

Double-blind, placebo-controlled clinical evaluation of an Ayurvedic formulation (GlucoCare capsules) in non-insulin dependent diabetes mellitus

R. K. Sharma, Pralhad S. Patki¹

Department of Dravyaguna and Rasashastra, Government Ayurvedic College, Guwahati, Assam, ¹R & D Center, The Himalaya Drug Company, Makali, Bangalore, India

ABSTRACT

Diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by insulin resistance, relative insulin deficiency and hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. The goal for treatment of diabetes is to prevent its acute manifestations and long-term microvascular and macrovascular complications. The present study was conducted to evaluate the efficacy and safety of an Ayurvedic formulation (GlucoCare Capsules) in non-insulin dependent diabetes mellitus. Fifty NIDDM patients of pitta-kapha prakriti attending the outpatient department of the Government Ayurvedic Medical College, Guwahati, Assam, India were included in the study, and randomly divided into 2 groups, GlucoCare and placebo. All received either GlucoCare or placebo in a dose of 2 capsules twice daily, before meals for 3 months. All 50 patients completed the study - no drop outs, withdrawals or patients lost to follow up. The GlucoCare group showed significant improvement in symptoms from the 2nd month till the end of the study. GlucoCare was well tolerated by all patients throughout the treatment period with no evidence of adverse effects. The study indicates clinical efficacy of GlucoCare Capsules in the management of NIDDM in those belonging to pitta-kapha prakriti. The formulation is well tolerated and appears safe in the dosage used.

Key words: Ayurvedic formulation, Ayurvedic formulation, non-Insulin dependent diabetes mellitus.

INTRODUCTION

In many countries, Non-Insulin Dependent Diabetes Mellitus (NIDDM) is one of the most prevalent and fastest growing diseases.^[1] Family physicians play a central role in its management. Though recognized as a distinct clinical syndrome for centuries, our understanding of the disease, its causation and mechanism of progression, are still evolving. In 2004, India had an estimated 37.76 million diabetics; 21.4 million in urban areas and 16.36 million in rural areas.^[2,3] The Chennai Epidemiological study (CURES) found percentages with diabetic retinopathy, microalbuminuria and peripheral neuropathy to be 17.6%, 26.9% and 26.1% respectively.^[4]

Address for correspondence:

Dr. Pralhad S. Patki,
R & D Center, The Himalaya Drug Company, Makali,
Bangalore - 562 123, India.
E-mail: dr.patki@himalayahealthcare.com

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Although many drugs improve glycemic control, they do not necessarily provide real-world benefits. In the recent ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trials, intensive glycemic control had minimal effect on clinical cardiovascular outcomes.^[5] In fact, in a recent meta-analysis, combination therapy with metformin and glyburide increased the risk of a composite end-point of cardiovascular events and mortality (relative risk 1.43, 95% confidence interval (CI) 1.10 to 1.85).^[6] Use of thiazolidinediones has recently been called into question because of increased risk of cardiovascular events and fracture.^[7] Compliance with medically advised medication is far from ideal. Cost of therapy and adverse effects of medication have been prime factors for inadequate patient compliance.

More than one-third of the world population uses complementary and alternative medicine (CAM) therapies, often without consulting or even informing their family physicians (FPs). It is important for FPs to ask patients about their CAM use and provide evidence-based information about the safety and efficacy of commonly used CAM therapies.

For diabetes, oral medication is usually the first line treatment after diet and exercise, which aim at management of acute conditions and prevention of long term complications. Exercise, diet and weight control continue to be essential and effective means of improving glucose homeostasis. However, lifestyle management measures may be insufficient or patient compliance difficult, rendering conventional drug therapies (i.e., oral glucose-lowering agents and insulin injection) necessary in many patients. In addition to adverse effects, drug treatments are not always satisfactory in maintaining euglycemia and avoiding late stage diabetic complications.

In Ayurveda, diabetes mellitus is named Madhumeha, a type of Prameha. Charaka and Sushruta classify 20 varieties of 'Meha' under 'Vata' 'Pitta' and 'Kapha' categories.^[8] Madhumeha includes three clinical types, Vataja, Pittaja and Kaphaja. Kaphaja Madhumeha may be related to high growth hormone levels, the pittaja type in particular to high levels of glucocorticoids. In the progression of diabetes, the initial stage of Prameha, Kapha dosha is at a high level later changing to Kapha Kshaya. Similarly Pittaja Prameha leads to Pitta Kshaya. However, in both Kaphaja and Pittaja Prameha Vata Vriddhi is a common denominator which in its terminal stage leads to Madhumeha: subtype 1 of Vataja Prameha. Specific treatments prescribed in Ayurvedic texts include herbs, detox therapies and dietetics. In recent times, the herbs have been subjected to scientific scrutiny and analysis.

Medicinal herbs with antihyperglycemic activities are increasingly sought after by diabetic patients and health care professionals. Commonly used herbs and other alternative therapies, are considered less likely to have the side effects of conventional treatments for NIDDM. Alternative therapies for diabetes have been extensively researched, particularly in India. Here, an Ayurvedic formulation GlucoCare capsules (manufactured by The Himalaya Drug Company, Bangalore, India) using a combination of herbs, is evaluated for use in NIDDM. Its composition is given in Table 1.

Aim of the study

The present study was conducted to evaluate the efficacy and safety of an Ayurvedic formulation (GlucoCare Capsules) in non-insulin dependent diabetes mellitus.

MATERIALS AND METHODS

Study design

Fifty NIDDM outpatients attending the Government Ayurvedic Medical College, Guwahati, Assam, India were randomly divided into GlucoCare and placebo groups. Patients underwent clinical examination on entry and at monthly intervals. They were given diaries to note incidence and severity of symptoms. Adverse effects if any were

Table 1: Composition of GlucoCare capsule

Name of the active ingredients	Quantity per capsules (mg)
Exts.	
<i>Commiphora wightii</i>	7.5
Shilajeet (Purified)	7.5
<i>Gymnema sylvestre</i>	35
<i>Pterocarpus marsupium</i>	30
<i>Glycyrrhiza glabra</i>	20
<i>Casearia esculenta</i>	25
<i>Syzygium cumini</i>	23
<i>Asparagus racemosus</i>	20
<i>Boerhaavia diffusa</i>	20
<i>Sphaeranthus indicus</i>	10
<i>Tinospora cordifolia</i>	10
<i>Tribulus terrestris</i>	10
<i>Phyllanthus amarus</i>	10
<i>Gmelina arborea</i>	10
<i>Gossypium herbaceum</i>	10
<i>Aloe vera</i>	5
Triphala	8
<i>Momordica charantia</i>	10
<i>Piper nigrum</i>	2.5
<i>Ocimum santum</i>	2.5
<i>Abutilon indicum</i>	2.5
<i>Curcuma longa</i>	2.5
<i>Rumex maritimus</i>	2
Trikatu	2

recorded. The study protocol was approved by the hospital's and institute's Ethics Committee. If they so desired, patients were free to withdraw from the study, which was conducted in accordance with the Helsinki Declaration, and the Government of India's Ministry of Health GCP Guidelines. Informed written consent was obtained from all study participants.

A questionnaire and clinician's observations and confirmation were used for Prakriti analysis.

Primary prakriti analysis was made based on a set of simple questionnaire and the clinician's observations and confirmation.

Inclusion criteria

Patients of Pitta-Kapha prakriti, aged 30 to 65, male or female, diagnosed with NIDDM characterized by plasma glucose concentration >200 mg/dL or fasting plasma glucose (FPG) >126 mg/dL or 2 hr post prandial glucose (PPG) >200 mg, positive urine sugar and having symptoms of polyuria, polyphagia and polydipsia, and willing to give written informed consent.

Exclusion criteria

Insulin-dependent diabetes mellitus (IDDM – Type I), with acute complications (nephropathy, neuropathy, retinopathy and gangrene), pregnant or lactating women, malignant

hypertension, history of severe unstable angina, myocardial infarction, cardiovascular accidents, renal failure, or allergy to medications, or not willing to give written informed consent.

Study procedures

Fifty patients of NIDDM attending the out-patient department of Government Ayurvedic Medical College, Guwahati, Assam, India were included in the study and were divided arbitrarily randomized into two groups, i.e., GlucoCare group and placebo group. All the patients received either GlucoCare or placebo in a dose of two capsules twice daily, before meals for three months in a random manner. Patients underwent clinical examination on entry and at monthly intervals for three months. They were provided with a diary to note down the incidence and severity of symptoms. Adverse effects if any were recorded. The prakriti other than Pitta-Kapha was rejected.

Follow-up and assessment

All subjects underwent clinical examination and evaluation of blood sugar levels on entry and at monthly intervals for the 3 month study period. At each monthly visit, subject evaluations were based on symptoms, fasting plasma glucose (FPG) and post-prandial glucose (PPG).

Primary and secondary outcome measure

The primary end-point was symptomatic relief, reduction and control of NIDDM symptoms, polydipsia, polyuria, polyphagia, burning sensation in hands and soles, pain/cramps, fasting and postprandial blood sugar levels. GlucoCare safety and toxicity profiles were secondary end points.

Statistical analysis

All the values are expressed as Mean \pm SD or incidence of symptoms. Statistical analysis was done by using Student's *t*-test or ANOVA. The minimum level of significance was fixed at $P < 0.05$. Statistical analysis was performed using GraphPad Prism software (Version 4.01).

RESULTS

The two groups' baseline characteristics on entry were comparable [Table 2]. Mean ages were 50.40 ± 6.50 years in the GlucoCare group and 53.50 ± 8.60 years in the placebo group. Male : female ratios were 15:10 (GlucoCare) and 16:9 (placebo).

All 50 patients completed the study. Patients on GlucoCare group showed significant symptomatic improvement from 1st month to the end of the study [Table 3].

Results indicate that from 2nd month onwards GlucoCare

Table 2: Baseline characteristics

Parameters	GlucoCare (n = 25)	Placebo (n = 25)
Mean age (years) (Mean \pm SD)	50.40 \pm 6.50	53.50 \pm 8.60
Mean weight (kgs) (Mean \pm SD)	60.00 \pm 4.50	64.00 \pm 5.50
Sex ratio (M:F)	15:10	16:9
Polydipsia (Pipasa)	17	19
Polyuria (Prameha)	14	16
Polyphagia (Adhyashana)	16	18
Burning sensation in hands and soles (Hastapadataladaha)	10	12
Pain/cramps (Sada)	9	11
Fasting blood sugar (FBS) (>140 mg%)	17	18
Post-prandial blood sugar (PPBS) (>180 mg%)	16	17
Prakriti	Pitta-Kapha	Pitta-Kapha
Both the groups are comparable		

subjects significantly decreased polydipsia, and continued to improve until the end of the study. Subjects on placebo did not respond significantly.

Polyuria observed in 14 patients on entry decreased to 12 patients after one month, and 1 patient by the end of study. Placebos showed no significant improvement in polyuria.

Similar trends were seen for other symptoms: polyphagia, burning sensation in hands/feet, and pain/cramps. By the 2nd month, most GlucoCare subjects showed overall improvement.

The GlucoCare group showed significant reductions in FBS from 180 ± 10.5 mg% to 130 ± 5.5 mg%, and PPBS from 200 ± 22.5 mg% to 140 ± 13.5 mg%. The placebo group showed no significant reductions in either [Table 3].

End of study evaluations assessed overall response to treatment. In the GlucoCare group, all subjects said they had excellent response to treatment, 76% were symptom-free [Table 4].

Adverse effects

GlucoCare capsules were well tolerated by all GlucoCare subjects throughout the treatment period. No serious hematological or biochemical abnormalities were experienced by any subject. There was no evidence of adverse side-effects.

DISCUSSION

Despite understanding NIDDM etiopathogenesis, rises in insulin-resistant cases and failure of oral hypoglycemic

Table 3: Effect of drug therapy on symptoms of non-Insulin dependent diabetes mellitus

Parameter (No. of patients with)	GlucoCare (n = 25)				Placebo (n = 25)			
	At entry	1 st month	2 nd month	End of study	At entry	1 st month	2 nd month	End of study
Polydipsia	17	15	9*	2*	19	19	15	8
Polyuria	14	12	10*	1*	16	15	12	10
Polyphagia	16	12	7*	2*	18	17	15	9
Burning sensation in hands and soles	10	7	4*	2*	12	11	10	7
Pain/cramps	9	6	3*	1*	11	10	10	6
Fasting blood sugar (Mean ± SD)	180 ± 10.5	150 ± 16.5	140* ± 13.5	130* ± 15.5	180 ± 12.5	170 ± 10.5	160 ± 19.5	150 ± 18.5
Post-prandial blood sugar (Mean ± SD)	200 ± 22.5	190 ± 18.5	160* ± 15.5	140* ± 13.5	210 ± 20.5	190 ± 18.5	180 ± 15.5	160 ± 17.5
Glycosylated hemoglobin (%)	6.35 ± 1.42	-	-	6.0 ± 2.5	7.0 ± 1.0	-	-	6.0 ± 1.5

*P < 0.05 as compared to respective 'At entry' values

Table 4: Overall response to treatment at 3rd month

Parameters	GlucoCare (n = 25)		Placebo (n = 25)	
	No. of patients	Response (%)	No. of patients	Response (%)
Symptom-free	19/25	76	7/25	28
Patient's impression				
Excellent	19/25	76	3/25	12
Good	4/25	16	1/25	4
No response	2/25	8	21/25	84

agents (OHAs) are alarming. The past two decades have seen explosive increases in numbers diagnosed with NIDDM globally. In India, an estimated 19.4 million are affected, a figure likely to increase to 57.2 million by 2025. Even today, India has the largest number of diabetics of any country in the world. In the 1970s, diabetes prevalence among urban Indians was 2.1%, a figure now standing at 12.1%.

Moreover, an equally large pool of individuals with impaired glucose tolerance (IGT) are at risk of developing NIDDM in the near future.

The prakriti of the two groups were matched (Pitta-Kapha) so their drug response was comparable. The present study indicates the efficacy of the Ayurvedic formulation in controlling fasting and postprandial blood sugar of Diabetic patients belonging to Pitta-Kapha prakriti. No significant benefit in glycosylated hemoglobin values was found, however. All subjects tolerated the drug, none withdrew. To evaluate safety and efficacy more accurately, future studies will need larger sample sizes.

Insulin lowers plasma glucose levels by stimulating glucose uptake into muscle and inhibiting hepatic glycogen breakdown. Catecholamines cause hyperglycaemia by stimulating hepatic glycogenolysis and inhibiting insulin

stimulated glucose utilisation in muscle. GlucoCare has been found to inhibit catecholamine induced hyperglycaemia and significantly improve liver glycogen storage. It has also been found to increase incorporation of C - 14 glucose in liver slices in alloxan-induced diabetes in rats.^[9] Now, a more specific analysis of GlucoCare ingredients: *Gymnema sylvestre*, (Mesasringi) one of the important ingredients of GlucoCare, has been found to be effective in diabetes by increasing beta cell function possibly by repair/regeneration of the beta cells.^[10,11] *Momordica charantia* (Karavallaka) seeds were found to contain molecules with insulin-like bioactivity.^[11] It is possible that GlucoCare reduced blood sugar levels by improving the plasma insulin, increasing peripheral utilization of glucose, improving liver glycogen storage, and by its intrinsic antidiabetic action.

In both insulin-dependent diabetes (IDDM) and non-insulin dependent diabetes (NIDDM), morbidity and mortality from cardiovascular disease is greatly increased, possibly due to increased serum lipid. Furthermore, there is considerable evidence that control of serum lipids results in the reduction of the incidence of coronary heart disease. It is therefore important to understand the effects of the treatments used in diabetes on serum lipids and lipoproteins.^[12] In this combination of GlucoCare, *Commiphora wightii* (Guggulu) plays a complementary role by renormalizing the serum lipids and cholesterol possibly

due to its androgen (AR), glucocorticoid (GR) antagonistic activities that potentially aids the person suffering from diabetes.^[13] Shilajit is a pale-brown to blackish-brown exudation, of variable consistency, exuding from layers of rocks in many mountain ranges of the world, especially the Himalayas. It has been used as a rejuvenator and an adaptogen for thousands of years, in one form or another, as part of traditional systems of medicine for treatment of diabetes.^[14]

Among crude components extracted from the leaves of *Gymnema sylvestre* is one of the triterpene saponins that suppress sweetness by a reversible effect on the sweet taste receptors. Pharmacological tests also show reduction in blood sugar. The extract suppresses increases in blood glucose by inhibiting its reuptake in the intestines.^[14] It also provides effective hyperglycemic control, which is crucially important to prevent the micro- and macrovascular complications of diabetes mellitus^[15] and enhances peripheral utilization of glucose.^[9]

Pterocarpus marsupium (Asana) can control diabetic-related metabolic alterations apart from controlling glucose levels.^[16] Its hypoglycemic action may be due to its reduced glucose absorption from the gastrointestinal tract.^[17] A clinical trial has shown that oral intake of *P. marsupium* extract has potent hypoglycemic activity (both fasting and postprandial) that can be comparable with tolbutamide.^[18]

Licorice flavonoid oil (LFO) from *Glycyrrhiza glabra* (Yashti) contains Hydrophobic flavonoids with abdominal fat-lowering and hypoglycemic effects in obese animal diabetic models. Mediation by PPAR-gamma activation has been suggested.^[19]

Casearia esculenta, (Cilhaka bheda) is an indigenous plant popularly used as an antidiabetic in South India. Oral administration of aqueous extracts lowers blood glucose levels under normal and glucose load conditions, possibly due to inhibition of blood glucose absorption from the gut^[20] and the presence of potent anti-hyperglycemic factor(s).^[21] It is also a potent antioxidant.

Seeds of *Syzygium cumini* (Jambu) show preferred hypoglycemic activity, establishing its positive pharmacological activity.^[22]

Extracts of *Asparagus racemosus* (Satavari) root contain large amounts of flavonoids, polyphenols and vitamin-C, and exhibit extreme antioxidant activity. They scavenge free radicals such as superoxide, hydroxyl radical, hydrogen peroxide and nitric oxide, all of which participate in various pathophysiologicals. They can thus play an important role in NIDDM.^[23]

Treating normal and diabetic rats with extracts of *Boerhaavia diffusa* (Punarnava) resulted in significant decreases in blood glucose and increases in plasma insulin levels, establishing their hypoglycemic action; also observed were significant reductions in glycosylated hemoglobin and increases in total hemoglobin.^[24]

Sphaeranthus indicus (Munditika) is a noted hypoglycemic herb.^[25] Fasting normal rats treated with its alcoholic extract significantly improved on oral glucose tolerance tests, suggesting an application to diabetes mellitus.^[26]

Tinospora cordifolia (Guduchi) shows hypoglycemic activity possibly by stimulating endogenous insulin secretion by altering the cell membrane permeability.^[27,28] It also has aldose reductase inhibitory actions, thus preventing cataract formation.^[29]

A trial has shown that extracts of *Tribulus terrestris* (Gokshura) significantly decrease fasting glucose levels. They also cause significant decrease in glycosylated hemoglobin levels, and total cholesterol, triglycerides and LDL-cholesterol.^[30]

Fruits of *Phyllanthus amarus* (Tamalaki) show hypoglycemic activity^[31-33] as does hydro-alcoholic extract of *Gmelina arborea*.^[34]

Gossypium herbaceum (Karpasa) has therapeutic action against elevated blood sugar, cholesterol and triglyceride, also exhibiting an ability to reduce blood sugar.^[35]

Aloe vera is noted for hypoglycemic activity and used in diabetes mellitus.^[38] Some studies have indicated that long-term *Aloe vera* (Kumari) gel treatment helps diabetic hyperglycemia. Administration of gel with a high fat diet prevents development of insulin resistance and glucose intolerance.^[36] Oral intake prevents progression of NIDDM-related symptoms.^[37]

"Triphala (equal proportion of *Terminalia chebula*, *Terminalia bellerica*, and *Embellica officinalis*) shows hypoglycemic activity.^[39]

It has been reported that isolates and extracts of *Momordica charantia* contain a hypoglycaemic principle - an insulin-like peptide called foetidin, momordicin or charantin (polypeptide p-insulin). According to some investigators, this glucoside (polypeptide p-insulin) is useful for management of both IDDM and NIDDM. Furthermore, it is possible that the plant extract mimics or improves insulin action at the cellular level, or even exhibits extra-pancreatic action.^[40]

Extracts of *Momordica charantia* enhance insulin secretion by the islets of Langerhans, reducing glycogenesis in liver tissue, enhancing peripheral glucose utilization and increasing serum protein levels.^[10]

Piper nigrum (Marica) seeds have a hypoglycemic effect, and also check antioxidant levels. This is necessary and sufficient for control of complications arising from glycation and glycooxidation of proteins and membranes.^[41]

Ocimum sanctum (Tulasi) leaf extracts greatly stimulate insulin secretion from the β -cells via physiological pathways.^[42] They prevent cataract in rat lenses by simultaneously restoring antioxidant defenses and inhibiting protein precipitation. Concurrent administration of Vitamin-E helps reverse changes in diabetic retinopathy.^[43] *Abutilon indicum* (Atibala) leaves show hypoglycemic activity.^[44] The plant also has good wound healing activity, and is helpful in management of wounds and other superficial dermatological infections in diabetes mellitus.^[45]

Curcumin, the yellow phenolic curcuminoid present in turmeric, has been reported to have a wide range of biological activities. Even very small dietary levels (0.002%) delay galactose induced cataract in rats.^[46] It exhibits very high lipid-soluble antioxidant action, and may be helpful in diabetes.^[47]

Curcuma longa root also contains Rumarin, used for its anti-pruritic activity, and may be helpful in reducing itching sensations in those with hyperglycemia.^[48] Its additional neuroprotective activity may be helpful in managing other neurological problems seen in diabetes.^[49]

Trikatu is a phyto-combination (*Piper longum*, *Piper nigrum* and *Zingiber officinale*) that increases bioavailability by promoting rapid absorption from the gastrointestinal tract, or preventing metabolism/oxidation during first passage through the liver after being absorbed, or a combination of these mechanisms, helping improve most drugs' therapeutic activity.^[50]

This study demonstrates GlucoCare's efficacy in a small population of a particular Prakriti. Further studies should include a larger population of patients, including all Prakritis.

CONCLUSION

Results of this clinical study of 50 patients of pitta-kapha prakriti suffering from NIDDM, indicate that GlucoCare Capsules have beneficial effects in relieving symptoms and bringing about overall improvement. 19 of the 25 patients on GlucoCare felt that they showed adequate response to treatment. The present clinical study indicates significant clinical efficacy of GlucoCare Capsules in management of NIDDM. The formulation was well tolerated and appeared to be safe in the dosage used.

DECLARATION

The authors declare that the WHO Criteria for Medicinal Drug Promotion (1986) were meticulously followed during this clinical study and its publication.

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