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Clinical efficacy of unani formulation in type ii diabetes-A randomized, single blind standard control clinical study

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Abstract
Background and objectives: Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. Unani system claimed for the efficacy of many anti-hyperglycaemic drugs, and all such drugs required validated on scientifically. Hence a clinical study was intended to evaluate the clinical efficacy of the Unani formulation in the management of diabetes.
Methods: This trial was conducted as single blind randomized standard control, on 60 patients of type 2 diabetes with the test (n =30) and control (n=30) groups for 45 days. Test group received Unani Formulation twice daily at a dosage of 5 g powder, and control group received 500 mg tablet metformin twice a day before meal. The subjective (at 0, 15th, 30th, 45th), and objective parameters were evaluated respectively as pre-post care.
Results: After treatment with Unani Formulation significant reduction was observed in subjective parameters (viz. polyuria, polydipsia, polyphagia and tiredness) in connotation of control group. In both groups the objective parameters FBS, PPBS, and HbA1c were found to be significantly reduced. The findings were statistically analysed using paired and non-paired tests.
Conclusion: Based on the above observation, it is concluded that there is substantial anti-diabetic effect of the Unani Formulation without any adverse drug reaction.

Keywords: Type 2 diabetes mellitus; unani formulation; metformin; ziabetus

1. Introduction
Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia [1]. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both [2]. According to the International Diabetes Federation (IDF), approximately 415 million adults between the ages of 20 to 79 years had diabetes mellitus in 2015 [3]. DM is proving to be a global public health burden as this number is expected to rise to another 200 million by 2040 [4]. Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 DM [5]. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol. Obesity has been found to contribute to approximately 55% of cases of type 2 DM [6]. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents [7]. Environmental toxins may contribute to the recent increases in the rate of type 2 DM [8]. A weak positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 DM. Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [9, 10].
Chronic hyperglycaemia in synergy with the other metabolic aberrations in patients with diabetes mellitus can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications, most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) and macro vascular complications leading to a 2-fold to a 4-fold increased risk of cardiovascular diseases [11, 12]. Through lifestyle and diet modification. Studies have shown that there was significant reduction in the incidence

of type 2 DM with a combination of maintenance of body mass index of 25 kg/m^2, eating high fibre and unsaturated fat and diet low in saturated and trans-fats and glycaemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol [13]. Biguanides, of which metformin is the most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases the absorption of glucose from the gastrointestinal tract [14]. These generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycaemia. Insulin is used alone or in combination with oral hypoglycaemic agents [15]. Augmentation therapy with basal insulin is useful if some beta cell function remains [16]. Prior preclinical and clinical studies have reported that ingredients of Unani Formulation (*Tukhm Hulba*, *Tabasheer*, *Shilajit, Maghz Khasta Jamun*, and *Afsanteen*) may reveal anti-diabetes properties [17-22]. These findings led us tosubstantiate Unani Formulation's exhibit hypoglycaemic activity among diabetes patients. Therefore, a study anticipated to evaluate the clinical efficacy of Unani Formulation in the management of Type 2 Diabetes.

2. Materials and Methods

2.1 Participants

Patients were identified and recruited from OPD/IPD Deoband Unani Medical College Hospital, and Research Centre, Deoband, India.

Inclusion Criteria: Diagnosed cases of Ziabetus Shakri (Diabetes Mellitus Type II) with Blood sugar level, Fasting blood sugar (FBS) > 126mg/dl, Post prandial blood sugar (PPBS) > 190mg/dl, HbA1c > 6.5%, Patients between 35-60 years of age of either sex, Patients ready to participate in the study and ready to follow in instructions, Patients having ALT, AST, Serum creatinine and Blood urea within normal limit, and

Exclusion Criteria: Patients below 35 and above 60 years of age, Patients of Insulin dependent diabetes mellitus (Type I), Patients of Gestational Diabetes (GDM), Patients of Malnutrition related diabetes mellitus (MRDM), complicated cases of Diabetes Mellitus (Diabetic ketoacidosis, retinopathy, neuropathy nephropathy, coronary artery disease, peripheral vascular disease, cerebrovascular disease liver disease [23-30].

2.2 Study Design

This study was conducted as single blind randomized standard control trial. Eligible patients with diabetes were enrolled. At first, all participants were informed about the study protocol by being given a complete description of the objectives, benefits and possible harm of the study. The study was approved by Ethics committee of Deoband Unani Medical College Hospital, and Research Centre, Deoband, India. Eventually 60 subjects who met the inclusion criteria were selected. Participants were randomly allocated into two (test=30 subjects and control=30 subjects) groups by simple randomization method.

2.3 Criteria for the Selection of the Patients

Informed Consent: Patients fulfilling the inclusion criteria mentioned above were given the information sheet having details regarding the nature of the study, the drug to be used, method of treatment etc. Patients were given enough time to go through the contents of informed consent sheet. They were given the opportunity to ask any question and if they agreed to participate in the study, they were asked to sign the informed consent form.

Clinical Evaluation of Disease: The clinical evaluation of Type 2 Diabetes Mellitus was done on the following basis as per designed case report form. (i) History taking (ii) General physical examination, and (iii) Investigations. Only those patients who fit with the inclusion criteria were selected for the trial and patients with inclusion criteria were, excluded to select for the trial.

Assessment of Mizaj: Temperament of patient was assessed on the basis of ten parameters that *are Ajnas-e-Ashra*` as described in the Unani literature (Temperament Chart is attached in annexure part) [16].

Subjective Parameters: Patients were selected on the basis of complain of the patients i.e. Dizziness, Polydipsia, Polyuria, Polyphagia, Pruritus vulvae**,** Tiredness**,** Progressive weakness Unexplained weight loss

Objective Parameter: Blood Sugar; Fasting and Post Prandial, and Glycosylated Haemoglobin (HbA1c).

Investigation Required: Following investigation were carried out in each patient of both the test group as well as standard group with follow-up fortnightly.

Unani Formulation: The Test drug was Unani formulation. This formulation contains Hulba (*Trigonella foenum graecum*) 10 gm, Tabasheer (*Bambusa indica*) 10 gm, Shilajit (*Asphaltum*) 5 gm, Magaze Khasta Jamun (*Syzygium cumini*) 15 gm, Afsanteen Rumi (*Artemisia absinthium*) 10 gm in form of fine powder and given 5 grams twice a day orally with water before meal for 45 days [17-22].

Standard Drug: The Standard drug was a Standard anti diabetic drug Metformin 500mg was given to the control group twice a day orally with water before meal for 45 days.

Diet: All the patient of Diabetes mellitus will be advised to take tailored made diet and exercises as per ICMR guidelines.

Study Procedure: After obtaining the consent form patients were randomly allocated in to test group and standard group, given patient I.D. no. both groups were given their drug to assess the difference in the clinical response. Patients were physically examined and clinical feature were recorded in the CRF, at each visit. Findings were compared before during and after the treatment. The compression was analysed statistically to evaluate the efficacy of the test drug in the treatment of type 2 diabetes mellitus.

3. Assessment of Results

Demographic observations: The results regarding the incidence of Ziabetus Shakri according to distribution, Age, Sex, family history and Mizaj in both Test and Standard group are observed, and efficacy on both groups were assessed, before and after the trial.

Statistical Analysis: Analysis of the data was done by using statistical methods. The data was calculated by using paired and non-paired "t" test.

Demographic observations: The results regarding the incidence of Ziabetus Shakri according to Age, Sex, family history and Mizaj in both Test and Control group are as follows:

Table 1: Effect on other clinical parameters in both groups

Other Parameters	Test group (n=30)						Control group(n=30)					
	Before		During		After		Before		During		After	
	P	A	P	A	P	A	P	A	P	A	P	A
Irritability	28	2	2	28	0	30	28	2	1	29	1	29
Weight loss	21	9	0	30	1	29	7	23	0	30	0	30
P. Neuropathy	16	14	3	27	1	29	11	19	2	28	2	28
Polyphagia	23	7	3	27	1	29	29	1	1	29	1	29
Delayed healing of wounds	0	30	0	30	0	30	0	30	0	30	0	30
Wasting of muscles	0	30	0	30	0	30	0	30	0	30	0	30
Paraesthesia	0	30	0	30	0	30	0	30	0	30	0	30
Vision Blindness	0	30	0	30	0	30	0	30	0	30	0	30
Nausea	12	18	0	30	0	30	18	12	9	21	7	23
Headache	19	11	2	28	0	30	28	2	2	28	3	27
Pruritus	7	23	0	30	0	30	1	29	0	30	0	30

P=Present; A=Absent

Table 2: Reduction in Blood Sugar Level (F) in Test and Control groups

Variable	Test Group (n=30)	Control Group (n=30)
BSF	131.66	131.66
SD	76	87

Table 3: Reduction in Blood Sugar Level (PP) in Test and Control drugs:

Variable		Test Group (n=30)	Control Group (n=30)
PPBS		193.6	181.3
SD		107	95

Table 4: Comparison of Reduction in HbA1c in Test and Control drugs

		Test Group		Control Group	
Sugar control	Hba1c levels	Before study	After study	Before study	After study
Excellent	< 6	5	30	5	29
Good	6.1 - 8	6	0	9	1
Action required	> 8	14	0	13	0

4. Discussion

The result and observations obtained from the study were depicted in tables and graphs in result part of the thesis. The detail discussion regarding the incidence of Ziabetus Shakri according to demography, efficacy and safety parameters are as follows [31-34].

Demographic observations: The results regarding the incidence of Ziabetus Shakri according to Age, Sex, family history and Mizaj in both Test and control group are as follows:

Distribution of the patient according to Age: According to Out of 60 selected patients of Ziabetus Shakri, the highest number of patients are 21 (35%) were from the age group 55-64 years and then19 patients (31.66%) patients were found in the age group of65-74 years, then 11 (18.33%) in age group 45-54years and the least 9 (15%) patients were in the age group of 35-44 yrs. This data is supported by the literature that Ziabetus Shakri is more common after the age of 40 years.

Distribution of the patient according to sex: Out of 60 patients there were 23 (38.33%) patients are male and 37 (61.66%) patient's female. Which reveals that the incidence of Ziabetus Shakri is more common in females than males.

Distribution of the patient according to Mizaj: The maximum patients recorded in present study were of Safrawi Mizaj which comprises 35 (58.33%) patients. Among the rest 18 (30%) were *Damwi Mizaj*, 7 (11.66%) were *Balghami* and 0 (0%) patients were *Saudawi*. According to classical Unani literature the mizaj of diabetic patients could be hot and dr. So these finding are conformity of the literature [11, 12, 25].

Distribution of the patient according to Family History: In this study family history of Diabetes was present in 34 (56.66%) patients, while the rest 26 (43.33%) patients were having absent family history. In this study, it is observed that the most patients come with family history of diabetes, which is supporting the literature [26, 27]

Assessment of Efficacy

Effect on polyuria in both groups: It is evident that before starting the treatment 30 patients were having polyuria in both groups (in test group: mild 11, moderate 12 and severe 7 patients; in control group: mild 2, moderate 9 and severe 19 patients). While During the study 18 patients in test group and 28 patients in control group were having polyuria. At the end of the study no any patients were having polyuria in test group but 10 patients in control group, who were having polyuria. There is statistically significant result is observed in both test and control group at the mid and end of the study. This shows that the test drug is as effective in polyuria as the control drug. But there was not statistically significant difference in between the test and control group, in the mid and end of the treatment. However, it is observed that the test

drug has a significant effect in polyuria. As per the line of treatment of Unani system of medicine (Ilaj-biz-zid), Shilajit is commonly used to reduce frequent urination occurring due to diabetes mellitus. It also prevents leakage of the sugar and albumin in the urine and effectively helps to treat mild to moderate type of glycosuria and proteinuria [12, 25, 35].

Effect on polydipsia in both groups: At the starting of the treatment 29 patients in test group and 30 patients in control group were having polydipsia. In the mid of the study 12 patients in test group and 16 patients in control group were having polydipsia and at the end of the study only 2 patients in test group and 9 patients in control group were having polydipsia. Statistically significant result is observed in both test and control group at the mid and end of the study. There is mild statistically significant difference observed in between test and control group at the mid and end of the study, that only 2 patients in test group and 9 patients were in control group were not improved. Shows that the test drug is more effective in polydipsia than the control drug. So the test drug has a valuable effect in polydipsia. This effect of test drug may be due to which may increase in the *Quwat-e-Masika* (retentive Faculty) of the kidneys and all organs, and indirectly it inhibits the thirst [17-22, 36, 37].

Effect on Nocturia in both groups: It is indicating that at the starting of the treatment 27 patients in test group and 30 patients in control group were having Nocturia. In the mid of the study 12 patients in test group and 12 patients in control group were having Nocturia and at the end of the study only 1 patient in test group and 3 patients in control group were having Nocturia. Statistically significant result is observed in both test and control group at the mid and end of the study. But there was not statistically significant difference in between the test and control group, in the mid and end of the treatment, that only 1 patient in test group and 3 patients in control group were not improved. The table 27 shows that the test drug is equally effective in polydipsia than the control drug. So the test drug has a valuable effect in Nocturia. This effect may be due to the glucose lowering effect of the test drug, that it contents all three are having quality of reducing blood sugar levels Hypoglycaemic. Moreover, Qabiz, Nutritive Tonic which may reduce polyuria and nocturia [17-22, 36, 37].

Effect on Tiredness in both groups: It is evident that before starting the treatment 30 patients in test group and control group were having tiredness. In the mid of the study 16 patients in test group and 13 patients in control group were having tiredness and at the end of the study only no any patients in test group and 4 patients in control group were having tiredness. There is statistically significant result is observed in both test and control group at the mid and end of the study, that only 1 patient in test group and 4 patients in control group were not improved. There is mild statistically significant difference in between test and control group at the mid and end of the study is observed that, the test drug has showed 30(100%) improvement in tiredness but 26(86.66%) patients in control group were improved. Tiredness is always associated with Ziabetus Shakri, therefore it can be declaring that the improvement in the tiredness in the diabetic patient is mainly due to the improvement in diabetic condition of the patient. Moreover, this effect of the test drug may be due to *Mufarreh* (cordial), *Qabiz*, Nutritive, Tonic characters of *Methi*, *Tabasheer* and *Salajeet*. The role of these pharmacological actions of the test drug in improving the tiredness cannot be denied [17-22, 36, 37].

Effect on Fatigue in both groups: It, is pointing out that before starting the treatment 30 patients in test group and control group were having Fatigue. In the mid of the study 10 patients in test group and 9 patients in control group were having Fatigue and at the end of the study only 1 patient in test group and 3 patients in control group were having Fatigue. There is statistically significant result is observed in both test and control group at the mid and end of the study, that only 1 patient in test group and 3 patients in control group were not improved. There is mild statistically significant difference in between test and control group, at the mid and end of the study is observed, that, the test drug has showed improvement in 29 (96.67%) patient, and the control drug showed 26 (90%) patients in control group were improved, in tiredness. This effect of the test drug may be due to its ingredients' Qualities. (*Mufarreh* (cordial), tonic (Muqawwi) activities of *tabasheer*, *Qabiz*, Nutritive, Tonic, characters of *Methi*. There is a very high anthocyanin content in *Jamun* fruits which attributes to its antioxidant and free radical scavenging activity. The role of these pharmacological actions of the test drug in improving the tiredness cannot be denied [17-22, 36, 37]

Effect on other parameters: It is observed from the table 30 that before starting the treatment 28 patients in each group and control group were having irritability, which disappeared after the study, may be due to overall improvement, feeling of wellbeing and anxiolytic property of shilajit, cordial, qualities of *tabasheer*. Similarly, before starting the treatment there were 21 in test group and 7patients in control group of weight loss, which improved significantly at the end of the study, this effect of the test drug may be due to *Qabiz*, Nutritive, Tonic property and characters of *Methi* and Tabasheer. In the study, 16 patients in test group and 11 patients in control group were having peripheral neuropathy at the beginning of the study, whereas at the end of the study only 1 patient in test group and 2 in control group had not showed improvement, while 29 in test group and 28 patients in control group showed improvement, which may be due to *Musakkin* (Sedative) property of tabasheer. 23 patients in test group and 29 patients in control group were having Polyphagia at the beginning of the study, whereas at the end of the study only 1 patient in test group and 1 in control group had not showed improvement, while 29 in test group and 29 patients in control group showed improvement may be due to tonic and nutritive properties of the contents of test drug. Before starting and till the end of the study, all patients in test and control group were not having complaints of Delayed healing of wounds, wasting of muscles, Paraesthesia and Vision Blindness. This finding may be due to selection of the patients in inclusion criteria only, the patients were having complication have not been selected for the study. 12 patients in test group and 18 patients in control group were having nausea at the beginning of the study, whereas at the end of the study no any patient in test group and 7 in control group had not showed improvement, while 30 in test group and 23 patients in control group showed improvement. Hence the study shows mild significance difference between test and control group. 19 patients in test group and 28 patients in control group were having headache at the beginning of the study, whereas at the end of the study no any patient in test group and 3 in control group had not showed improvement, while 30 in test group and 27 patients in control group showed improvement. Hence the study shows mild significance difference between test and control group. 7 patients in test group and 1 patient in control

group were having Pruritus at the beginning of the study, whereas at the end of the study all patients in test group and control group had showed improvement [17-22, 36, 37].

Comparison of Reduction in Blood Sugar (F) in Test and Control drugs

According to Table no.31 and chart no.13, Mean BSL (F) in first visit was 246mg/dl, in test group whereas in control it was 282mg/dl. The mean reduction in BSL (F) in between the study, in test group was 188 and 196 in control group. In the end of the study the mean reduction was 114 in test group, while 131 in control group. Mean reduction in BSL (F) in Control and Test drug is almost equal. The probability was P=0.9888. So the difference is not significant for mean reduction in BSL (F) between Control and Test drugs [17-22, 36-38].

Reduction in Blood Sugar Level (PP) in Test and Control drugs

According to Table no.32and chart no.14, Mean BSL (pp) in first visit was 363mg/dl in test group, whereas in control it was 366mg/dl. The mean reduction in BSL (pp), in between the study was, in test group 279 and 270 in control group. In the end of the study the mean reduction was 159 in test group while 184 in control group. Mean reduction in BSL (PP) in Control and Test drug is almost equal. The probability was 0.636. The difference is not significant for mean reduction in BSL (PP) between Control and Test drugs [17-22, 36-38].s

Hence, statistically significant result is observed in both test and control group for BSL (F) and BSL (PP) at the mid and end of the study. This effect of test drug is showing conformity, with the literature, in which *Maghz Khasta Jamun*, *Tabasheer*, *Salajit* and *Methi* individually, proved as Hypoglycaemic drugs [Methi (Hypoglycemic) Jamun, (Hypoglycaemic) by clinical and experimental studies [17-22, 36-38]

Comparison of Reduction in HbA1c levels in Test and Control drugs: Mean**Hba1c levels** at first visit was 7.3, in test group whereas in control it was 8.8. The mean reduction in BSL (F) in between the study, in test group was 188 and 196 in control group. In the end of the study the mean was 3.3 in test group, while4.4 in control group. Mean reduction in HbA1c in Control and Test drug is almost Excellent. The probability was P=0.03. So the difference is significant for mean reduction in HbA1c levels between Control and Test drugs [17-22, 36-38].

5. Conclusion

Ziabetus Shakri is a Stone age disease but still complete management, have not been evaluated for it, though Millions of currency used and thousands of researches are being done. The number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless vital preventive steps are taken. At this point in time throughout the world the human is turning again towards alternative system of medicine, particularly (WHO permitted) Unani System of Medicine, in search of answers to their sufferings. In this scenario Unani scholars must concentrate to perform in a way to search a complete treatment for this epidemic ailment. As evident from result and discussion there is statically significant result has been observed in both test and standard group and no statically significant difference is observed in between test and Standard group. Except urine sugar levels in which significant difference observed in between test and Standard group. The test drugs an Unani formulation is effective for the treatment of Ziabetus Shakri and it reduces HbA1c, blood sugar fasting and post prandial as approximately as equal to the standard drug Metformin. It also gives a valuable relief in clinical symptoms of Ziabetus Shakri like: Polyuria, Polydipsia, Nocturia, Tiredness, Fatigue, Irritability, Weight loss, Peripheral Neuropathy, Polyphagia, Delayed Healing of Wounds, Wasting of Muscles, Paraesthesia, Vision Blindness, Nausea, Headache, Pruritus (Uvulitis / Balanitis). It may also prevent diabetic nephropathy, neuropathy and other minor or major complications. Since the short duration and small sample size, the long term safety and efficacy of the Unani formulation used in this study can't be elaborated at the moment but for short term use, it was found safe and effective. Hence long term study (phase III and Phase IV clinical trials), will be required to explore the long term prospective of the test drug for its safety, toxicity and to make it a standard formulation for the management of type 2 Ziabetus Shakri.

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