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A CLINICAL STUDY ON MANAGEMENT OF STRESS IN TYPE-2 DIABETES MELLITUS (*MADHUMEHA*) WITH *ASHWAGANDHA (WITHANIA SOMNIFERA)*

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KEYWORDS: Stress, effect, Type – 2 DM, management, *Madhumeha*, *Ashwagandha*, *withania somnifera.*

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ABSTRACT

Extensive worldwide research on diabetes has established the complexities of the relationship between stress and diabetes. Evidence suggests that stress can affect diabetes, in terms of both its onset and exacerbation. Stress can have a deleterious effect on glycaemic control and can affect quality of life in diabetics. On the other hand emerging evidence strongly suggests that interventions that help individuals prevent or cope with stress can have an important positive effect on quality of life and glycaemic control.

In this clinical study we have approached to assess the different stresses like Emotional burden, Physician related distress, Regimen related distress & Interpersonal distress in Type – 2 diabetic populations with Diabetes Distress Scale (DDS). Those diabetics having a considerable stress level (DDS Score > 3) were given treatment with *Ashwagandha (Withania somnifera)* capsules for six weeks and once again their stress level was reassessed.

Ashwagandha significantly reduced the stress level and other stress related complains along with a better glycemic control as compared to placebo without any adverse effect. The positive effect of the drug also continued for another six weeks even after withdrawing the medication.

Therefore *Ashwagandha* can offer comprehensive benefits as an adjuvant in Type – 2 diabetics suffering from stress.

INTRODUCTION

The word “stress” is defined by the Oxford Dictionary as "a state of affair involving demand on physical or mental energy". In other words it is a state of mental or emotional strain or tension resulting from adverse or demanding circumstances. It is a condition or circumstance which can disturb the normal physiological and psychological functioning of an individual. In medical parlance “stress” is defined as a perturbation of the body’s homeostasis. This demand on mind & body occurs when it tries to cope with incessant changes in life. A “stress” condition seems “relative” in nature. Extreme stress conditions, psychologists say, are detrimental to human health but in moderation stress is normal and, in many cases, proves useful. [1]

Stress is basic elements of various human diseases and mental illness. Stress is a term that refers to the sum of the physical, mental, and emotional strains or tensions on a person. Stress is the "wear and tear" our mind and body experiences as we attempt to cope with our continually changing environment. Stress is also called as anxiety, tension etc. [2]

A stressor is defined as a stimulus or event that provokes a stress response in an organism. Stressors can be categorized as acute or chronic, and as external or internal to the organism.[3]

When stress occurs, the body prepares itself to take action. This preparation is called the fight-or-flight response. In the fight-or-flight response, levels of many hormones go higher than their normal concentration in the body. Their net effect is to make a lot of stored energy i.e. glucose and fat available to cells. These cells are then primed to help the body get away from danger. The initial stage of arousal remains the same whether we are faced with a major or minor stressor. But under extreme, prolonged, or persistent pressure the body continues to manufacture extra quantities of stress chemicals, triggering further processes to maintain energy. If arousal continues, the adrenal glands manufacture anti-inflammatory chemicals that simultaneously speed tissue repair while depressing the body’s immune defence system. If all these changes continue, the body goes on trying to adapt under increasing strain and pressure.[4] Eventually it breaks down. Exhaustion, variety of illnesses and even death may be the outcome of uninterrupted, excessive stress. [5]

Ayurveda also emphasizes the psychosomatic basis of every disease condition which literally means any

problem of the body will cause a mental problem and vice versa. Similarly most of the diseases have their roots linked to both mind (Psyche - *Mana*) & body (Soma-*Deha*).

More recently, numerous studies have been performed, elucidating the role of emotional stress as a risk factor for the development of type - 2 diabetes. The majority of these studies focus on depression. However, there is growing evidence that other forms of emotional stress can contribute to the development of type- 2 diabetes as well [6]. More over patient of diabetes may face stress at a single or multiple levels like physician related stress, regimen related stress, emotional stress, interpersonal stress etc. Not only the development or onset of Type - 2 DM but also stress affects diabetes control and care in many ways. Increased blood sugar level, increased insulin resistance, weight gain, compromised self care etc are but a few ways of intervention of stress to set up or complicate Type - 2 DM.

Hence comprehensive diabetes care should also include stress management as a part of the program. Effective stress management will result in many positive outcomes in a patient of Type - 2 DM. It will not only keep the blood sugar and glycated haemoglobin (HbA1C) in the optimum level but also improve the quality of life in diabetics.

Stress management is one of the important therapeutic areas where *Ayurveda* has really gained ground. *Ayurvedic* way of stress management includes purificatory *Panchakarma* therapies, use of *Rasayana ousadhis* in the form of anti stress herbs, polyherbal & herbomineral compounds, adherence to right sociopersonal & behavioural conduct (*Achara rasayana*), practice of *yoga* and beneficial diets (*Pathyahara*). Many herbs possess proven antistress & adaptogenic properties.

Ashwagandha (*Withania somnifera*) is widely used as a *Rasayana* drug by *Ayurvedic* physicians for stress management. Many experimental & clinical trials have proved its antistress[7], adaptogenic[8], immuno-modulatory[9], neurotrophic[10], anti-inflammatory[11] and antioxidant[12] properties of *Ashwagandha*. Its effectiveness and safety in different long term therapeutic use is beyond doubt.

In this study we have chosen *Ashwagandha* as the trial drug in the management of stress in type – 2 diabetes patients as such type of specific studies are need of the hour. The results of the study are encouraging and it has added one more chapter to the therapeutic success of *Ashwagandha*.

MATERIALS & METHODS

60 ambulatory patients were selected from the OPD of Gopabandhu Ayurveda Mahavidyalaya, Puri, Odisha during the period June 2012 to June 2013 after screening many Type-2 DM patients for their stress levels. Only patients with a considerable stress level (DDS17 Score ≥ 3 were registered. They were randomly allocated to the Trial Group (TG) & Control Group (CG). But during the study 2 patients from TG and 3 patients from CG dropped out from the study before completion due to some reason or the other. So the study was completed having 28 subjects in TG and 27 subjects in CG. This clinical study was conducted as per the Good Clinical Practice (GCP) guidelines and regulatory norms of India. The approval of the Institutional Ethical Committee (IEC) was obtained before starting the trial. Written informed consent was obtained from every patient as a prerequisite to be included in the trial. After registration, a primary screening and systemic examination was conducted for every patient and Laboratory investigations were done as per the protocol of the study. All these information were recorded in a well designed research case sheet. The patients were explained about the follow up schedule.

Criteria for Inclusion

- Already Diagnosed Type II Diabetics who are being treated with fixed Oral Hypoglycaemic allopathic drugs (Metformin 500 mg + Glimepride 1 mg) within the age group of 21 – 70 years
- FBS ≥ 126 & ≤ 180 mg/dl and PPBS ≤ 240 mg/dl
- HbA1C ≥ 7%
- Mean Total DDS scoring ≥ 3

Criteria for Exclusion

- Diabetics on Insulin
- Presence of major diabetic complications like nephropathy, retinopathy, neuropathy, ulcers
- Gestational DM
- Women planning pregnancy in next six months

DDS17 Scoring

Diabetes Distress Scale (DDS) is a published & internationally accepted scale to measure different diabetes related psychosocial stress levels having seventeen questionnaires to be self answered by the patient.[13]

Drug, Dosage & Duration

The patients of the trial group were given soft gelatine *Ashwagandha* (*Withania somnifera*) capsules containing 300 mg of root extract in ground nut oil base manufactured by Dabur India Limited as the trial drug in a dose of 1 cap b.i.d with a cup of Luke warm milk for a period of 6 weeks.

Placebo soft gelatine capsules containing only ground nut oil were given to the patients of control group in a dose of 1 cap b.i.d with a cup of Luke warm milk for six weeks.

The anti diabetic regimen for all the patients was kept fixed during the study period i.e. Metformin 500 mg + Glimepride 1 mg, 1 tab bid.

Duration of the Study and Follow up Schedule

Duration of the Study was 12 weeks. It included two phases. First six weeks were active treatment phase and the next six weeks were follow up phase after completion of active treatment. The follow up schedule was at the end of every 2 weeks i.e. end of 2nd, 4th, 6th, 8th, 10th & 12th weeks.

Dietary & Exercise Regimen

Patients were advised to restrict their dietary schedule as per given instruction and do light exercise like brisk walking for 2 k.m. per day or swimming or jogging for half an hour per day etc. during treatment. All patients were advised to stop smoking, alcohol abuse or any other addiction completely. This information was provided to the patient in the form of an information booklet in regional language.

Assessment Criteria

Clinical Parameters

In clinical assessment DDS17 score was considered for measuring improvement in different psychosocial stress levels. Therefore DDS17 score was calculated at beginning and end of the study with the help of seventeen questionnaires to be self answered by the patient.

Laboratory Investigations

FBS, PPBS, Lipid Profile, Urine – RE & ME, HbA1C tests were done at the beginning and end of the study in order to assess the blood sugar control and alteration in Lipid profile as both the trial drug and placebo contained ground nut oil.

Reporting of Adverse Events

Adverse events if any with any of the patients either in trial or control group were recorded in every visit and they were compared with their baseline symptoms. Any reported adverse event was recorded carefully in the research case sheet.

Statistical Analysis

The mean ± Standard Deviation (SD) was calculated for each subjective & objective parameter before and after treatment. The same was also calculated after the end of the follow up. Then Paired t-test was applied to test the significance of the outcomes. Finally the effectiveness of trial drug and control drug was accessed by calculating the p – value. All the statistical calculations were done using Graph Pad software. Data was presented in both tabular & graphical form under the guidance of a qualified statistician.

OBSERVATION & RESULTS

It was observed that the sample size was dominated by males, patients within the age group of 41 – 50 years, mixed non-vegetarians and tobacco users. It was also observed that there is a positive co-relation between obesity and diabetics under stress.

Table1: Effectiveness of Trial & Control Drug on DDS Score

Parameter	Group	n	Before Treatment Mean ± SD	After Treatment Mean ± SD	↑ ↓	SED	D.F	t Value	p Value	Inference
Emotional Burden	T	28	4.12 ± 0.54	2.82 ± 0.61	↓	0.15	27	8.3	< 0.0001	ES
	C	27	4.23 ± 0.57	4.13 ± 0.55	↓	0.05	26	1.95	0.0617	NS
Physician Related Distress	T	28	4.16 ± 0.72	2.92 ± 0.96	↓	0.17	27	7.17	< 0.0001	ES
	C	27	4.28 ± 0.65	4.02 ± 0.71	↓	0.08	26	3.11	0.0047	VS
Regimen Related Distress	T	28	4.5 ± 0.56	2.94 ± 0.78	↓	0.17	27	9.17	< 0.0001	ES
	C	27	4.42 ± 0.58	4.4 ± 0.62	↓	0.06	26	0.38	0.7045	NS
Interpersonal Distress	T	28	4.6 ± 0.69	2.97 ± 1.24	↓	0.27	27	5.92	< 0.0001	ES
	C	27	4.52 ± 0.71	4.44 ± 0.68	↓	0.07	26	1.06	0.2984	NS
Total Diabetes Distress Score	T	28	4.33 ± 0.34	2.91 ± 0.47	↓	0.1	27	13.32	< 0.0001	ES
	C	27	4.35 ± 0.39	4.24 ± 0.33	↓	0.1	26	1.11	0.271	NS

Note : T (Trial Group), C (Control Group), SED (Standard Error of Deference), DF (Degree of Freedom), ES (Extremely Significant, S (Significant), NS (Not Significant)

- The Emotional Burden, Regimen related distress, Interpersonal distress and total DDS score reduced in both the trial and control group after completion of the treatment. But the improvements were statistically significant in the trial group and not statistically significant in the control group taking placebo.
- The Physician related distress reduced after treatment in both trial & control group as compared to before treatment scores. The change was extremely significant in trial group (TG) and very significant in control group (CG).
- During the post treatment follow up phase (without giving any medicine or placebo) it was observed that the different elements of the DDS score did not change much in control group but they almost returned to their baseline values in the placebo controlled group.

Table 2: Effectiveness of Trial & Control Drug in Objective Parameters

Parameter	Group	n	Before Treatment Mean ± SD	After Treatment Mean ± SD	↑ ↓	SED	D.F	t Value	p Value	Inference
Fasting Blood Sugar	T	28	167.04 ± 8.94	129.86 ± 8.05	↓	1.87	27	19.84	< 0.0001	ES
	C	27	164.7 ± 6.88	136.07 ± 9.32	↓	1.47	26	19.44	< 0.0001	ES
Post Prandial Blood Sugar	T	28	200.46 ± 10.87	141 ± 7.92	↓	1.71	27	34.72	< 0.0001	ES
	C	27	204 ± 18.2	151.96 ± 11.23	↓	4.14	26	12.56	< 0.0001	ES
HbA1C	T	28	7.85 ± 0.49	6.8 ± 0.23	↓	0.09	27	11.25	< 0.0001	ES
	C	27	7.73 ± 0.42	7.01 ± 0.39	↓	0.06	26	10.66	< 0.0001	ES
Total Cholesterol (mg/dl)	T	28	203.61 ± 20.77	193.94 ± 15.93	↓	1.35	27	7.18	< 0.0001	ES
	C	27	205.12 ± 25.38	199.81 ± 24.1	↓	6.16	26	0.86	0.397	NS

Note : T (Trial Group), C (Control Group), SED (Standard Error of Deference), DF (Degree of Freedom), ES (Extremely Significant, S (Significant), NS (Not Significant)

- FBS was reduced significantly in both trial and control group. But the difference of mean FBS in before and after treatment was higher in trial group.
- There was statistically significant reduction in PPBS in both the trial & control group. But the difference of mean PPBS in before and after treatment was higher in trial group.
- The glycated haemoglobin (HbA1C) was also reduced significantly in both trial & control groups. But here also the difference of mean HbA1C in before and after treatment was higher in trial group.
- The total cholesterol was also reduced in both the groups. However the change was extremely significant in trial group where as it was statistically not significant in control group and may be occurring by chance.

DISCUSSION

The emotional burden, regimen related stress, interpersonal stress & total DDS Score reduced extremely significantly after treatment in the trial group but the change was not at all statistically significant in the Placebo controlled group.

Sitoindosides and acylsterylglucosides in *Ashwagandha* are anti-stress agents. Active principles of *Ashwagandha,* for instance the sitoindosides VII–X and Withaferin-A, have been shown to have significant anti-stress activity against acute models of experimental stress [14]. This proves that these positive changes in different stress levels in trial group were due to some evidence based strong pharmacological actions of *Ashwagandha* like antistress, antidepressant, adaptogenic, anxiolytic, antioxidant etc and not due to any placebo effect.

The physician related stress was reduced in both trial & control groups extremely significantly & significantly respectively. This effect in the placebo treated control group might be due to the positive interaction of the patients with the physician, care & concern of the doctors shown to the patients but not due to any pharmacological action.

These effects of *Ashwagandha* were also long lasting and did not alter after stopping the medication during the follow up phase.

The FBS, PPBS & the HbA1c were significantly reduced after treatment showing good control of diabetes as both the groups were treated with fixed dose OHA (Glimepride 1 mg + Metformin 100 mg). But the control was little better in the trial group. This may be due to some proven anti diabetic effect of *Ashwagandha* [15]. Secondly the patients of the trial group improved significantly from stress after 6 weeks treatment with *Ashwagandha* capsules. This low level of stress must have helped the better overall diabetes control of the patients of the trial group than that of the group treated with placebo.

Since *Ashwagandha* soft gel capsule & placebo capsule contained ground nut oil, it was decided to keep a watch on the Lipid Profile of the patients. Surprisingly the total cholesterol was reduced significantly after treatment in the trial group. This effect of the trial drug may be due to hypolipidaemic effect of *Ashwagandha.* [15]

It was also lowered in the control group but the change may be occurring by chance and was not statistically significant. The safety of *Ashwagandha* has been proven beyond doubt by many experimental and clinical trials.

It is generally safe on long term therapeutic use.[16] It is usually very well tolerated by most of the patients. Therefore none of the patients in the trial group reported adverse effects of any kind during the study period.

CONCLUSION

In summary, research has proved that stress has negative impact on diabetes. Stress has a role in the onset of diabetes and poor glycemic control affecting lifestyle. Interventions to manage stress in diabetics can

have an important positive effect on quality of life and glycemic control. [17]

Based on the findings of this study it can be broadly concluded beyond doubt that *Ashwagandha (Withania somnifera)* offers significant improvement in stress and related complains in patients of Type – 2 DM. Not only this but also it helps in over all control of diabetes and improves the quality of life in Type – 2 diabetes Patients. The best part of the study is that *Ashwagandha* reduces stress level and other related complains without creating any undue effect. *Ayurveda* has included *Ashwagandha in Rasayana Dravyas* which can fight the disease and restore the health, vigour and vitality. There is a sea change in the management approach of Type – 2 DM. Not only controlling the blood glucose but also preventing complications and improving the quality of life have emerged as newer challenges for diabetologists. In this study *Ashwagandha* acted in multifaceted role to offer multiple benefits safely & economically. Therefore it can be prescribed as a therapy to diabetics with stress & as an adjuvant to other diabetics as well.

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