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CLINICAL EVALUATION OF SYNERGISTIC EFFECT OF *AYASKRITI* AND ORAL HYPOGLCEMIC AGENT IN THE MANAGEMENT OF *PRAMEHA* VIS-A-VIS TYPE-2 DIABETES MELLITUS

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ABSTRACT

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the aetiology of the DM factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. DM-2 is a heterogenous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion, and increased glucose production. The *Ayurvedic* texts reflect two major categories of *Prameha* 1. *Sahaja Prameha* 2. *Apathyanimittaja Prameha,* out of these two, *Apathya nimittaja Prameha* is closely resemblance with the contemporary concepts of Type-2 Diabetes mellitus. In modern medicine many oral hypoglycemic agents (OHA) has been used to control blood sugar level. In spite of meticulous use of OHA, in many cases complications develop and there is no satisfactory control over blood sugar. In *Ayurveda, Ayaskriti* has been said for the treatment of *Prameha* by *Astang Hridya*. Thus in this study, *Ayaskriti* has been given with OHA to control hyperglycemic state and its complications.

KEYWORDS: *Prameha*, Type 2 Diabetes Mellitus, *Ayaskriti*, OHA.

INTRODUCTION

Diabetes is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications like retinopathy, neuropathy, nephropathy etc

and increased risk of macrovascular complications i.e ischemic heart disease, stroke and peripheral vascular disease and diminished quality of life. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health economy of our country.

Type 2 DM is characterized by three pathophysiologic abnormalities: *impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production.* Obesity, particularly visceral or central, is very common in type 2 DM. Insulin resistance associated with obesity augments the genetically determined insulin resistance of type 2 DM. Adipocytes secrete a number of biologic products (leptin, tumor necrosis factor, free fatty acids) that modulate processes such as insulin secretion, insulin action, and body weight and may contribute to the insulin resistance. In the early stages of the disorder, glucose tolerance remains normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets become unable to sustain the hyperinsulinemic state. Impaired glucose tolerance, marked by elevations in postprandial glucose, and then DM develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue.

Caraka has given exhaustive description of the disease *Prameha* which ultimately progresses towards *Madhumeha* or the sweetness of urine in addition to Polyurea.

It is worth mentioning that *Ayaskriti*, unlike the modern drugs, is not merely an act to beta cells of pancreas, but is a complete therapeutic remedy which has systemic effects, is considered the treatment for morbid and increased *dosas* of *prameha*. Out of these, *Vata & kapha* has major role in the develpoement of Diabetes. As *Ayaskriti* contains *vatsakadi gana* which has *vata kapha samak* properties, has been selected for DM. Nowadays, Diabetes Mellitus is becoming a great problem for society causing impediment in normal life. In present research work, an attempt is made to adjuvant effect of OHA by planning *Ayaskriti* with it.

Aims and Objectives

1. To reflect an over view on the concept of DM-2 vis-a-vis *Prameha*.

2. To evaluate the synergistic effect of *Ayaskriti* with *OHA* on subjective and objectives parameters.

3 To evaluate the *Ayaskriti* own effect on DM-2.

MATERIAL AND METHOD

Selection of cases

Cases of DM-2 were selected randomly from OPD and IPD of kayachikitsa *(Panchkarma)*, S. S. Hospital, IMS, B.H.U., Varanasi from august 2013 to September 2014 after thorough history taking, clinical and laboratory examination.

Diagnostic Criteria

Patients of different age group, sex and socio-economic status were selected from the kayachikitsa *(Panchkarma)* OPD & IPD, S.S. Hospital, IMS, BHU, on the basis of following criteria.

Inclusion criteria

• Age 30-60 yrs.

• Family History of Diabetes, HTN, Dyslipidemia

• Plasma glucose level:

Fasting: ≥ 126 mg/dl

Postprandial: ≥ 200 mg/dl

HbA1c: ≥ 6.5%

BMI: 18.5 – 29.9

• Patients having classical symptom of diseases without marked weight loss.

Exclusion criteria

• Age <30yrs. and >60yrs.

• Type 2 Diabetes Mellitus with complications.

• Type 1 Diabetes Mellitus associated with and without complications.

• Diabetes due to endocrinopathies e.g. Phaeochromocytoma, Acromegaly, Cushing's syndrome, hyperthyroidism etc.

• Drug or chemical induced diabetes mellitus e.g. Glucocorticoids, Thyroid hormone, Thiazides, Phenytoin etc.

• Certain genetic syndromes sometimes associated with diabetes mellitus e.g. Down's syndrome, Klinefelter's syndrome, Turner's syndrome etc.

• Patients suffering from any severe systemic disease.

• Patient having fasting blood glucose level ≥ 250mg/dl and pp blood sugar ≥350.

INVESTIGATION

1. Blood Examination

- Routine blood was examined for total leukocyte count, differential leucocytes count, hemoglobin percentage and erythrocyte sedimentation rate to exclude any infection.
- Blood urea and serum creatinine were done to assess the renal status.
- Liver function test.

2. Urine Examination

Urine for each case was examined for specific gravity, reaction, sugar, albumin and acetone routinely and microscopic examination for crystals, casts and cells.

Study design and treatment schedule

A total 20 patients with evidence of DM-2 and fulfilling the proposed criteria of selection were enrolled for clinical trial of Ayaskriti (dose 20ml bd after meal) & OHA.

Assessment criteria

The assessment of the treatment was based on both subjective and objective parameters.

i. Subjective Assessment

This completely depends upon the symptomatology and its grades. Improvement in symptoms is directly proportional to the improvement in the patient's condition and his metabolic state. To assess the subjective features of DM-2, the clinical symptomatology was graded into four grades (0-3) scale on the basis of severity and duration. The changes in the gradations of each symptom were noted on a prepared protocol to assess the therapeutic response of trial treatment.

The clinical gradations of symptoms were as follows.

0 : No symptom present.

1 : Mild symptoms present.

2 : Moderate symptoms present

3 : Severe symptoms present.

ii. Objective Assessment

Objective assessment was done on the following basis

- Weight
- BMI (body mass index)
- Fasting blood Glucose
- Postprandial blood Glucose
- Serum Cholesterol
- Serum Triglyceride
- Serum LDL
- HbA1c

Follow up Studies

After the initial registration and basal study, all the patients were recruited randomly in respective trial groups and given the treatment regularly as per schedule. They were advised to come after 1 month interval for the assessment of therapeutic response. Total duration of study was 90 days. For each follow up of 30 days, the patients were assessed for clinical symptoms, including physical examination; Estimation of blood sugar (Fasting and Postprandial) and status of *HbA1c*, BMI, Sr. Cholesterol, Sr. Triglyceride & Sr. LDL were assessed before and after the treatment.

I. Therapeutic Studies and Clinical Trial

Table 1: Polydipsia

Group	No. of Cases (%age)					Within the group comparison (Friedman Chi-square)
	Grade	BT	F1	F2	F3	
Group (n=20)	0	1	4	7	16	χ^2 =35.47 P<0.001 HS
	1	10	8	10	4	
	2	7	8	3	0	
	3	2	0	0	0	

Table 2: Burning sensation

Group	No. of Cases (%age)					Within the group comparison (Friedman Chi-square)
	Grade	BT	F1	F2	F3	
Group (n=20)	0	2	3	5	12	χ^2=26.55 P<0.001 HS
	1	6	8	13	6	
	2	8	8	2	2	
	3	4	1	0	0	

Table 3: Weakness

Group	No. of Cases (%age)					Within the group comparison (Friedman Chi-square)
	Grade	BT	F1	F2	F3	
Group (n=20)	0	1	2	4	11	χ^2=34.63 P<0.001 HS
	1	7	7	14	7	
	2	9	9	2	2	
	3	3	2	0	0	

Table 4: Polyurea

Group	No. of Cases (%age)					Within the group comparison (Friedman Chi-square)
	Grade	BT	F1	F2	F3	
Group (n=20)	0	2	4	10	15	χ^2=30.80 P<0.001 HS
	1	6	11	8	5	
	2	7	5	2	0	
	3	5	0	0	0	

Table 5: Polyphagia

Group	No. of Cases (%age)					Within the group comparison (Friedman Chi-square)
	Grade	BT	F1	F2	F3	
Group (n=20)	0	0	2	6	14	χ^2=36.42 P<0.001 HS
	1	7	8	11	5	
	2	10	9	3	1	
	3	3	1	0	0	

Table 6: Effect of treatment on FBS (n=60)

Group	FBS Mean ±SD				Within the group comparison, Paired 't' test, (BT - FU3)
	BT	FU1	FU2	FU3	
Group (n=20)	196.90±41.66	116.05± 29.96	100.10±13.43	95.50± 9.66	101.40± 37.94 t = 11.94 p < 0.001 HS

Table 7: Effect of treatment on PPBS (n=60)

Group	PPBS Mean ±SD				Within the group comparison, Paired 't' test, (BT - FU3)
	BT	FU1	FU2	FU3	
Group (n=20)	280.90± 47.18	166.50± 38.54	141.05± 25.13	132.55± 19.77	148.35 ± 42.29 t = 15.68 p < 0.001 HS

Table 8: Effect of treatment on Sr. Cholesterol

Group	Sr. Cholesterol Mean ±SD		Within the group comparison, Paired 't' test, (BT - AT)
	BT	AT	
Group (n=20)	268.40 ± 44.81	173.7 ± 14.92	94.6 ± 39.22 t = 10.79 p < 0.001 HS

Table 9: Effect of treatment on Sr. Triglyceride

Group	Sr. Triglyceride Mean ±SD		Within the group comparison, Paired 't' test, (BT - AT)
	BT	AT	
Group (n=20)	217.25 ± 33.14	145.4 ± 11.28	71.8 ± 30.85 t=10.41 p < 0.001 HS

Table 10: Effect of Trial Treatment on Sr. LDL

Group	Sr. LDL		Within the group comparison, Paired 't' test, (BT - AT)
	BT	AT	
Group (n=20)	186.30 ± 31.63	115.90 ± 9.82	70.4 ± 28.77 t = 10.94 p < 0.001 HS

Table 11: Effect of Trial Treatment on HbA1c

Group	HbA1c		Within the group comparison, Paired 't' test, (BT - AT)
	BT	AT	
Group (n=20)	8.40 ± 1.66	7.33 ± 1.09	1.06 ± .854 t = 5.57 p < 0.001 HS

Table 12: Effect of treatment on BMI

Group	BMI Mean ±SD		Within the group comparison, Paired 't' test, (BT - AT)
	BT	AT	
Group (n=20)	26.51 ± 1.84	25.28 ± 1.56	1.23 ± 1.28 t = 4.29 p < 0.001 HS

Observation and discussion

The majority of the patients were registered with negative family history (68.33%). 31.67% of total cases had the positive family history of diabetes in their first degree relatives (Bijadosaja). Besides, it was also observed that maximum no. of DM-2 fall in *Rasa* dominant Dusya (58.33%) followed by *Meda* (41.67%).

This indicates that not only familial impact but other factors also kept in mind at the time of describing etiopathogenesis of diabetes. This view is very relevant to concepts of *Prameha* / *Madhumeha* of *Ayurveda*.

The present study shows that the duration of illness in patients of DM-2, 41.67% were newly diagnosed, 31.67% had duration of illness > 3 years, 26.67% patients had duration of illness <3 years. In this, Incidence of clinical symptomatology in patients of DM-2 revealed that the maximum number of patients (93.33%) had Polydipsia followed by Polyurea, Burning

sensation, Weakness (95.0%) and Polyphagia (96.67%). This refuse that the clinical features of DM-2 described in *Ayurveda* are very scientific & comparable to the latest knowledge in this field.

The changes of BMI were statistically highly significant (P<0.001). *Ayaskriti & OHA* had showed a good degree of difference in BMI level (1.23 ± 1.28), this indicates that not only familial impact but other factors also kept in mind at the time of describing etiopathogenesis of diabetes. This view is very relevant to concepts of *Prameha* / *Madhumeha* of *Ayurveda*.

While studying body weight of the patients it was found that most of them were having weight 71-80 kg (35%) followed by 61-70 kg (31.67%).This is the strong evidence for the obesity as a factor for DM-2. Body mass index was also calculated to identify the exact level of obesity and it was found that maximum patients (44%) were registered as normal (18.5-24.9 kg/m^2) followed by 37.33% in over weight category (25.0-29.9 kg/$m^{2)}$ and 18.67% patient were registered under obese category (30.0 – 39.9 kg/m^2).

Fasting Blood Sugar

In this series the mean reduction in fasting blood sugar was found to be statistically significant. The absolute changes in fasting blood sugar was (101.40± 37.94) (p<0.001).

Postprandial Blood Sugar

The mean reduction in PP blood sugar was found statistically highly significant. The absolute fall in PP blood sugar was 148.35 ± 42.29(P < 0.001).

This indicates that *Ayaskriti* along with OHA measures we can well control blood sugar level and improves the clinical symptoms along with weight loss.

Besides this, most probably *Ayaskriti* cleans the body channel and enhances mobilization of blood sugar from central to peripheral compartment either by decreasing insulin resistance or by increasing insulin secretion, due to which there is better control of blood sugar with least side effect and complication at same dose of OHA alone in patients who were known diabetics.

Lipid Profile

In the present study the serum cholesterol, serum triglyceride & serum LDL level of patients showed highly significant changes (P < 0.001) due to *Ayaskriti* & OHA. This study reveals

that the trial treatment have tendency to reduce Serum Cholesterol & Serum TG level in patients Type-2 DM, which is not possible only with the help of OHA only.

HbA1c

In the present study, HbA1c shows difference of (1.06 ± .854) BT to AT. So it shows that *Ayaskriti* with OHA measure can maintain blood sugar level for long term.

Safety Profile

For the safety profile of the patients, we have done Serum Creatinine & Blood Urea, LFT, CBC, ECG and CXR before & after treatment & we did not get any unwanted effect on the major metabolic organs of the body. Therefore this is suggesting that selected *Ayaskriti* were safe in regards to renal function, liver function & cardiac function.

Probable mode of action of Ayaskriti

Special Method of Preparation -Decoction of Asanadi gana (drugs 1 to 23) is first prepared. Jaggery and honey (drugs 25 and 26) are added to the decoction. *Kalka* of Vatsakadi gana *Drayas* (drugs 27 to 49) is made separately and added to the decoction. After making iron sheet red hot, it has been dipped into this decoction repeatedly upto the dissolution of iron sheet into the decoction, then decoction is used in dose of 20 ml bd after meal.

Asanadi gana, is group of 23 drugs which are well described in ancient *Àyurvedic* classics. The ingredients of the Asanadi gana are Tinisa,, *TiniÐa*, *Bhojapatra*, Swetawaha Prakirya, *Khadira* etc .Many of these drugs like Pterocarpus marsupium, Ougeinia Oojeinensis, Holoptelea integrifolia, G. sylvestre, Berberis aristata have anti diabetic, hypolipidemic property.

CONCLUSION

With the help of *Ayaskriti* & OHA not only blood sugar level decrease in Type-2 DM but lipid profile, BMI & clinical symptoms also improved which is not possible only with OHA alone. This suggested the selected *Ayaskriti* either improves the mode of action of OHA or cleans the body channels and potentiate the peripheral utilization of glucose and due to peripheral utilization of glucose, lipid profile automatically improved. The patients who were taking OHA initially in higher dose after adding *Ayaskriti* there is gradual decrease in dose of OHA upto certain limit, to achieve desirable blood glucose level in both fasting and post prandial states along with good control on dyslipdemia.

The Present study reveals that *Type-2 DM* was well conceived in *Ayurvedic* lexicons in the context of *Prameha*. In *Ayurveda*, Vyadhi kriyakala described by Sushruta gives an idea about the consecutive stages of the disease and accordingly management measures can be contemplated to control DM-2 & also to overcome complications. Early diagnosis of disease helps to cure the disease successfully without its progression. *Vyaktavastha* stage of Kriyakala represents *symptomatic stage* which indicates the presence of disease. So prescription of medication in the form of *Ayaskriti* and *OHA* is more important for controlling the disease process and stop its progress further to complication stages.

In this study, the selected *Ayaskriti* and *OHA* not only have encouraging results in terms of well control blood sugar level along with weight loss but also seems to be helpful to check the complications in Type-2 DM by controlling dyslipidemia. Besides, this studies also overview that if *Ayaskriti* and *OHA* applying in DM-2, it normalise the blood sugar and also cut off its progression to insulin dependence. Thus, this approach of *Ayurvedic* classics have significant preventive & curative role in DM-2. The leads available from this work open new *Ayurveda*-inspired holistic approach to the management of Type 2 Diabetes Mellitus.

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