ORIGINAL ARTICLE

Effect of integrative Unani personalized regimen in reducing risk factors of Metabolic Syndrome. A randomized open-labeled controlled clinical study

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Abstract

Background: Metabolic syndrome is a cluster of risk factors for CVD and diabetes. The number of individuals with metabolic syndrome continues to rise. The current study aimed to test the efficacy and safety of an Integrative Unani personalized regimen (IUPR) in reducing the risk factors of metabolic syndrome. **Materials and Methods:** Patients according to NCEP ATP III criteria were selected, 50 patients (30 in the test group and 20 in the control group) completed the study. The test group was treated with an IUPR and the control group was treated for respective risk factors with standard drugs for 2 months. The response was measured by changes in TC, TG, HDL, FBS, BP, WC, and Weight. **Results:** IUPR was found superior in reducing body weight, waist circumference, and BP ($P < 0.01$), equivalent in reducing serum triglyceride and fasting blood sugar level and inferior in reducing total cholesterol compared to standard drugs provided for respective risk factors after 2 months of intervention. HDL increased by 1.033 mg/dl in the test and decreased in the control group by 4.850 mg/dl. **Conclusion:** In metabolic syndrome lipid storage increases due to the deterrence of the pathological mechanisms. Unani regimen caused a reduction in risk factors of the metabolic syndrome might be by attenuation in physiological changes possibly by reverting rate-limiting enzymes and increasing energy expenditure. Long-term high-quality trials with dietary modification are needed to get optimal results.

Key words: Metabolic syndrome, *Sue mizajbarid*, Integrative unani personalized regimen

INTRODUCTION

The metabolic syndrome is a cluster of disorders (obesity, dyslipidemia, hyperinsulinemia, and hypertension) that individually or collectively lead to an increase in the risk for CVD and Diabetes Mellitus Type 2. It is associated with endothelial dysfunction, raised markers of chronic inflammation, insulin resistance, and clotting dysregulation.[1] There are different diagnostic criteria for metabolic syndrome. The most accepted definition uses the criteria suggested by the Adult Treatment Panel (NCEP-ATP III). According to the NCEP ATP III, metabolic syndrome is technically diagnosed when three or more of the following five conditions are present: (1) Central obesity waist circumference >90 cm (Male) and >80 cm (Female), (2) triglycerides ≥150 mg/dl, (3) HDL cholesterol <40 mg/dl (males) and <50 mg/dl (females), (4) BP ≥130/85 mmHg, and (5) fasting plasma glucose ≥100 mg/dl. However, the criterion for waist circumference is slightly different for each country and race.[2]

Various epidemiological studies reported that ≈ 25% of the world's population suffers from metabolic syndrome[3] and 20% of the western population is suffering from metabolic syndrome.[4] From the data 1975 to 2014, the number of victims continues to rise. In India itself, this number reached to 10.8% prevalence rate, among them, the male contributes 8.1% and females contribute to13.6%.[3] It is becoming a major socioeconomic problem worldwide affecting the productive efficacy of nations.[3] The prevalence of the metabolic syndrome is increasing due to an increasing trend of

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a sedentary lifestyle, high-calorie intake, smoking, and stress, associated is an increase in obesity, type 2 diabetes, cardiac disease, stroke, and death. People with metabolic syndrome have a 5 times greater risk of developing Type 2 diabetes.[3] It is estimated that by the year 2030 the maximum number of diabetic patients will be in India and cardiovascular disease will be the leading cause of death in India.[3] Metabolic risk factors are associated with one another and together the risk factors promote atherosclerotic cardiovascular disease.[5] The main underlying risk factors for metabolic syndrome are abdominal obesity and insulin resistance.[6] Therefore, preventing atherosclerotic cardiovascular disease by controlling waist circumference and insulin resistance is the key to managing metabolic syndrome. Clinically treatment of hyperglycemia, hypertension, and hyperlipidemia has been prescribed according to each patient's state. Drugs used to treat hypertension including Enalapril and Captopril may cause adverse events such as cough, increased serum creatinine, headache, and skin rash.[7,8] Amlodipine causes swelling of the legs and ankles, dizziness, irregular or very fast heart rate, abnormal muscle movement, muscle pain, heartburn, etc.[9] Metformin is used to treat diabetes mellitus Type 2 causes stomach problems, tiredness, weakness, unusual muscle pain, trouble breathing, dizziness irregular heart rate, etc.[10] Statin used for dyslipidemia causes muscle pain, tiredness, weakness, drowsiness, dizziness, nausea, muscle toxicity, liver damage, and neurological side effects.[11] Due to the side effects of the drugs used to treat metabolic syndrome, the researchers of various systems of medicine are concentrating on safe and effective therapies for the prevention and treatment of metabolic syndrome. Therapies that offer efficacy, safety, and easy access without causing much financial burden to the patients can offer an alternative treatment for metabolic syndrome.

Metabolic syndrome/obesity in classical literature of Unani medicine may correlate with *Sue mizaj barid maddi* (abnormal substantial cold temperament). The concept of *talteef mawaad* (the act of liquefying thick/viscid matter) and *istifragh* (evacuation) is the distinguishing feature to prevent diseases caused by *Sue mizaj barid maddi*. The concept aims at maintaining the balance in humors qualitatively and quantitatively.[12] Unani physicians recommend *mulattif advia* and *aghzia* (drugs and diet which liquefies viscous matter), *mufattite sudud* (deobstruent), *mohallil advia* (resolvent drugs), *dalak khashn* (rough massage) with *mohallil roghan* (resolvent oils), *hammam* (steam bath), *riyazat* (exercise), strong *mudirre bol* (diuretic) *moarriq* (diaphoretic) drugs, *tadabeer* (regimens) for the prevention and treatment of diseases caused by *Sue mizaj barid maddi/obesity*.[12] In Unani medicine philosophy, an important principle of treatment is the severity of disease and degree of derangement in *mizaj* (temperament, i.e., coldness/hotness) and the power of a drug must be equal. In case, the disease severity and degree of derangement in *mizaj* are more than the single drug, more drugs of the same actions and temperament are added to the formulation to meet desirable effects and to reduce side effects.[13] The complex Synergistic interactions among the herbs in compound formulation and regimens in Unani medicine are believed to be able to enhance the effect of drug and heat/cold in the body. Based on these recommendations an Integrative Unani personalized regimen (IUPR) was designed. The present study was planned with the aim to test the efficacy and safety of the IUPRs in reducing the risk factors of metabolic syndrome.

MATERIALS AND METHODS

After obtaining approval of protocol from the Institutional Ethics Committee for Biomedical Research of NIUM Bengaluru, India vides no. NIUM/IEC/2015-16/016/TST/01this study was registered in the clinical trial registry of India vide no. CTRI/2018/06/014407. Informed written consent was obtained from all participating individuals on recruitment. The trial was conducted at the National Institute of Unani Medicine, Hospital Bengaluru, India between Feb-2016 and March 2017. Patients visiting the OPD of the hospital were enrolled in the trial. This was an imbalanced randomized open-labeled standard controlled parallel-group trial conducted with an objective to test the role of an IUPR in reducing the risk factors of metabolic syndrome.

Subjects of either sex, 20–60 years of age with three or more of the following features (NCEP-ATP III criteria), namely; central obesity waist circumference >90 cm in male, >80 cm in female, triglycerides ≥150 mg/dl, low HDL cholesterol <40 mg/dl in males and <50 mg/dl in females, BP ≥130/85 mmHg, and fasting plasma glucose ≥100 mg/dl were included in the study. Subjects with known heart, liver, and kidney diseases, type 1 diabetes mellitus, uncontrolled diabetes mellitus type 2, uncontrolled hypertension, pregnant and lactating women, and subjects on weight loss medication were not included in the study.

Sample Size Estimation

The sample size was calculated as 48 which increased to 60, 35 in the test group and 25 in the control group. Based on the previous study findings[14] on outcome variable HDL, and on the assumption of 80% statistical power, 5% significance for the two-sided alternative hypothesis, with sample size in two groups taken in the ratio of 2:3, the sample size calculated to detect a difference of 4 (HDL) and common standard deviation of 15, including 10% lost to follow-up. The formula used for sample size estimation was as follows: $N = (r+1)(Z_{\alpha/2} + Z_{1-\beta})^2 \sigma^2/rd^2$. Where $Z\alpha$ is the normal deviate at α level of significance ($Z\alpha$ is 1.96 for 5 % level of significance) $Z_{1-\beta}$ is the normal deviate at 1-β % power with β % of type 2 error (0.84 at 80 % statistical power) $r = n_1/n_2$ is the ratio of the sample size required for two groups, it was kept as 0.6 for the sample size distribution in two groups as 2: 3, σ and dare the pooled standard deviation and difference of means of two groups.

Screening of Study Subjects

A total of 80 subjects were screened among them 70 subjects were found eligible for the study. Ten subjects refused to participate in the study. Sixty subjects enrolled in the study. Selected subjects were allocated to the test group (35 subjects) and control group (25 subjects) using random allocation software to ensure concealment and prevent selection bias, ten subjects five in the test group and five in the control group were lost to follow-up. Thus, 50 subjects (30 in the test group and 20 in the control group, i.e., in the ratio of 3:2) completed the study [Figure 1].

Interventions

Test group treated with IUPR for 2 months and in control group patients with increased blood sugar level (FBS ≥ 100 mg/dl) treated with Metformin 500 mg (Glyciphage 500 mg – Franco Indian pharmaceuticals PVT. LTD) twice daily before meal, patients with increased blood pressure (BP ≥ 130/85 mm Hg) given Amlong 5 mg (Micro, Labs P.LTD) orally once daily after breakfast. Whereas, patients with dyslipidemia (TG ≥ 150 mg/dl, HDL<40 mg/dl in males, HDL < 50 mg/dl in females) were treated with Atorvastatin 10 mg (Avas.Micro labs. P LTD) daily at bedtime for 2 months. *Riyazat, Dalk,* and *Hammam* were not included in the control group intervention. No dietary advice was provided among either of the groups. To assure the quality of the interventions under the personalized regimen*, Dalk* and *hammam* were carried out at the Regimenal unit of NIUM, Bengaluru, India under the guidance and observation of the investigator. *Dalk* was done by the investigator herself on female patients and by the male therapist on male patients. The male therapist was well trained by the investigator. A brisk walk was taken by patients before administration of decoction.

IUPR

IUPR composed of

1. Medicated drink: One cup decoction prepared from 5 gm of the formulation (*Filfil siyah* [fruit of *Piper nigrum* Lin] two parts, *tukhm e karafs* [seeds of *Apium graveolans* Lin] two parts, *beekh e Asaroon* [root of *Valeriana wallichii* Lin] half part, *tukhm e Anisoon* [seeds of *Pimpinella anisum* Lin] half part) 2 times daily with *sirkaunsul* 12 ml.
2. Whole-body *dalak khashn* (rough massage) with *Roghan Shibbat* for 30 min 2 times weekly.
3. Brisk walking for 45 min daily.
4. *Dalak Isterdad* (Restorative massage) 10 min twice weekly.
5. Hammam (steam bath) 20 min twice weekly.[12]

Method of Preparation, Dosage and Mode of Administration of Components of the IUPR

1. Medicated drink: The ingredients of medicated drink identified and provided by the chief pharmacist, National Institute of Unani Medicine, Bengaluru, India in crude form. The drugs were cleaned to remove any unwanted material and impurities and then powdered. 5 g coarsely powdered formulation soaked in two cups of water for 10–12 h then boil until the original volume is reduced to one cup. Strained out the herbs using a filter, and filtrate obtained was given as a whole 2 times daily with 12 ml *sirkaunsul*.
2. *Sirkaunsul* prepared in NIUM, Pharmacy Bengaluru India by boiling peeled and cleaned onion (*Allium cepa* Lin bulb) in sugarcane vinegar (procured from A. B. General Bengaluru) in the ratio of 1:8 till onion completely dissolved in vinegar then filtered. 12 ml of this filtrate was given to patients with medicated drink 2 times daily.[15]
3. *Roghan Shibbat* prepared by boiling *Qust* (root of *Sasurea lappa* Lin) 10 g, *Gul e Babuna* (flowers of *Matricaria chamomilla* Lin) 10 g, *Zanjabeel* (dry rhizome of *Zingiber officinalis* Lin) 10 g and *Ispand* (seeds of *Peganum harmala* Lin) 10 g in *Joshanda Shibbat* (decoction of seeds of *Anethum sowa* Lin) 1 liter and *Roghan e Kunjad (*oil of *Sesame indicum* Lin) 1 liter till water evaporates. Strained out herbs with filter and filtrate obtained was used for *Dalk*.[16]
4. *Dalk Khashn, Riyazat, Dalk isterdad,* and *Hammam. Dalk khashn* was done 2 times weekly with a handheld electric massager using a golden cautery stick attachment (Magic King Massager, KS Healthcare). The rate of vibration was 28/min. After *Dalk khashn* participants were instructed for brisk walking for 45 min followed by *Dalk isterdad* with hands using *roghane shibbat*. Finally, participants were exposed to *hammam* for 20 min. Temperature in *Hammam* was 110-115 F°.

Assessment of the Efficacy of the Drug

Efficacy assessment is made by primary outcome (Lipid Profile [TC, TG, and HDL] and fasting blood sugar) and secondary outcome (body weight, waist circumference, and blood pressure). Patients were kept under strict observations and called in OPD to check progression or regression in their symptoms. Body weight, waist circumference, and blood pressure were assessed every 15th day till 8 weeks. All measurements were taken twice, and the average was used for data analysis while primary outcome measures were assessed pre- and post-treatment.

Safety Assessment

The safety of the treatment is assessed by clinical assessment at every visit of follow up (15th day), Hematological assessment before and after treatment (Hemoglobin, Total Leukocytes Count, and Differential Leukocytes Count Erythrocyte Sedimentation Rate), and Biochemical assessment before and after treatment (Renal Function Test and Liver Function test).

Statistical Analysis of the Data

Results on continuous measurements presented on Mean ± SD (Min–Max) Significance assessed at 5% level of significance. Student *t*-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (Intergroup analysis) on metric parameters. Student *t*-test (two-tailed, dependent) was used to find the significance of study parameters on a continuous scale within each group. The Statistical software SPSS 18.0 and R environment ver.3.2.2 were used for the analysis of the data, and Microsoft Word and Excel were used to generate tables.

OBSERVATION AND RESULTS

Our study population comprised predominantly of females 60% (30) while the remaining 40% (20) were males. In this study, the maximum number of subjects 42% (21) was in the age group of 31–40 years. At the commencement of the study, the number of subjects with increased fasting plasma glucose, blood pressure, and waist circumference is shown in Table 1.

Efficacy Assessment

Efficacy assessment made on the basis of the primary outcome and secondary outcome. Mean decrease in FBS in the test group after 2 months of intervention was 4.01 mg/dl (mean ± SD 103.97 ± 22.21 vs. 99.96 ± 32.76). The mean decrease in FBS in the control group after 2 months of intervention was 3.2 mg/dl (mean ± SD 162.1 ± 56.51 vs. 158.90 ± 55.12). After 2 months of intervention, the FBS was not significantly different between the two groups and improvement was suggestively significant from the baseline in the test group which indicates the effect of the IUPR on FBS [Table 2].

The mean decrease in total cholesterol in the test group after 2 months of intervention was 4.867 mg/dl (mean ± SD 179.00 ± 27.42 vs. 174.13 ± 27.24). The mean decrease in total cholesterol in the control group after 2 months of intervention was 35.500 mg/dl (mean ± SD 207.75 ± 50.26 vs. 172.25 ± 35.500). After 2 months of intervention, the total cholesterol significantly decreased in the control group with respect to the test group. The decrease in the test group was not significant [Table 2].

The mean decrease in serum triglyceride in the test group after 2 months of the intervention was 21.5 mg/dl (mean ± SD 144.03 ± 56.30 vs. 122.53 ± 42.01). The mean decrease in serum triglycerides in the control group after 2 months of intervention was 12.550 (mean ± SD 197.55 ± 148.1 vs. 185 ± 151.79). After 2 months of intervention, the serum triglyceride was not statistically different in patients in the test group and control group, but it decreases significantly from baseline in the test group which indicates the IUPR has an effect on serum triglyceride [Table 2].

After 2 months of intervention, the mean serum HDL slightly increased (1.033 mg/dl) in the test group but it significantly reduced in the control group (4.850 mg/dl). The decrease in HDL indicates oxidation in LDL which is a marker of atherosclerosis. It means IUPR prevents lipid peroxidation[17,18] [Table 2].

After 2 months of intervention, the mean decrease in body weight and waist circumference in the test group was highly significant compared to the control group ($P < 0.001$**) [Table 3].

After the intervention, the mean decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the test group was strongly significant compared to baseline and control group $P < 0.05$ [Table 4].

Safety and Tolerability

During the course of the study, no adverse events were reported in either group. It was found that all the safety parameters were within the normal range after completion of the trial [Table 5]. Patients reported good tolerability of drugs and regimens used in the IUPR. This suggests that the IUPR is safe and very well tolerated.

DISCUSSION

Drugs used in conventional medicine for the management of metabolic syndrome are responsible for many serious side effects. The quest for safe and effective drugs and regimens continues to combat metabolic syndrome and its complications. For the management of *sue mizaj barid maddi*/obesity Unani physicians recommend drugs and regimens that produce heat in the body, break thrombus into small pieces, liquefy thick and viscid humors and excrete them through urine and sweet.[12] Keeping this in view IUPR was designed to explore scientifically. In the present study, IUPR was found to be superior in reducing the body weight,

Table 1: Number of subjects according to (NCEP-ATP III criteria) at base line

Group	Patients with FBS ≥ 100 mg/dl	Patients with BP ≥ 130/85 mmHg	Patients with waist circumference ≥ 90 cm (M), ≥ 80(F)
Test group (*n*=30)	16	20	30
Control group (*n*=20)	16	10	18

Table 2: Fasting blood sugar, serum cholesterol, serum triglycerides, and high density lipoprotein (mg/dl): Comparative assessment in two groups studied (*n*=50) (Mean±SD)

Fasting Blood Sugar (mg/dl)	**Test Group IUPR (Mean±SD)**	**Control Group Treated for respective risk factor (Mean±SD)**	**Total**	***P* value**
Before Treatment	103.97±22.21	162.1±56.51	133.03±39.36	<0.001**
After Treatment	99.96±32.76	158.90±55.12	129.43±43.94	<0.001**
Difference	4.01	3.2	3.605	-
P value	0.061+	0.2719	0.667	-
Serum Cholesterol (mg/dl)	**Test Group**	**Control Group**	**Total**	**P value**
Before Treatment	179.00±27.42	207.75±50.26	190.50±40.34	0.012*
After Treatment	174.13±27.24	172.25±43.97	173.38±34.49	0.852
Difference	4.867	35.500	17.120	-
P value	0.338	0.007**	0.005**	-
Serum Triglycerides (mg/dl)	**Test Group**	**Control Group**	**Total**	***P* value**
Before Treatment	144.03±56.30	197.55±148.1	165.44±105.27	0.078+
After Treatment	122.53±42.01	185±151.79	153.76±96.9	0.037*
Difference	21.5	12.550	11.68	-
P value	0.0056**	0.279	0.540	-
High Density Lipoprotein (mg/dl)	**Test Group**	**Control Group**	**Total**	***P* value**
Before Treatment	36.40±3.44	40.65±6.82	38.10±5.43	0.005**
After Treatment	37.43±4.62	35.80±4.92	36.78±4.76	0.238
Difference	1.033	–4.850	-1.320	-
P value	0.310	0.002**	0.152	-

Test used: Between group – Student's *t*-test (Two tailed, Independent) and within group – Student's *t*-test (Two tailed, dependent).
IUPR: Integrative Unani personalized regimen.

waist circumference, and systolic, diastolic blood pressure equivalent in reducing serum triglyceride and fasting blood sugar levels, and inferior in reducing total cholesterol compared to standard drugs provided for respective risk factors after 2 months of intervention. IUPR improves HDL but not significantly. These results suggest a significant effect of the IUPR in reducing risk factors of metabolic syndrome.

In a study, Brahma Naidu *et al*. (2014) reported a significant increase in plasma glucose, insulin resistance, total acetyl-CoA carboxylase (ACC), total fatty acid synthase (FAS), HMG-CoA reductase, plasma amylase, and lipase activity and decrease in carnitine palmitoyltransferase (CPT), lecithin-cholesterol acyltransferase, lipoprotein lipase (LPL), in high-fat diet (HFD) induced obese rats over their normal control rats.[12] Indicating increased absorption and endogenous biosynthesis of lipids (increased lipids accumulate in triglycerides) and increased production of glucose and reduction in HDL in HFD induced obese rats over their normal control rats. An increase in triglycerides decreases fat oxidation. Inhibition of CPT leads to the accumulation of fat in skeletal muscle.[19,20]

About 90% of dietary fat is triglyceride. Triglycerides are not absorbed directly from the intestine. Pancreatic lipase hydrolyses triglycerides into glycerol and fatty acids. The drugs that suppress pancreatic lipase reduce dietary fat absorption. The previous studies reported that Piperine[21] *P. anisum* Lin seeds,[22,23] *Apium graveolens* Lins seeds,[22,24] *A. cepa* Lin bulb[25] inhibits pancreatic lipase activity, and Piperine,[21] *A. cepa* Lin bulb,[26] *Apium graveolens* Lin seeds[27] inhibit lipoprotein lipase activity in animal models. Thus, these drugs reduce the fatty acid synthesis and cellular fatty acid uptake. The previous studies reported that *A. graveolence* Lin seeds[28,29] Piperine[21] and vinegar[30,31] downregulate ACC, FAS. *A. graveolence* Lin seeds[29,32] Piperine,[21] *P. anisum* Lin seeds,[23] and *A. cepa* Lin bulb inhibits the activity of HMG-CoA reductase in animal models[26] *A. cepa* Lin bulb also inhibits lipogenic enzyme Glucose 6 phosphate dehydrogenase and malic enzyme.[26] Suppression of ACC, FAS,[33] HMG-CoA reductase,[34] Glucose 6 phosphate dehydrogenase, and malic enzyme activity[35] reduces biosynthesis of endogenous lipids. Reduced absorption and endogenous synthesis of lipids lower the availability of free fatty acids to the liver thus contributing to improving triglycerides levels. Essential oil (VOL) present in *Valeriana wallichii* Lin rhizome imparts a remarkable hypolipidemic effect (Hu *et al*. 1999, Si *et al*. 2003).[36,37] Further *A. graveolence* Lin seeds contribute to reducing fat by increasing cholesterol/metabolites excretion through increased bile acid excretion.[32,38,39] It is concluded

Table 3: Body weight and Waist circumference: Comparative assessment in two groups studied (n-=50) (Mean±SD)

Weight (kg)	**Test Group (IUPR) *n*=30 (Mean±SD)**	**Control Group Treated for respective risk factor *n*=20 (Mean±SD)**	***P* value.**
0 day	88.066±14.333	74.55±14.142	
15 day	87.233±14.350	74.55±14.021	
30 day	86.1±14.150	74.55±13.744	T_{15} vs. C_{15}, 0.0655
45 day	85±14.113	74.15±13.642	
60 day	83.933±14.142	73.95±12.88	T_{30} vs. C_{30}, 0.007
Difference from 0 day			
15 day	0.8333	0.00	T_{45} vs. C_{45}, 0.0001
30 day	1.967	0.100	
45 day	3.067	0.4000	
60 day	3.133	0.600	
P value from 0 day			
15 day	0.0001	1	T_{60} vs. C_{60}, 0.0001**
30 day	0.0001	0.79	
45 day	0.0001	0.24	
60 day	0.0001	0.0967	
Waist Circumference (cm)	**Test Group (Mean±SD)**	**Control Group (Mean±SD)**	***P* value**
0 day	111.8±12.08	101.80±14.28	T_{15} vs. C_{15}, 0.0655
15 day	109.23±11.80	100.90±14.37	T_{30} vs. C_{30}, 0.127
30 day	104.7±11.64	100.45±14.52	
45 day	103.23±12.01	100.4±14.29	T_{45} vs. C_{45}, 0.061
60 day	100.43±11.83	100.90±13.70	
Difference from 0 day			T_{60} vs. C_{60}, 0.006**
15 day	2.57	0.900	
30 day	7.10	1.350	
45 day	8.567	1.40	
60 day	11.36	0.90	
P value from 0 day			
15 day	<0.05	>0.05	
30 day	<0.05	>0.05	
45 day	0.00001**	>0.05	
60 day	<0.00001**	>0.05	

Test used: Between group – Student's *t*-test (Two-tailed, Independent), within group – Student's *t*-test (Two-tailed, dependent.
IUPR: Integrative Unani personalized regimen, vs.: Versus

that the IUPR reduces the absorption and endogenous synthesis of fatty acid possibly by suppressing pancreatic lipase, lipoprotein lipase, ACC, FAS, and HMG-CoA reductase activity thus decreasing the availability of free fatty acids. A study to investigate the underlying mechanisms in regulating lipid metabolism in humans is needed.

Pancreatic Amylase and Alpha Glucosidase are the key enzymes involved in the digestion and absorption of carbohydrates in the form of glucose.[40] The previous studies reported that Piperene,[21,23] *P. anisum* Lin seeds,[23] *A. graveolens* Lin seeds,[41,42] and *A. cepa* Lin bulb[43,44] inhibits pancreatic amylase and alpha-glucosidase. The inhibition of these enzymes lowers the rate of glucose absorption through delayed carbohydrate digestion and extended digestion time. It is concluded that the integrative Unani personalize regimen slows down the carbohydrate digestion and absorption might be by inhibiting pancreatic amylase and alpha-glucosidase hence reducing energy intake.

Energy expenditure comprises multiple entities of which the most important are basal metabolic activity and skeletal

Table 4: SBP and DBP: Comparative assessment in two groups studied (*n*=50) (Mean±SD)

SBP (mm Hg)	Test Group IUPR *n*=30 (Mean±SD)	Control Group Treated for respective risk factor *n*=20 (Mean±SD)	Total	*P* value
0 day	126.83±10.16	127.00±12.34	126.90±10.96	0.959
15 day	121.27±12.80	126.35±13.90	123.30±13.35	0.190
30 day	122.67±9.49	123.05±11.10	122.82±10.05	0.897
45 day	122.83±9.337	124.15±10.41	123.49±9.87	0.5060
60 day	121.10±8.73	122.45±10.84	121.77±9.78	0.494
Difference from 0 day				
15 day	5.567	0.650	3.600	-
30 day	4.167	3.950	4.080	-
45 day	4.000	2.850	3.425	-
60 day	5.73	4.550	5.14	-
P value from 0 day				
15 day	0.049+	0.815	0.074+	-
30 day	0.067+	0.163	0.019*	-
45 day	0.0216	0.215	0.041*	-
60 day	0.0002**	0.040+	0.015*	-
DBP (mm Hg)	**Test Group**	**Control Group**	**Total**	**P value**
0 day	84.97±5.22	83.25±4.93	84.28±5.12	0.250
15 day	81.03±5.03	81.75±6.90	81.32±5.79	0.673
30 day	82.07±4.74	81.70±4.91	81.92±4.76	0.793
45 day	82.43±5.01	82.60±4.82	82.50±4.88	0.907
60 day	81.67±3.11	82.25±5.45	81.90±4.16	0.632
Difference from 0 day				
15 day	3.933	1.500	2.960	-
30 day	2.900	1.550	2.360	-
45 day	2.533	0.650	1.780	-
60 day	3.300	1.000	2.380	-
P value from 0 day				
15 day	0.001**	0.276	0.001**	-
30 day	0.024*	0.201	0.009**	-
45 day	0.019*	0.544	0.021*	-
60 day	0.001**	0.440	0.003**	-

Test used: Between group – Student's *t*-test (Two-tailed, Independent), within group – Student's *t*-test (Two-tailed, dependent).
IUPR: Integrative Unani personalized regimen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

muscle activity. Basal metabolic activity can be increased by thermogenesis induction and skeletal muscle activity can be stimulated by increasing physical activity[45-49] Studies of humans by the groups of Jécquier (1983), Ravussin *et al*. (1988), Roberts *et al*. (1988) have shown that a decrease in thermogenesis is one predictive feature of weight gain.[50-52] The previous studies reported that onion, Piperine, steam bath, vinegar, and exercise stimulate thermogenesis through different mechanisms. Onion induces thermogenesis/upregulates energy expenditure by activating the sympathoadrenal system[53] and by increasing skeletal muscle mitochondrial number and function through differentiated regulation of mtDNA-encoded gene expression.[54] Piperine increases the ATPase activity of relaxed fibers in animal models and upregulates the metabolic rate of resting muscles (Nogara *et al*. 2016).[55] Further Piperine enhances energy expenditure by activation of the sympathoadrenal system (Kawada *et al*. 1988).[56] Steam bath enhances energy expenditure and fat oxidation by stimulation of sympathoadrenal system mediated by uncoupling protein 1.[57] It has been reported that vinegar[30,31] and exercise[58] activates AMPK promotes the catabolic process and generate ATP.[31] During exercise large amount of ATP is yielded and 20–25% of which is utilized in muscular work. The remainder is released in non-useable form as heat

Table 5: Safety parameters: Comparative assessment in two groups studied (*n*=50) (Mean±SD)

Parameters	Test (*n*=30)		Control (*n*=20)	
	B.T.	A.T.	B.T.	A.T.
Hemoglobin (gm%)	12.29±1.46	12.82±1.52	12.58±1.51	13.06±2.02
TLC (cells/mm^3)	6923.33±1743.89	6970.00±2423.33	6660.00±2454.30	5950.00±1696.28
DLC				
P	68.33±8.28	64.37±6.89	67.00±6.70	67.75±6.80
L	22.73±8.60	25.63±6.59	21.85±6.5	22.15±6.60
E	4.83±1.76	5.07±1.23	5.65±1.04	5.25±1.12
M	4.13±1.87	4.63±1.27	5.50±1.47	4.85±1.23
B	0.00±0.00	0.00±0.00	0.05±0.22	0.00±0.00
ESR (mm/h)	33.02±20.59	37.59±20.65	32.00±23.62	38.35±22.51
Blood Urea (mg/dl)	25.00±4.73	25.83±5.25	25.45±4.08	24.30±4.52
Serum Creatinine (mg/dl)	0.78±0.11	0.76±0.13	0.82±0.12	0.77±0.11
SGOT (IU/L)	0.78±0.11	0.76±0.13	0.82±0.12	0.77±0.11
SGPT (IU/L)	23.53±7.25	22.70±8.59	24.65±10.14	28.30±16.06

Test used -- Between group – Student's *t*-test (Two tailed, Independent), within group – Student's *t*-test (Two tailed, dependent).
IUPR: Integrative Unani personalized regimen, B.T.: Before treatment, A.T.: After treatment

energy which raises the body temperature[59] and after exercise heat is produced through UCP1 synthesis in brown adipose tissues.[60] It is concluded that the IUPR reduces triglycerides, and energy intake might be by regulation of absorption and endogenous synthesis of lipid and carbohydrates possibly by regulating rate-limiting enzymes and increasing energy expenditure/fat oxidation.

In the present study, HDL slightly increased in the test group and significantly decreased in the control group. Improvement in the test group might be due to the regulation of lipid metabolism by the regulation of rate-limiting enzymes.

Analysis of obesity indicators showed that the IUPR decreases significantly weight and waist circumference compared to western medicine. This might be due to reduced absorption and endogenous synthesis of lipids, reduced absorption of glucose, increased energy expenditure, and excretion of waste products/metabolites. The thermogenic effect of the IUPR leads to hemodynamic changes or liquefy the viscid matter. Physical forces applied to the body tissues by massage move fluid from areas of relative stasis to higher pressure areas by creating a hydrostatic pressure gradient. Once fluid leaves the cells or interstitial fluid, it can enter the lymphatic or vascular system[61] and from circulation, it is excreted with sweat during the steam bath, exercise and with urine due to the diuretic effect of *P. anisum* Lin seeds[62] and *A. graveolans* Lin seeds.[63]

After 2 months of intervention, the FBS was not significantly different between the two groups and improvement was suggestively significant from the baseline in the test group which indicates a positive effect of IUPR on FBS level. In obesity/metabolic syndrome increased free fatty acids and circulating glucose cause dysfunction of insulin-producing pancreatic beta cells. A decrease in free fatty acids protects the pancreas and restores regular insulin production from the pancreatic beta cells.[1] In the present study test group showed a decrease in triglycerides hence lowering the availability of free fatty acids and improving insulin sensitivity. Insulin plays important role in the reduction of glucose levels by glucose transport from the blood into skeletal muscle cells. Further, this regimen regulates glucose metabolism by regulating rate-limiting enzymes.

In metabolic syndrome increased levels of free fatty acids and insulin resistance contribute to hypertension.[1] In the present study, test group showed a significant reduction in systolic and diastolic blood pressure. Experimental studies reported antihypertensive activity of *P. nigrum* Lin,[64] *P. anisum* Lin seeds, *A. graveolans* Lin seeds[65] *V. wallichii* Lin rhizome,[66] massage, and steam bath, and diuretic activity of *P. anisum* Lin seeds[62] and *A. graveolans* Lin seeds.[63] *P. nigrum* Lin[62] and *A. graveolans* seeds[63] act in a similar manner as calcium channel blockers, *V. wallichii* Lin rhizome activates KATP channel.[64] *A. graveolans* Lin seeds dilate blood vessels impacting prostaglandin.[65] Massage exerts vasodilatory effect through sympathetic nervous system inhibition,[67] steam bath also dilates peripheral blood vessels due to heat.[68] It is concluded that the antihypertensive activity of the IUPR might be due to the combined hypolipidemic, antihypertensive, diuretic, vasodilatory, and diaphoretic activity of the components of the IUPR.

Oxidative stress plays an important role in the pathogenesis of many metabolic disorders, including obesity, diabetes, atherosclerosis, and hypertension.[69] Antioxidants are reducing agents which inhibit the oxidation of other molecules

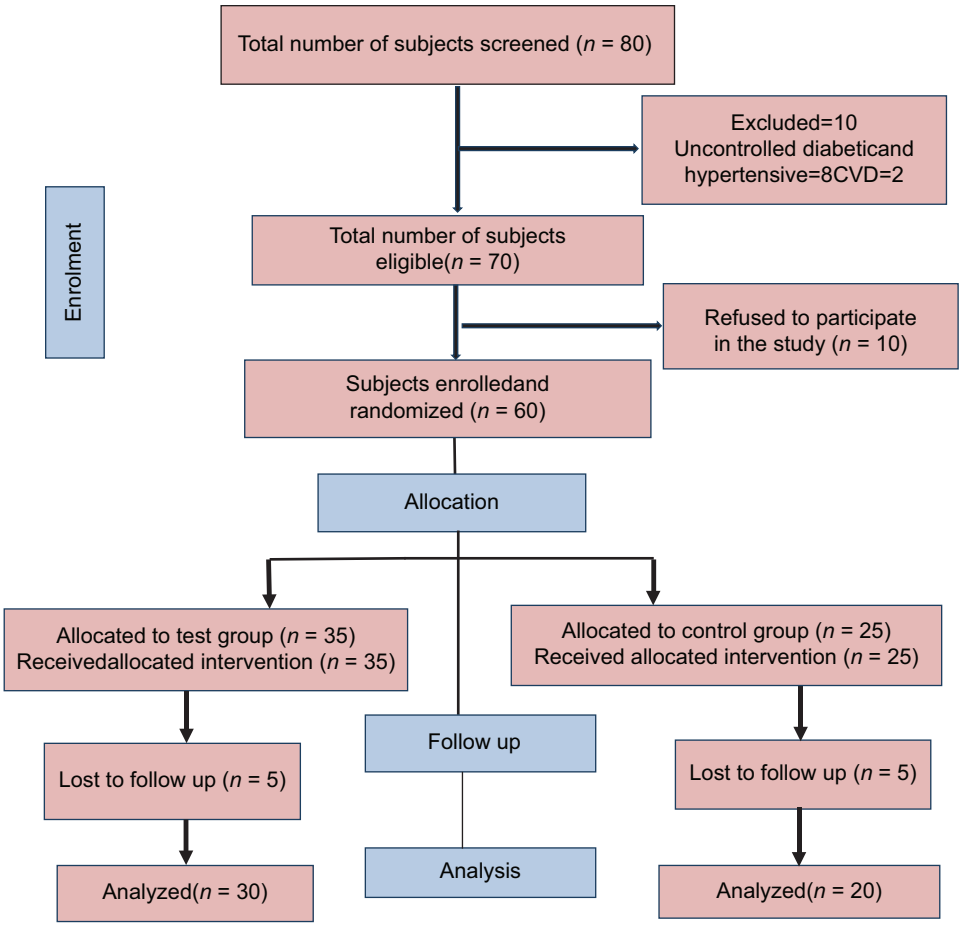

Figure 1: CONSORT flow diagram showing the recruitment and retention of study patie

and can be used not only to prevent but also to treat health complications of metabolic syndrome and atherosclerosis. Experimental studies showed that piperine,[70] *P. anisum* Lin seeds,[71] *A. graveolence* Lin seeds,[72] *V. wallichii,* Lin rhizome[73] and *A. cepa* Lin bulb[44] reduce HFD-induced oxidative stress to the cells. The antioxidant activity of these drugs might be due to the polyphenolic compounds present in these drugs.[74] Thus, the antioxidant activity of the components of the IUPR may contribute in reducing the risk factor of metabolic syndrome.

In Unani medicine the components of IUPR are reported to be *mulattif, mufattit e sudud*, *muhallil*, *mukhrij e balgham wa sauda* (agents which expel out the phlegm and atrabilious humors)*, mudirr e bol and muarriq* and their use is recommended for the prevention and treatment of *sue mizaj barid maddi* and its associated conditions. *V. wallichii* Lin rhizome,[75] *sirka unsul*,[12] *hammam*,[76-79] and *Dalk khashn*,[76,80,81] by virtue of their *mulattif* property liquefies the *ghaleez madda* (Viscid matter) by their moderate heat. *A. graveolens* Lin seeds,[75,82,83] *V. wallichii* Lin rhizome,[75] *roghan shibbat*,[12] *dalk khashn*,[77] *hammam*,[76,78,80,84,85] and *riyazat*,[77,80,81,86,87] due to their *muhallil* property, resolve the thick and viscous humors. *P. nigrum* Lin,[75] *V. wallichii* Linrhizome,[75,83] *P. anisum* Lin seeds,[83] *Sirka unsul*,[12] *Dalk khashn*,[76,80] by their *mufattit e sudud* property break the *akhlaat luzuja* (viscous humors) in small pieces which can be evacuated from the body. *P. anisum* Lin seeds,[82] *A. graveolens* Lin seeds,[75,82,83] *Dalk khashn*[88] and *riyaazat* due to their *Mohillil* and *mufatteh* (vasodilator)[77] effect, dilates blood vessels and dissolves the thick and viscous matter to remove the obstruction, thus reduces the vascular pressure, widens the lumen and facilitates smooth flow of humors. *P. nigrum* Lin,[75] *P. anisum* Lin seeds,[83] *A. graveolens* Lin seeds,[75,82,83] *V. wallichii* Lin rhizome[75] by virtue of their *mudirr e bol* property and *A. graveolens* Lin seeds,[75,82,83] *hammam* and *riyaazat*[77] by virtue of their *muarriq* property, remove the waste and excess humor from the body. Thus, the mechanism proposed by the Unani physicians appears to be comprehensive and very much in commensuration with the modern approach to treatment.

Limitation

The limitation of this study was that dietary modification in both groups and *riyazat*, *Dalk*, and *Hammam* was not included in the control group intervention and the 8 weeks duration of the study was relatively short. Long-term research and observation with the inclusion of dietary modification may demonstrate the optimal effect of the IUPR.

CONCLUSION

In obesity and metabolic syndrome lipid storage increases due to the deterrence of pathological mechanisms. IUPR caused a reduction in risk factors of metabolic syndrome by attenuation in physiological changes possibly by reverting LPL, pancreatic lipase, total ACC, Total FAS, HMG-CoA reductase, Glucose 6 phosphate dehydrogenase, and malic enzyme, pancreatic amylase, alpha-glucosidase activity, and increasing energy expenditure. These observations strongly suggest that the IUPR serves as an effective regimen for the reduction of risk factors of metabolic syndrome. However, long-term, high-quality trials with dietary modification are needed to get optimal results from the IUPR.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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