i>Safravi</i> )     | 7                      | 11.66    |
| Phlegmatic ( <i>Balghami</i> ) | 47                     | 78.33    |
| Melancholic ( <i>Saudavi</i> ) | 2                      | 3.33     |

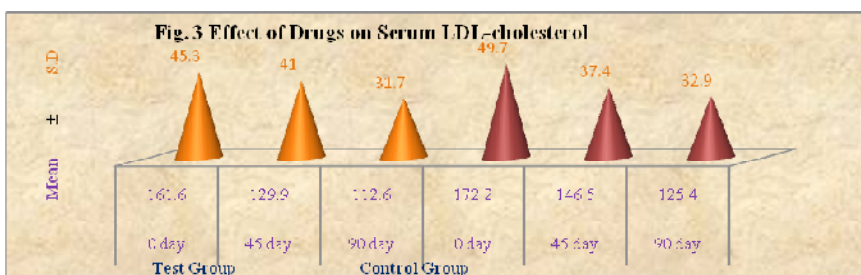
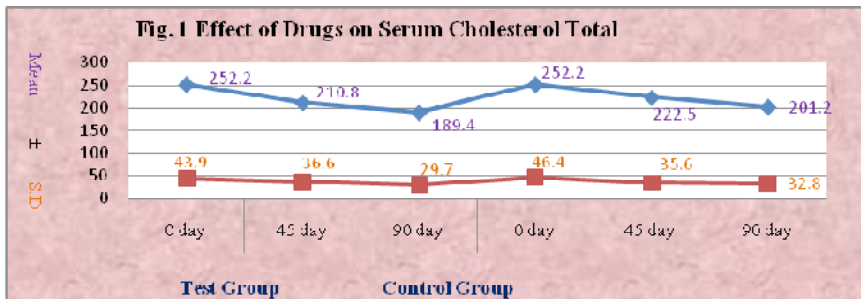
The serum total cholesterol and triglyceride are the main markers for abnormal lipids. The effect of test drug was highly significant in reducing the levels of serum total cholesterol  $t=5.4$  ( $p<0.001$ ) the most



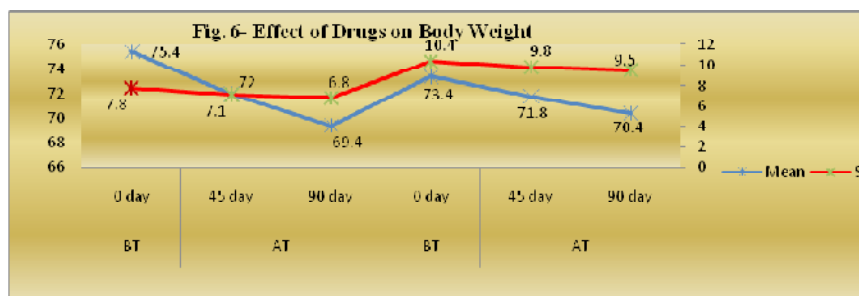
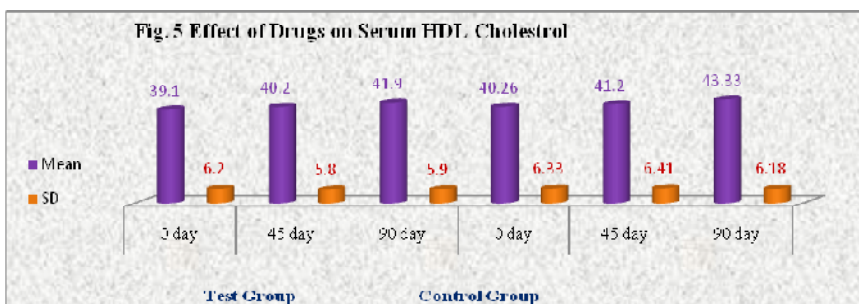
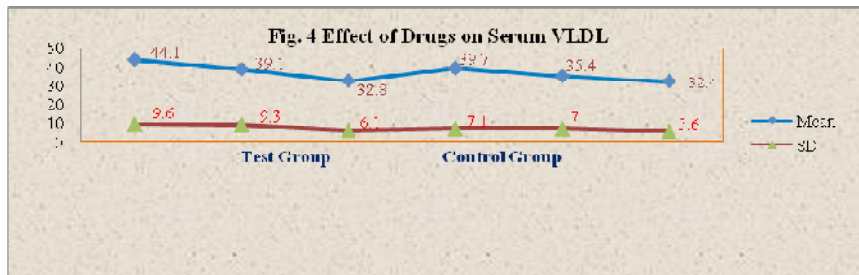
probable mechanism encountered in reducing a total cholesterol is presence of niacin (nicotinic acid) in Kalonji (*Nigella sativa*) which has lipid lowering property in general and total cholesterol and serum triglycerides in particular (Fig. 1). The nigellin present in *Nigella sativa* seeds also play an important role in reduction of abnormal lipid profile. At the same time presence of omega-3



fatty acids as well as fractions of polyunsaturated fatty acids, which has well known effect on abnormal lipid. The husk of *Asaphol* (*Plantago ovata*) acts as a cholesterol absorption inhibitor within the lumen of small intestine and the inhibition of intestinal cholesterol absorption is likely to be reduction in hepatic cholesterol and an increase in hepatic LDL-cholesterol is negligible. It is therefore the effect of *Saboos-e-Asaphol* along with powdered *Nigella sativa* becomes more effective, due to its additive effect in combination. *Nigella* powder is also working as bile acid sequestrants which bind bile acids in the intestine and promote the excretion of bile acids through stool. To maintain the bile acid pool size the liver diverts cholesterol to bile acid synthesis. The decreased hepatic intracellular cholesterol content results in up-regulation of the LDL-receptor and enhanced LDL-clearance from the plasma. It is therefore it has LDL-C lowering effect<sup>3</sup>. During the study most of the patients of test group have complaints about gastrointestinal symptoms like bloating, abdominal fullness and loose stools, which was mainly due to excretion of fat contents through stool in form of steatorrhea. At the same time the effect on serum triglycerides was highly significant ( $t=8.9$ ,  $p<0.001$ ) due to the similar mechanism encountered in this regard (Fig. 2). The effect of kalonji seeds in reduction of serum triglycerides is mainly due to nicotinic acid present in kalonji (*Nigella sativa*) seeds which is a known lipid lowering agent. The effect of test drug on serum LDL-cholesterol was not found significant in comparison to control drug but both the drugs have significant LDL-cholesterol reducing property for test drug ( $t=5.5$ ,  $p<0.001$ ) and for control drug ( $t=7.0$ ,  $p<0.001$ ). (Fig. 3).



The effect of our combination of test drug is mainly due to presence of omega-3 fatty acids and n-3 polyunsaturated fatty acids have known and significant reducing effect of LDL-cholesterol. In combination with Asaphol (*Plantago ovata*) which acts as bile acids sequestrants is very effective in LDL-cholesterol level while the effect of control drug i.e. HMG-CoA reductase inhibitors (statins) is known for lipid disorder. Hence our drug can be used at par to the statin (atorvastatin 10 mg used in control group) because both have no significant difference ( $t=0.011$ ,  $p>0.05$ ). Similarly the effect of test drug in reducing serum triglyceride and serum total cholesterol was highly significant and also at par to the control group. Hence the effect of both the drugs in lowering the serum VLDL-cholesterol was highly significant. However, when compared there was statistically significant difference between two groups ( $t=2.4$ ,  $p<0.05$ ) (Fig. 4). HDL-cholesterol is a human friend cholesterol because of its scavenging property, therefore its low level is considered risk factor while as high HDL-cholesterol is considered as cardio-protective and beneficial in other aspects i.e., in the prevention of atherogenesis. During the treatment, the HDL-cholesterol was raised and it was highly significant in both test and control group respectively and there was no significant difference between two groups ( $t=0.29$ ,  $p>0.05$ ) (Fig. 5). The effect of both the drugs in reducing body weight was highly significant. However, when compared there was statistically significant difference between two groups ( $t=5.5$ ,  $p<0.001$ ) (Fig. 6).



During the study all the patients were advised for low cholesterol diet and also to avoid saturated fat along with reduction of simple carbohydrates. Exercise particularly aerobic exercise was advised to all patients along with medications for both the groups during the study period. Apart from these, the significant improvement was noted in general well being of the patients and the test drug was well tolerated by all the patients and there were no observable side effects was noticed except abdominal bloating, loose stool and frequent stool habit while as in control group the patients regularly complaint about fatigue, lethargy, muscular aches and cramps and nausea.

As a safety profiles the serum trans-amylases such as AST and ALT was also measured to see any observable effects particularly on

liver as well as on skeletal muscles, it was found that the drug is completely safe for liver and muscles. Similarly there was no any nephrotoxic effect of test drug was noticed during the study period for this regular renal function was carried out with follow up.

### Conclusion

The hyperlipidaemia is a common public health problem because it is considered as one of the important modifiable risk factor for coronary artery disease and cerebrovascular disease. Therefore there is always a need for safe, effective and easy acceptable lipid lowering agent. Our combination of drug of test group shows significant lipid lowering property, particularly on total serum cholesterol, serum triglyceride, LDL-c etc. and also showing effective in HDL cholesterol improvement and at par to the control drug Atorvastatin in all aspect but observable and apparent no known side effect was the in test group as compared to control group. Therefore we can propose the combination of test group as one of the best lipid lowering agent.

We can generate the data at larger extent through exhaustive double blind control clinical trial along with collaborative approach by involving experts from other disciplines like biochemistry and pharmacology before any final conclusion. Such strategies can contribute for an important health risk factor responsible for atherogenesis and related problems, in future.

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