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International Journal of Current Research
Vol. 9, Issue, 03, pp.48377-48381, March, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

THERAPEUTIC EVALUATION OF UNANI FORMULATION AS AN ADJUVANT IN THE TREATMENT OF ALBUMINARIA IN DIABETIC NEPHROPATHY

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ARTICLE INFO

Article History:
Received 29th December, 2016
Received in revised form
06th January, 2017
Accepted 18th February, 2017
Published online 31st March, 2017

Key words:
Microvascular,
Diarrhea Urinosa,
Albuminaria.

ABSTRACT

Diabetes mellitus is one of the most common non communicable diseases and remains today a worldwide and increasing health problem. A recent international study reported that nephropathy is the most common complication of diabetes mellitus accounting for 21.1% renal issues. Diabetic nephropathy is a long term chronic progressive microvascular complication of diabetes mellitus. It has been clinically defined by the presence of protein in urine more than or equals to 300 mg/ 24 hr in diabetic patients with the absence of other renal diseases. In classical unani literature, Buqrat (Hippocrates 460 BC) mentioned a disease with excessive urinary flow and wasting of body. Jalinoos (Galen 131-201 AD) defined diabetes as "Diarrhea Urinosa" (diarrhoea ofurine) and "dipsakos" (thirsty disease). He described it as a disease specific to kidneys because of weakness in their retentive ability. The present study entitled as "evaluation of efficacy of unani formulation as adjuvant in the treatment of diabetic nephropathy" has been carried out at Majeedia unani hospital Jamia Hamdard New Delhi from 2016-2017. A compound formulation mentioned in zakheera khawarrzam shahi containing Samaghe Arabi (acacia arabica), Gulnaar (punica granatum) Dam-al-akhwain pterocarpus marsupium), shibbe yamani (hydrated form of potassium aluminium sulphate), Badaam (prunus amygdalus) and gond kateera (sterculia urens) has been mentioned for the treatment of bole zulali in diabetes. The study reveals that the test drug has good response in treatment of albuminaria in diabetic nephropathy, as compared to control drug.

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Citation: Shah Alam, M. Akhtar Siddiqui, Dr. M. Maaz, Sunil Kohli and Mridu Dudeja, 2017. "Therapeutic evaluation of Unani formulation as an adjuvant in the treatment of Albuminaria in diabetic nephropathy", *International Journal of Current Research*, 9, (03), 48377-48381.

INTRODUCTION

Diabetes mellitus is one of the most common non communicable diseases and remains today a worldwide and increasing health problem. At least one in 10 deaths among adults between 35-64 years is attributed to diabetes. According to international diabetes federation report diabetes kills one person every second and kills about 3.2 million every year worldwide. With the global epidemic of diabetes, diabetic nephropathy has become an important clinical and public health challenge. A recent international study reported that nephropathy is the most common complication of diabetes mellitus accounting for 21.1% renal issues. Diabetic nephropathy is defined as diabetes with the presence of albuminuria, impaired glomerular filtration rate or both. Unnikrishnan RI and colleagues reported that the prevalence of diabetic nephropathy with microalbumianria was 26.99% among type 2 diabetic patients in urban citizens in India. Diabetic nephropathy is a long termchronic progressive microvascular complication of diabetes mellitus. It has been clinically defined by the presence of protein in urine more than or equals to 300 mg/ 24 hr in diabetic patients with the absence of other renal diseases. (IbneSina and Al Qanoon Fit Tib, 1st edition) Renal failure typically occurs after 20 years of diabetes. The patient must undergo either dialysis or kidney transplant. In classical unaniliterature, a medical condition producing excessive thirst, continuousurination and severe weight loss has interested medical authors for over 3000 years. Ebers Papyrus which was written around 1500 BC was first written reference to diabetes by ancient Egyptians physicians. Around 230 BC Apollonius of Memphis for the first time used the term diabetes which in Greek means to pass through (dia- through, bêtes- to go). He and his contemporaries considered diabetes as a disease of the kidneys and recommeneded among other treatments measures a such as blood letting and

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dehydration. The word Diabetes has been derived from Greek word "*Diabanmo*" which means "passing through" or "to run through" or Siphon" because of excessive urination. The disease is characterized by excessive thirst, excessive urination, presence of sugar inurine, increased appetite, gradual loss of bodyweight etc. *ArabAtibba* mentioned Diabetes with the name *Ziabetus,* as a disease of kidneys. They had described *Ziabetus* by some other terms like *Moattasha, Atsha, Intesae Anmas, Zalaqulkulliya, Dolab, Dawwarah, Barkar, Barkarya, Qarameese*etc. Buqrat (Hippocrates 460 BC) mentioned a disease with excessive urinaryflow and wasting of body. (IbneHubal B. KitabulMukhtarat Fil Tib, 2005) Jalinoos (Galen 131-201 AD) defineddiabetes as "Diarrhoea Urinosa" (diarrhoea ofurine) and "dipsakos" (thirsty disease). Hedescribed it as a disease specific to kidneys because of weakness in their retentive ability.

IbneSina (Ave Sina 980-1037 AD), whotermed the disease "aldulab" (water wheel) and "zalqulKulliya" (diarrhea of the kidneys) also described the complications as mental troubles, impotence, gangrene, and furunculosis. IbneSina was first who wrote differentiating feature of *Ziabetus* associated with emaciation form other causes of polyuria.

According to the presence or absence of sugar in the urine, *Ziabetus*is divided into two types:

1. *ZiabetusSada*: it is also called *Ziabetusghairshakari*. It is characterized by excessive thirst and excessive urination but there is no sugar in the urine.
2. *ZiabetusShakari*, it is characterized by excessive thirst and urination and presence of sugar in the urine. In this disease patient has excessive thirst and takes plenty of water and passes all the water he consumed without any metabolic change.

According to the *khiffat*and *shiddat* (intensity) of the sign and symptoms, it is also divided into two types:

1. ***ZiabetusHaar:*** Acute symptoms of the *Ziabetus* with abrupt onset occur like excessive thirst (polydipsia) and increase urination (polyuria) with other symptom and sign of *su-i-mizajhaar* like heat in flanks and dryness of the body, due to *su-i-mizajhaarsada* of kidneys.
2. ***ZiabetusBarid:*** In which the thirst and frequency of urine is comparatively less. In this disease *Mizaj*of kidneys disturbed so they absorb water from blood and send to the urinary bladder immediately due to weakness in *quwwatemasika* (retentive power). So kidneys attract the water from the circulation, liver, stomach and intestine because of which patient has the immoderate thirst (polydipsia).

Jalinoos described it as a disease specific to kidneys because of weakness in their retentive ability. He has expressed the thought that the weakness of quwwat-e-mughayyarah may be a causative factor of diabetes. He mentioned that, when hot temperament is associated with moisture, then absorption (into the kidneys) is less, urine is dark in colour and viscous and, if cold temperament is predominant along with dryness, then the power of absorption is very strong and this is the most lethal form of diabetes. ZakariyaRazi mentioned in Al-Hawi Fil- Tib states that this disease is basically caused due to abnormal hot temperament of the kidneys. This hot temperament affects the urinary bladder also. Due to the increased heat of the kidney, the kidneys absorb a lot of fluids from the gastro-intestinal tract. Due to weakness of quwwat-e-masika, the kidneys are not able to retain these fluids and other material they are immediately passed to the bladder, and excreted as such. The loss of fluids is again responsible for increasing the abnormal hot temperament. This gives rise to a vicious cycle of intake and excretion. The disease is, therefore, difficult to treat. According to IbneNafees in diabetes, quwwate- masika of the kidneys is weakened due to the abnormal hot temperament, therefore, they are unable to retain the fluids in the body. The quwwat-e-dafi'a is stimulated and expels the fluids immediately after intake. Thus, the cycle of absorption (into the kidneys) and excretion continues". On this basis, it has been named dulaab (water-wheel) and dawwarah (rotatory, revolving, whirling etc). Basic etiology of disease is considered to be seated in the kidneys and the liver. *Ziabetus* is caused by one of more of the following factors:

- *Sū mizājḥārrkulya* (Hot derangement in the temperament of kidneys),
- *Barūdat-i-kabidwakulya* (Cold Derangement in Temperament of Kidneys and liver),
- *Ḍu f al-Kulya* (Renal insufficiency),
- *Ittisā al-kulyawaMajrā-i-Bawl* (Dilatation of Kidneys and urinary tract).

A compound formulation mentioned in *zakheerakhawarrzamshahi* containing Samagh e Arabi (acacia arabica), Gulnaar (punicagranatum) Dam-al-akhwain (pterocarpus marsupium), shibbeyamani (hydrated form of potassium aluminiumsulphate), Badaam (prunusamygdalus) and gondkateera (sterculiaurens) has been mentioned for the treatment of bole zulali in diabetes. These drugs are havingqabiz, habis, muqawwigurda, mulattif, dafaebole shakridafae bole zulali therefore the present study has been envisaged to evaluate the efficacy of this formulation in albuminaria in diabetic nephropathy.

MATERIALS AND METHODS

The present study entitled as "evaluation of efficacy of unani formulation as adjuvant in the treatment of diabetic nephropathy" has been carried out at Majeedia unani hospital Jamia Hamdard NewDelhi from 2016-2017. It was an open label randomized standard controlled study. Patients were randomised on the basis of preassigned case numbers as per computer generated chart into test group and control group. Before starting study, the protocol was submitted for ethical clearance accordingly and Institutional Ethical Committee hadapproved the protocol. Subjects from OPD and IPD of Hospital, fulfilling the inclusion criteria were included in the study after clinical examination with detail history of the disease and necessary haematological, biochemical investigations. A total of 68 patients were enrolled in the study after screening for diabetic nephropathy. Out of them 30 patients completed the study which were allocated into 15 in test group and 15 in control group. Patients of either sex between the age group of 18-65 years have type 2 diabetes mellitus with microalbuminaria (30-300mg /g Creatinine), serum Creatinine not more than 2 mg/dl, blood sugar post prandial ranging between 250-300mg /dl were included. Female patients with the pregnancy and lactating mothers were excluded. Patients with type 1 diabetes mellitus, urinary tract infections haematuria, renalfailurecardiac failure and febvrile

illness were not included in the study. Preliminary investigations like CBC, LFT, KFT, Lipid Profile, Blood Sugar HbA1CUrinary Microalbuminaria, Urine Routine Examination, Urine Culture and Sensitivity X-Ray Chest, USG – KUB and ECG were done for the inclusion of the subjects in the study. Patient fulfilling the inclusion criteria were included in the study after taking their written consent. Test group was advised the formulation of Samagh e Arabi (acacia arabica), Gulnaar (punicagranatum) Dam-al-akhwainpterocarpus marsupium), shibbeyamani (hydrated form of potassium aluminiumsulphate), Badaam (prunusamygdalus) and gondkateera (sterculiaurens) is to be used in this study for the manangement of chronic renal failure. This was mentioned by eminent unani physician Ismail jurjani his book ZakhiraKhawarzamshahi. The composition of this formulation is as under : each compressed tablet weighing 500mg of above mentioned formulation contains:

- Samagh e Arabi (Acacia arabica) -62.50 mg
- Gulnaar (Punicagranatum) -62.50 mg
- Dam-al-akhwain (Pterocarpusmarsupium) 62.50 mg
- Shibbeyamani (hydrated form of potassium aluminiumsulphate) - 62.50 mg
- Badaam (Prunusamygdalus) - 62.50 mg
- Gond kateera (Sterculiaurens) - 62.50 mg
- Dosage: 2 tablets thrice daily with water for 3 months

Control group was given 5mg Ramipril daily. During the protocol therapy subjects were asked to adhere to the diet chart

Table 1. Demographic characteristics

S.No	Characteristics		Test group		Control group		Total	
			No	%	No	%	No	%
1	AGE	35-44	6	40	4	26.66	10	33.33
		45-54	3	20	6	40	9	30
		55-64	6	40	3	20	9	30
		65-74	0	0	1	6.66	1	3.33
		75-84	0	0	1	6.66	1	3.33
2	Gender	Male	11	73.33	6	40	17	56.66
		Female	4	26.66	9	60	13	43.33
3	SES	LIG	3	20	3	20	6	20
		MIG	7	46.66	9	60	16	53.33
		HIG	5	33.33	3	20	8	26.66
4	Chronicity	1-5	6	40	4	26.66	10	33.33
	Of DM	6-10	8	53.33	9	60	17	56.66
		11-15	1	6.66	2	13.33	3	10
5	BMI	<19	2	13.33	4	26.66	6	20
		19-24	5	33.33	4	26.66	9	30
		24-30	7	46.66	5	33.33	12	40
		>30	1	6.66	2	13.33	3	10

Table 2. Distribution of patients according to Mizaj (Temperament)

Mizaj	Test grouip		Control group		Total	
	No	%	No	%	No	%
Phlegmatic	1	6.66	3	20	4	13.33
Sanguineous	12	80	11	73.33	23	76.66
Bilious	1	6.66	1	6.66	2	6.66
Melancholic	1	6.66	0	0	1	3.33

Table 3. Assessment of efficacy

		Test group		Control group	
Parameters	Follow up	Mean $_{+- SEM}$	percentage change	Mean +/_ SEM	percentage change
Systolic blood pressure	Baseline	155.73 ± 4.41		161.06±5.91	
	4 weeks	153.20±3.98	1.82	158.93±4.39	1.32
	8 weeks	147.73±3.36	5.76	156.66±4.63	2.72
	12 weeks	143.47±3.10	8.84	154.8±4.19	3.88
Diastolic blood pressure	Baseline	75.60±1.34		76.66±1.34	
	4 weeks	72.66±1.88	2.49	73.86±1.02	2.57
	8 weeks	69.60±1.48	5.10	78.80±1.02	1.96
	12 weeks	66.93±1.52	7.37	71.86±0.86	4.41
Fasting blood sugar	Baseline	180.13±10.26		163.80±15.60	
	4 weeks	140.53±6.02	7.23	146.07±8.47	2.28
	8 weeks	124.93±2.58	10.07	127.73±5.28	4.65
	12 weeks	116.07±4.63	11.69	126.07±4.29	4.86
Post prandial blood sugar	Baseline	265.07±16.06		197.00±6.88	
	4 weeks	187.60±9.30	8.37	185.33±6.15	3.74
	8 weeks	162.53±5.23	11.08	183.47±6.07	4.34
	12 weeks	150.07±3.88	12.42	180.20±5.47	5.39
Glycosylated haemoglobin	BT	8.34±0.23		8.9±0.26	
	AT	7.00±0.12	16.06	8±0.23	10.11
Urinary microalbumin	BT	90.00±13.01		106.20±13.38	
	AT	52.70±8.47	41.44	95.40±13.33	10.16
Urinary microalbumin to Creatinine ration	BT	95.91±21.96		115.27±17.90	
	AT	51.35±12.85	46.46	104.38±18.04	9.44
Serum Creatinine	BT	0.94±0.079		0.90±0.073	
	AT	0.84±0.076	10.63	0.83±0.067	8.43

provided by the dietician according to their daily needs of calories in order to achieve glycaemic control \in addition to the diet 45 min of briskwalking was advised daily. Safety assessment was done by laboratory parameters. Efficacy of unani formulation was done using both clinical parameters and laboratory parameters. Clinical parameters include blood pressure and improvement in the sign and symptoms. Laboratoryparameters include Blood sugar fasting and post prandial were estimated at 0, 4 , 8 and 12 weeks of treatment. Glycosylated haemoglobin, serumC reatinine, urinary microalbumin, urine albumin to Creatinine ratio were done before and after treatment.

DISCUSSION

All demographic parameters have been illustrated in the table no 1.93 of the total patients in test as well as control group were nonvegetarian.53.33% belonged to middle income group+out of the total study population, 70% of the patients were the smokers. Most of the patients ie 76.66% had sanguneous temperament which is in accordance with the unani concept of ziabeteshaaroccurs due to sue mizajhaargurda i.e. hot derangement in the temperament of the kidney leading to diabetes mellitus (majoosi 1889, samarqandi) (khan 2006) (Qarshi, 2011) All ingredients of this test drug were having cold and dry temperament except prunusamygdalus which is considered as hot and moist. It is in accordance with the anatagonistic treatment principle of unani medicine. Only 10% patients had BMI >30.Out of the total only 16.66% patients had significant past history such as HTN, CAD, PVD, neuropathy. Family history of DM and HTN was significant in 50% of the patients. There was a significant reduction in test group as well as control group in blood pressure. But the percentage change in test group was three times more in test group as compared to control group. It is attributed to the constituents of the test group having antihypertensive activity

In test group there was a significant reduction in blood sugar fasting with mean values from 180.13± 10.26 to 116.07 ± 4.63 after 12 weeks of treatment ($p<0.001$). The percentage change was 7.23%, 10.07% and 11.69% respectively at 4, 8, 12 weeks of treatment. Similarly there was a significant reduction in post prandial blood sugar with mean values 187.60±9.30 before treatment to 150.07±3.88 ($p<0.001$) after 12 weeks of treatment. The percentage change was 8.37, 11.08, 12.42% respectively.HbA1c was significantly reduced from mean values 8.34±0.23 before treatment to 7.00±0.12 after treatment. ($p<0.001$).This can be attributed to antihyperglycaemic properties of the drugs included in the composition. In test group before treatment had a mean microalbumin level of 90.0±13.01 which was significantly reduced to 52.70±8.47 ($p<0.001$) after treatment with a percentage change of 41.44% whereas in control group which had a mean microalbumin level of 106.20 ±13.38and was significantly reduced to 95.40±13.33 ($p<0.05$) after treatment with a percentage change of 10.16%. Urinary microalbumin Creatinine ratio (UMCR) was significantly reduced to 51.35±12.85 post treatment with a percentage change of 46.46% in test group as compared to control group where percentage change was 9.445 only. Nasir et al in 2012 has explained the effect of Acacia arabica on microalbumin in their study and concluded that GA treatment decreases blood pressure and proteinuria in diabetic mice and may thus prove beneficial in diabetic nephropathy. Serum Creatinine values had also undergone significant change which is attributed to the muqawwigurda property of the constituents of the test drug. All safety parameters do not depicted any abnormal change and had no bearing with patient's health, therefore it can be used as an safe medicine. The effect observed in the present study is well in accordance with the properties described classicalunani literature as having qabiz, habis, muqawwigurda, mulattif, dafaebol e shakriand dafae bole zulali. Modern studies on these individual drugs are also reported to having anti hyperglycaemic, antialbuminaric, antioxidant and anti-inflammatory properties.

Conclusion

The study reveals that the test drug has good response in treatment of albuminaria in diabetic nephropathy, as compared to control drug. No side effects or toxicity was seen during and after trial. Hence, it can be concluded that the test drug is effective and safe in the treatment of albuminaria in diabetic nephropathy. Further studies to get much more data to establish the facts with more statistical and scientific strength are needed.

Acknowledgement

I deeply acknowledge my sincere thanks to Department of Moalajat and Majeedia Unani hospital, Jamia Hamdard New Delhi for providing financial support. I am highly thankful to patients who have been included in this study and completed it.

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