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Original Research Article

Therapeutic efficacy and safety of Unani formulation in patients of Fasaad-e-tashahhum-e-dam (dyslipidemia): a randomized open standard controlled clinical study

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ABSTRACT

Background: Hyperlipidemia which is interchangeably used with the term dyslipidemia essentially refers to the condition of abnormality of lipid levels measured in the blood typically due to the disorder of lipoprotein metabolism. The objective of this study was to determine the therapeutic effect and safety of newly formulated drug on patients with Fasaad-e-Tashahhum-e-Dam (dyslipidemia) and compare it with the effect of Unani formulation and rosavastatin.
Methods: The present study was open randomized controlled clinical study. The study subjects were divided in two groups, one group was given test drug (test group) and another group was given control drug (control group). All the patients who qualified the inclusion criteria were randomly placed in either test or control group.
Results: In the present study we observed that both the groups were comparable with respect to age, sex lifestyle, family history and mizaj. We found that both Unani formulated drug and standard drug rosavastatin significantly improves the lipid parameters after the treatment with a p value of (<0.001*).
Conclusions: We concluded that the overall effect of the proposed Unani formulated drug was found quite fascinating in the treatment of dyslipidemia. Apart from drug safety, visible improvements were evident in objective parameters like cholesterol, triglyceride and LDL, VLD. However, the present study did not revealed that Unani drug is superior to standard drug instead both the treatments are equally effective on the improvement of lipid profile parameters.

Keywords: Fasaad-e-tashahhum-e-dam, Lipid, Unani, Rosavastatin

INTRODUCTION

Hyperlipidemia which is interchangeably used with the term dyslipidemia essentially refers to the condition of abnormality of lipid levels measured in the blood typically due to the disorder of lipoprotein metabolism. Dyslipidemia which includes either overproduction or deficiency of lipoproteins or both manifests an elevation of serum total cholesterol or triglyceride or both, or low density lipoprotein (LDL) and decrease in high density lipoprotein (HDL) concentration.[1,2] Evidently, health care providers face a great deal of challenge to deal with dyslipidemia and its associated comorbidities, since it plays a significant role in development of coronary artery disease (CAD) and immensely contributed to the annual death rates globally.[3] There is a 4 fold prevalence of coronary heart disease in Asia as compared with general USA population. The unattended dyslipidemia vulnerably invites certain catastrophic consequences like atherosclerosis, stroke and ischemic heart disease (IHD).[4] The cause responsible for such lipid disorder could be primary, and more commonly secondary to diabetes mellitus, nephrotic syndrome and hypothyroidism.[5,6] It is important for a patient with dyslipidemia to have a full clinical assessment and thereby timely appropriate treatment so that the life-threatening consequences of disease may be controlled or halted optimally. Despite

remarkable advancement in dyslipidemia therapy, it continues to raise significant economic and personal burden as risk factor of cardiovascular disease. The management of dyslipidaemia is a two-way process; non-pharmacological and pharmacological. The non-pharmacological approach includes diet, food and additives and reduction of weight and exercises. The pharmacological approach consists of drug therapy to aim at maintaining lipids in recommended range. Currently available drug classes that affect lipoprotein metabolism are listed in Table 1.

Table 1: Available drug classes that affects lipoproteins metabolism.[7]

Drug class	Daily close	Mechanisms	Lipid/lipoprotein in effects	Side effects	Contraindications
HMGCoAre ductase in hibitors (statin)	Lovastatin (20 80 mg), pravastatin (20-40 mg)	Cholesterol synthesis, hepatic	LDL-C 18-55% HDL- C%-15%	Myopathy increased liver enzymes	Absolute: active or chronic liver disease relative
	Simvastatin (20-80 mg), fluvastatin (20-80 mg) atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg)	LDL receptor VLDL production	TG 7-30%		<concomitant use of certain drugs
Cholesterol absorption inhibitors	Ezetimible (10 mg)	Intestinal cholesterol absorption	LDL 17% HDL, TG-minimal change	Elavated tranaminases anngioedema headache	Hypersensitivity
Bile acid sequestrant	Cholestyramine (4-32 g), cholesterol (5-40 g), colesevelam (3750-4375 mg)	Bile acid excretion and LDL receptors	LDC-C 15-30 % HDL-c n3-5% TG no change or increase	Gastrointesti-nal distress, constipation, decreased absorption of other drugs	Absolute: dysbetalipoproteine mia TG>400 mg/dl relative TG>200 mg/dl
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic (niaspan) (1- 2 g), sustained release nicotinoic acid (1-2 g)	VLDL hepatic synthesis	LDL-C5-25% HDL-C 15-35% TG 20-50%	Flushing, Hyperglyce-mia, Hyperuricae-mia (or gout), upper GI distress, Hepatotoxici-ty	Absolute chronic liver disease severe gout, relative diabetes, hyperuricaemia, peptic ulcer disease
Fibric acid	Gemfibrozil (600 mg BID), fenofibratew (200 mg), clofibrate (1000 mg bid)	Dyspepsia, myalgia, gallstonezs, Gemfibrozi 1600 mg bid 600 mg bid elevated transminases	LDL-C 5-20% (may beincresed in patients with high TG) HDL-C 10-20% TG 20-50%	Dyspepsia, gallstones, myopathy	Absolute severe renal disease, severe hepatic disease

Presently, the treatment of dyslipidemia is lipid lowering agents; these are statins (atorvastatin, simvastatin, pravastatin and lovastatin, etc), bile-acid sequestrants (cholestyramine and colestipol), resins, niacin, fibric acid analogs (fenofibrate, bezafibrate, and ciprofibrate) and ezetimibe. Administration of these pharmacological agents produces several adverse effects or side effects along with antilipidemic activity like hepatotoxicity, myopathy, renal dysfunction, dyspepsia, bloating, constipation, flushing, pruritus of the face and upper trunk, skin rashes, acanthuses nigricans, urticaria, hair loss, myalgias, fatigue, headache, impotence, and anaemia.[8-10] Hence, there is pressing need for novel therapeutic agents for better management to prevent from adverse effect of conventional therapy. In conventional Unani system of medicine, there are large number of drugs; like Gugulipid (*Camifora mukul*), Alfalfa (*Medicago sativa*), Asian ginseng (*Panax ginseng*), and Fenugreek (*Trigonella foenum graecum*), Garlic (*Allium sativum*) and onions (*Allium cepa*), Turmeric (*Crucuma longa*), Lilly of the valley (*Convallaria majalis*), Black cumin (*Nigella sativa*), etc.[11]

These drugs are Haar (hot) in mizaj (temperament) to modulate liver functions and also scientifically have been reported to have lipid lowering effects, like Gugulipid

(*Camifora mukul*), Alfalfa (*Medicago sativa*), Asian ginseng (*Panax ginseng*), and Fenugreek (*Trigonella foenum graecum*), Garlic (*Allium sativum*) and onions (*Allium cepa*), Turmeric (Crucuma longa), Lilly of the valley (*Convallaria majalis*), Black cumin (*Nigella sativa*), etc.[11]

Aim and objectives

The aim of the study was to determine to evaluate the therapeutic effect and safety of a newly formulated Unani drug in the patients with Fasaad-e-tashahhum-e-dam (dyslipidemia) and to compare it with the effect of rosavastatin by open randomized controlled clinical study.

METHODS

The Present study was conducted at postgraduate department of Moalijat, Regional Research Institute of Unani medicine (RRIUM), Srinagar, University of Kashmir from 2018-2019. A newly established Unani drug consists of several botanical ingredients- Zeera (Carum cabrilinu, Tukhm Karafs (*Apium graveolens* Linn), Marzenjosh (*Oliganum vulgare* Linn), Boora surkh (Armenianbole), Tukhm Suddab (Rutagraveolanslinn) and Nankhaw (*Trachyspe rmumammi* Linn). These ingredients were first dried at 40°C and then grounded to powder and thereafter were taken in different quantity, mixed together properly and then packed.

The active investigation product was supplied to the patients in the powder form on each visit in small disposable poly packs from the day one. The investigational products were stored in dry and cold place and the patients of test group were also instructed for the same, the daily dosage of 4.5 g was advised orally for two months. The standard drug rosavastatin in the form of tablet with daily dosage of 10mg orally was administered to control group for two months.

Sample size calculation

Using GPOWER software (version 3.0.10), it was estimated that the least number of patients required in each group with 80% power, 0.91 effect size and 5% significance level is 20. Since we had to include two groups in our study, therefore a total of 40 samples was included in our study.

Statistical methods

The recorded data will be compiled and entered in a spreadsheet (Microsoft excel) and then exported to data editor of SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables will be summarized as frequencies and percentages and continuous variables will be expressed as mean±SD.

Unpaired t-test for difference between two independent groups will be applied to analyze the recorded data and paired t-test will be employed to analyze the difference within groups.

Inclusion criteria

Patients with following criteria's were included (a) known case of dyslipidemia with disease history of <3 years with or without anti hyperlipidemia medication- total cholesterol ≥240 mg/dl, triglycerides <499 mg/dl (high), LDL ≥189 mg/dl, HDL >40 mg/dl in men and >50 in woman, VLDL <0.930-1.006 g/l, ratio LDL to HDL <6.3 in man and 5 in woman; (b) patients of both sex; (c) age between 20-50 years; and (d) patients who follow the protocol.

Exclusion criteria

Patients with following criteria's were excluded- (a) known case of dyslipidemia with disease history of >3 years total cholesterol <240 mg/dl, triglycerides >499 mg/dl (high), LDL <189 mg/dl, HDL <40 mg/dl in men and <50 in woman, VLDL>0.930-1.006 g/l, ratio LDL to HDL >6.3 in man and >5 in woman; (b) known cases on use of corticosteroids and contraceptives; (c) history of cardiovascular, renal, liver disease, AIDS and TB; (d) history of alcoholism; (e) pregnant and lactating mothers; and (f) age <20 and >50 years of age.

To minimize the selection bias, participants fulfilling the inclusion criteria and willing to participate in the study were randomly divided into test and control group. Due to time constraint, lottery method was used for randomization. The study was carried out strictly according to guide lines of good clinical practices, embodying the principles mentioned in Declaration of Helsinki. Informed consent was obtained from all participants and approval from the Institutional Review Board was obtained.

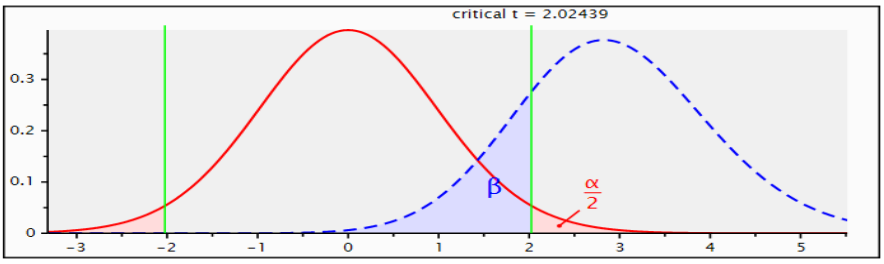

Figure 1: Displays graphical justification of sample size determination.

RESULTS

The age distribution of patients of test group and control group is shown in Table 2. Mean age was 23.55±0.762 years, among test group and 23.6±1.110 years, among control group. Maximum numbers of patients were between the age group of 31-40 years in both test and control group.

Table 3 displays sex wise distribution of patients among test group and control group. The above table indicated that in test group 55% were male and 45% were female while in control group 65% were male and 35% were female.

Table 4 exhibits life style distribution among test and control group. We observe that majority of patients accounting about (50%) was having sedentary life style and (35%) participants were had hardworking lifestyle followed by (15%) who were very hard working in test group. In control group (60%) of patients were having sedentary life style followed by (20%) in hard working and (20%) very hardworking.

Table 5 shows family history among test and control group. In test and control group, majority of participants had family history of hyperlipidaemia (60%) and (75%) respectively. Only (40%) and (15%) had no family history of hyperlipidaemia in test and control group respectively.

Table 2: Distribution according to age (N=40).

Age (years)	Test group (N=20)	Percentage within group (%)	Control group (N=20)	Percentage within group (%)
20-30	1	5	2	10
31-40	10	50	11	55
40-50	09	45	7	35
Total	20	100	20	100

Note: The age of the participants was calculated by history and anecdotal event calendar.

Table 3: Distribution according to sex (N=40).

Sex	Test group (N=20)	Percentage within group (%)	Control group (N=20)	Percentage within group (%)
Male	11	55	13	65
Female	9	45	7	35
Total	20	100	20	100

Table 4: Distribution according to life style of patients (N=40).

Life style	Test group (N=20)	Percentage within group (%)	Control group (N=20)	Percentage within group (%)
Sedentary	10	50	12	60
Hardworking	7	35	4	20
Very hard working	3	15	4	20
Total	20	100	30	100

Table 5: Distribution based on family history of hyperlipidaemia (N=40).

Family history of hyperlipidemia	Test group (N=20)	Percentage within group (%)	Control group (N=20)	Percentage within group (%)
Present	12	60	15	75
Absent	8	40	5	15
Total	40	100	30	100

It is evident from above Table 6, that majority of patients i.e.; 40% patients among test group while in control group (50%) had balghami temperament. In the present study, 40 patients of hyperlipidaemia were registered and were randomly placed under test and control group. 20 patients were treated in test group with Unani formulation and 20 patients in control group were treated with rosavastatin. The effect of these treatment on the subjective and objective parameters are presented. In

Table 7, illustrates that in test group S. cholesterol was reduced by 16.9%, S. triglyceride was reduced by 14.66%, LDL was reduced by 15.53%, VLDL was reduced by 22.12% which were all statistically significant at $p<0.0001$ whereas HDL was raised by 4.91%. The change that occurred with the treatment is not great enough to exclude the possibility that the difference is due to chance $p=0.142$. In Table 8, illustrates that in test group S. cholesterol was reduced by 20.73%, S. triglyceride was reduced by

21.59%, LDL was reduced by 18.02%, VLDL was reduced 33.75% which were all statistically significant at p<0.0001 whereas HDL was raised by 4.01%. The change that occurred with the treatment is not great enough to exclude the possibility that the difference is due to chance p=0.072. In Table 9, the comparison of test and control group with respect to cholesterol, triglyceride, HDL, LDL and VDL. We observed from the table that both the treatments drastically improve the parameters but none of the treatment can be considered superior to other because statistically there is an insignificant difference (p value>0.05) between test and control group with respect to cholesterol, triglyceride, HDL, LDL and VDL.

Table 6: Distribution based on mizaj (N=40).

Mizaj	Test group (N=20)	Percentage within group (%)	Control group (N=20)	Percentage within group (%)
Damvi	4	20	4	20
Balghami	8	40	10	50
Safrawi	5	25	6	30
Saudawi	3	15	0	0
Total	20	100	20	100

Table 7: Effect on lipid profile of test group.

Lipid values	Mean score		Difference in mean	% relief	Paired t test			
	BT	AT			SD	SEM	t value	P value
Cholesterol	223.950	186.050	37.900	16.9	25.876	5.012	5.201	<0.0001
Triglyceride	168.450	143.750	24.700	14.66	20.222	3.722	5.781	<0.0001
HDL	40.720	42.720	2.100	4.91	5.128	1.272	1.53	0.140
LDL	110.850	125.250	10.600	15.53	19.234	3.497	1.781	0.183
VLDL	30.980	24.000	6.980	22.12	6.985	1.563	5.09	<0.0001

Table 8: Effect on lipid profile of control group.

Lipid values	Mean score		Difference in mean	% relief	Paired t test			
	BT	AT			SD	SEM	t value	P value
Cholesterol	230.00	187.100	43.100	20.73	16.403	3.485	14.043	<0.0001
Triglyceride	180.400	120.800	59.6	21.59	16.222	3.482	9.950	<0.0001
HDL	44.900	49.150	4.25	4.01	4.476	1.225	1.838	0.072
LDL	140.600	113.874	26.726	18.02	7.945	2.001	12.376	<0.0001
VLDL	31.850	21.100	10.75	33.75	4.844	1.083	8.926	<0.0001

Table 9: Effect on both groups.

Parameters	Group	N	Mean score	Unpaired t test			
				SD	SEM	t value	P value
Cholesterol	Test group	20	186.05	43.692	9.776	-0.079	0.937
	Control group	20	187.1	39.836	8.908		
Triglyceride	Test group	20	143.75	60.212	20.706	-0.967	0.44
	Control group	20	120.8	50.002	16.198		
HDL	Test group	20	42.72	8.436	1.808	-1.025	0.331
	Control group	20	49.15	5.225	1.111		
LDL	Test group	20	100.25	30.636	6.231	-1.461	0.13
	Control group	20	113.874	31.726	6.121		
VDL	Test group	20	24	10.117	3.81	1.312	0.423
	Control group	20	21.1	6.591	1.71		

DISCUSSION

In present study, we observed that the incidence of patients with dyslipidaemia were highest in the age group of 31-45 years constituting (52.5%) of total numbers of patients followed by (40%) patients in the age group of 46-50 years and (7.5%) were in the age group of 16-30 years. This is in concurrence with the increased incidence of dyslipidaemia in the middle age group. This data shows that more prevalence of dyslipidaemia found in age group of 31-45 years, second high incidence was found in age over 50 years. Our study is closely related with the study conducted by Sawami et al (2008) who reported that prevalence of dyslipidaemia is high in 31-40 years of

patients.[12] It is also reported that prevalence over the age 60 years is also high suggested by Estari et al (2009).[13] In the sample taken for the study, 65% patients were male in comparison to 35% of female patients. This indicates the increased incidence of dyslipidaemia among male population but the conclusion cannot be drawn as the sample size is small. Present data correlates with the observation of Goff et al, Sawami et al (2008), Estari et al (2009) and IC Health New Delhi Data base (2004).[12-14.] Majority of the patients (60%) belonged to upper class followed by (20%) in middle class and (20%) in lower class in test group.

Majority (50%) were in upper class followed by (25%) in middle class and (25%) in lower class in control group. This is in concurrence that dyslipidaemia is ubiquitous regardless of economic status. In the current study, majority of patients (50%) were having sedentary life style and (35%) participants were hardworking followed by (15%) who were very hard working in test group. In control group (60%) of patients were having sedentary life style followed by (20%) in hard working and (20%) very hardworking. This result is coinciding with the statement of Sina et al and Kabiruudin et al.[15,16]

According to Sina et al, rest is always cooling and moistening in nature. It is cooling because of which there is no excitation of heat and there is an inward collection and aggregation of waste matter. In the present study, 60 of patients had a positive family history of dyslipidaemia, while 40% did not have any family history of same. This data shows that the incidence of positive family history (primary dyslipidaemia) is higher. Present data may be interpreted as incidence of primary dyslipidaemia is varying according to type of gene involved in mutation. We observed that majority of patients i.e.; 40% had balghami temperament in test group and 50% had balghami temperament in control group. It is mentioned that Baroodate Jigar produces more Khilte balgham. Ultimately temperament of organs becomes balghami (phlegmatic). It is suggested by Ibne Rushd in Kitabul Kulliyat.[17] We calculated mean and standard deviation of lipid profile (S. cholesterol, triglyceride, HDL, LDL, VDL) among both test and control group patients before and after the treatment and observed that lipid profile significantly improved within both test and control group after the treatment because the observed p value was <0.001* for all the lipid parameters; however, there was an insignificant difference with respect to lipid profile parameters between test and control group after the treatment because the observed p value was >0.05 for all the parameters which indicates that both the treatments are equally effective in improving the lipid profile. Statistically no side effect was observed in test group, compliance to the treatment was found good.

CONCLUSION

The overall effect of the Unani formulation was found quite encouraging in the treatment of dyslipidaemia. Marked improvements were evident in objective parameters like cholesterol, triglyceride and LDL, VLD. Both test and control drugs have same effects on lipid profile parameters.

Statistically no side effect was observed in test group, compliance to the treatment was found good. These results conclude that the test drug is quite safe in the treatment of dyslipidaemia. Hence, we recommend practitioners to opt for proposed Unani formulated drug for optimal results.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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