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A PROSPECTIVE STANDARD CONTROLLED CLINICAL TRIAL OF BHUDHATRIKADI YOGA WITH LIFESTYLE MODIFICATION IN MADHUMEHA (TYPE -2 DIABETES MELLITUS)

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BACKGROUND

Dozens of preventive and therapeutic drugs have been developed and examined for its potential benefits in Type-2 Diabetes mellitus (DM) in past decades. Regardless of the efforts putforth, the disease has now emerged as a major public health problem that is approaching epidemic proportions globally. Based on the previous investigative studies on the restorative and curative therapeutic potential of the components of the drug *Bhudhatrikadi Yoga* (i.e., *Bhudhatri* and *Maricha*), it is assumed to curtail the risk of complications related to the disease along with controlling the glycemic index. However, the study needs further authentication in substantial samples, standard-controlled, and randomized clinical trials.

OBJECTIVE

This clinical study is designed to determine the efficacy and safety of *Bhudhatrikadi Yoga* in *Madhumeha* DM2 compared with Metformin.

MATERIAL AND METHODS

This prospective, open-label, randomized, active control, parallel-group trial will be conducted at Uttarakhand Ayurved University, Rishikul Campus Haridwar. A total of 60 participants in patients of any gender aged 30-60 years with DM2 having Fasting blood glucose levels>110mg/dl <250mg/dl & post-prandial blood sugar levels>140mg/dl and <350mg/dl and HBA1C >6% to <10% will be considered for enrolment in the study. The enrolled participants will be randomly divided into two groups. Group A patients will be administered 5 gm *Bhudhatrikadi Yoga* twice daily before meal. Patients of group B will be administered metformin 500 mg twice daily before meals for 90 days. The outcome measures are changes in Blood Sugar- Fasting, Blood Sugar- Post-prandial, HbA1c, Urine Sugar, and BMI. Patients will also be assessed for graded subjective parameters on each visit. Safety will be assessed based on the incidence of adverse events and changes in the liver and kidney function tests.

DISCUSSION

Ayurvedic formulations have been used for the management of *Madhumeha* in routine clinical practice. However, the use of Ayurvedic intervention with lifestyle modification is less common. So it is expected that the outcomes of this trial will suggest probable therapeutic options for the effective management of *Madhumeha* DM2.

TRIAL REGISTRATION

CTRI/2022/07/043884(clinical trial registry of India) registered on 11/07/22.

KEYWORDS

Madhumeha, Diabetes, Bhudhatrikadi Yoga.

INTRODUCTION

Type 2 Diabetes is a complex, multifactorial disorder characterized by both a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. In 2021 more than 1 in 10 adults worldwide developed Diabetes. The estimated prevalence of diabetes in adults (20 to 79 years) has more than tripled since the first edition in 2000, rising from an estimated 151 million (4.6% of the world's population at the time) to 537.5 million (10.5%) of the world's population today. The prevalence rate will be higher than 12.8% by 2045. In addition, studies indicate that the incidence of diabetes in the world, Southeast Asia, and India was 10.5%, 8.8%, and 9.6%, respectively throughout 2021, and will rise to 12.5%, 11.5%, and 10.9%, respectively by 2045.[1] Diabetes may lead to serious complications in multiple organ systems such as retinopathy, nephropathy, neuropathy, etc. *Madhumeha* is one among 20 types of prime urological disorders described in various *Ayurvedic* classics, viz. *Charaka Samhita*, *Sushruta Samhita*, *Ashtanga Sangraha*, and *Madhava Nidana*. Ancient seers have narrated that excess use of *Guru* (heavy to digest), *Snigdha* (unctuous), *Amla* (sour), *Lavana* (salt), *Navanna* (food prepared from newly harvested grains), new wine, *Asya-Sukha* (sedentary lifestyle), *Atinidra* (excess sleep), *Avyayma* (lack of exercise), obtaining from *Samshodhana* (purification) therapy as the major causes of *Madhumeha*.[2] All these factors (*Nidana*) lead to an imbalance of *Doshas*, causing *Manda-Agni* and the formation of *Amadosha* which increases *Kleda* and also leads to *Margavarana*. The clinical and the prodromal features of *Prameha* are *Prabhuta Mutrata* (Excessive urination (polyuria), *Avil Mutrata* (Turbidity in urine), *Ati-Kshudha* (Excessive hunger (polyphagia), *Pipasa-adhika* (Excessive thirst (polydipsia), *Karpada-Daha* (Burning sensation of hands and feet), *Daurbalya* (Weakness). This clinical representation can be correlated with the symptoms of Diabetes mellitus and is regarded as *Madhumeha* in *Ayurveda*.[3] Drugs mentioned for the aforestated condition should have *Lekahana, Deepana, Pachana, Pramehagana, Yakrut Uttejaka, Nadi Uttejaka, and Balya* properties.[4] Lifestyle intervention programs promoting healthy diets, physical activity, and modest body weight reduction can prevent or delay the onset of diabetes among high-risk populations, such as those with impaired glucose tolerance.[5] Keeping this point of view in mind, the present

study is planned entitled "A standard controlled clinical trial of *Bhudhatrikadi Yoga* with lifestyle modification in *Madhumeha* (Type-2 Diabetes mellitus)". The assessment of the effect of *Bhudhatrikadi Yoga* in Type-2 DM is the primary objective of the study, and its efficacy is also compared with the standard conventional medicine Metformin usage as the secondary objective, for better replacement of modern drugs by putting forward a safe and effective alternative medicament in *Ayurveda.*

OBJECTIVE

This study is designed to evaluate the efficacy of ***Bhudhatrikadi Yoga*** along with lifestyle modification.

To compare the Efficacy of ***Bhudhatrikadi Yoga*** along with lifestyle modification with standard control (**Metformin**) along with lifestyle modification.

MATERIAL AND METHODS

Study design and setting

This study is a randomized, open-label, parallel-group trial. It is being conducted at Uttarakhand Ayurved University, Rishikul Campus Hospital, Haridwar, Uttarakhand, India. The study protocol is designed based on the standard protocol items.

STUDY PARTICIPANTS

INCLUSION CRITERIA: Patients between the age group of 30-60 years with a maximum Chronicity of 5 years. Patients have Fasting blood glucose levels between 110 mg/dl to 250mg/dl and Postprandial blood sugar levels between 140mg/dl to 350mg/dl. HBA1C between 6% to 10% will be included trial.

EXCLUSION CRITERIA Patients with Type 1 Diabetes Mellitus, below 30 years and above 60 years with more than 5 years of Diabetic history, Fasting blood sugar level of more than 250 mg/dl, post-prandial blood sugar level above 350mg/dl, and HBA1C beyond 10% will not be included for trial. Patients having Diabetic complications and patients suffering from any serious medical or surgical illness history will be excluded from the trial.

STUDY INTERVENTION

The enrolled participants of group A will receive *Bhudhatrikadi Yoga* in a dose of 5 gm twice daily, 30 minutes before meal. Group B participants will receive Metformin 500mg twice daily before meals. The intervention period will be of 90 days. Participants will be asked to come for follow-up after15 days completion of trial. The trial *Ayurvedic* intervention is manufactured by MIDBACK Pharmacy, India. The control medication, Metformin is manufactured by a GMP-certified company and is procured from the market.

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OUTCOME MEASURES

The primary outcome measure is the change in Blood glucose level, which will be assessed at baseline and on the 30th, 60th, and 90th day. The secondary outcome measures are changes in HbA1c, urine sugar, and BMI, and will be assessed at baseline and on day 90. Participants will also be assessed for graded subjective parameters [Table 1] on each assessment visit. The schedule of enrolment, intervention, assessment, and follow-up visits for the study participants is given in Table 2.

SAFETY OUTCOME

Safety will be assessed based on the occurrence of adverse events on each assessment visit. Further, liver and kidney function tests will be assessed at baseline and on day 90. The adverse events, if any, will be recorded as per Good Clinical Practice guidelines.

TABLE 1: GRADING OF SUBJECTIVE CLINICAL PARAMETERS

Parameters	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Prabhuta Mutrata **(Frequency of urine)**	Urination 3-5 times per day, no or rarely at night	Urination 6-8 times per day, and 1-2 times per night	Urination 9-11 times per day, and 3-4 times per night	Urination >11times per day, and >4times per night
Pipasa - Adhikya **(Polydipsia)**	The feeling of thirst 7-9 times / 24 hours, consuming1.5 - 2.0 litre /24 hours	The feeling of thirst 9-11 times / 24 hours, consuming 2.0 - 2.5 litre /24 hours	The feeling of thirst 11-13times / 24 hours, consuming2.5 - 3.0 litre /24 hours	The feeling of thirst> 13 times / 24 hours, consuming>3.0litre /24 hours
Avila-Mutrata **(Turbidity in urine)**	Crystal clear fluid	Faintly cloudy or hazy with slight turbidity	Turbidity is clearly present and newsprint is easily read through test tube	newsprint is not easily read through test tube
Kshudha- Adhika **(Polyphagia)**	As usual/ routine	Slightly increased (extra 1-2 meals)	Moderately increased (extra 3-4 meals)	Markedly increased (extra 5-6 meals)
Daurbalya **(Weakness)**	No weakness in doing routine work and exercise	Mild weakness in doing routine work and exercise	Moderate weakness in doing routine work and	Severe weakness in doing routine work and exercise

			exercise	
Kara-Pada Daha	No *Daha*	Mild kara pada daha for short period	kara pada daha continuous but bearable	kara pada daha continuous but Unbearable

TABLE 2: STUDY SCHEDULE

	Screening	**Baseline**	**Day 30**	**Day 60**	**Day 90**
Written informed consent	✓				
Screening	✓				
Laboratory investigations (HBA1C, SGOT, SGPT, Hb, TLC, DLC ESR, Sr. Cholesterol, serum Creatinine, Urine Sugar, Urine routine, and microscopic)	✓				✓
Laboratory investigations (Blood sugar Fasting and Postprandial, HBA1C, Urine sugar, BMI)	✓		✓	✓	✓
Demographic & Medical history		✓			
Clinical assessment		✓	✓	✓	✓
Oral administration of the drug		**Daily for 90 days**			
Rescue medication (if required)			✓	✓	✓
Assessment of adverse events			✓	✓	✓

WITHDRAWAL CRITERIA

A study participant who develops any serious adverse event or adverse drug reaction during the study period

will be withdrawn from the study. Such patients will be given appropriate medical care or referred to a higher medical facility. Participants who are not willing to continue in the study or show less than 80% compliance with the trial therapeutic regimen will also be withdrawn from the study.

SAMPLE SIZE

The sample size according to this formula comes out to be 30. $n = \frac{2(z\alpha+z\beta)^2P(1-P)}{(P1-P2)^2}$ zα =level of significance is 1.96 zβ = 0.84 P1 = 25% **{Bhudhatryadi Yoga in Madhumeha (Diabetes mellitus type 2): An open label single arm clinical study**}[5] P2 = 62% (assumed) P = (P1+P2) ÷2. So minimum of 30 patients will be selected in each group.

RANDOMIZATION

Computer generated the random number sequences will be adopted by using the Statistical Package for Social Sciences software. The randomized allocationof the participants in the two study groups will be concealed using sequentially numbered, opaque, and sealed envelopes.

RECRUITMENT

After obtaining written informed consent from participants, eligible subjects with *Madhumeha* will be screened for eligibility to participate in the study. The participants will be enrolled from the Uttarakhand Ayurved University, Rishikul Campus Hospital, Haridwar, Uttarakhand, India, based on the predefined inclusion and exclusion criteria.

ETHICAL CONSIDERATION

The study is approved by the Institutional Ethics Committee of the Uttarakhand Ayurved University, Rishikul Campus, Haridwar. Written informed consent will be obtained by the investigator before enrollment from the potential subjects after they comprehend the concepts of the study. **ICMR National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017) will be followed to execute the study.**

CONCOMITANT AND RESCUE MEDICATIONS

Study participants will be enquired about concomitant medication for any undue affliction, and if any information is there, the same will be recorded in the case record form (CRF). In case of a need for any rescue medicament, it will be prescribed and noted in the CRF.

COMPLIANCE

Compliance will be assessed by the quantity of trial medication consumed during the intervention period. The same is evaluated through the compliance assessment form issued to the study participants. The participant's

compliance should be more than or equal to 80%.

DATA COLLECTION AND DOCUMENTATION

Data from the enrolled participants will be collected at baseline and on days 30th, 60th, and 90th. The same will be recorded in the predesigned CRF. An attempt will be made to collect the outcome data from the participants who discontinue from the study through intermittent follow-up if the participant are willing for the same.

DEVIATION FROM PROTOCOL

Any deviation from the study protocol will be implemented in the study only after approval from the IEC.

CONFIDENTIALITY

All the information and records of the study participants will be kept confidential and their name and identity will not be disclosed.

MONITORING

As this study is a PhD research work, it will be monitored by the concerned supervisor & department research committee (DRC) of the department where this study will be conducted.

STATISTICAL ANALYSIS

The categorical variables will be summarized a numbers (percentage) and compared using Within-group **Wilcoxon's Signed rank test** and for inter-group comparison **Mann- Whitney test** will be applied. Continuous data will be represented as mean (standard deviation). Within-group analysis will be done using the paired sample t-test for normal data, whereas an unpaired T-test will be used for the comparison of nonnormal data.

DISCUSSION

Diabetes mellitus is a disease of metabolic dysregulation that results in the buildup of aberrant sugar levels in the bloodstream. At the molecular level, chronic hyperglycemia leads to the accumulation of toxic advanced glycation end products (AGEs). AGEs are a diverse array of compounds formed through a non-enzymatic reaction known as glycation in which sugars or sugar metabolites attach to different biomolecules, such as proteins, impairing their function. Given that glycation is a sugar concentration-dependent reaction, high levels of glycated-stress are a key pathophysiological feature in DM.[6] Type 2 Diabetes comprises of derangement in the beta cell of the pancreas secreting Insulin, and a decreased response of peripheral tissues to respond to insulin. *Madhumeha* or Diabetes mellitus is a multifactorial silent killer that requires prompt treatment to avoid complications. Conventional anti-DM therapies include lifestyle modifications (nutrition, exercise, and weight

loss), oral pharmacological agents (like metformin, etc), and subcutaneous pharmaceutical Insulin.[7] Oral anti-hyperglycemic agents are used as monotherapy or in combination. This polypharmacy strategy shows multitudes of side effects.[8] To minimize these unwanted and hazardous effects many DM patients choose to combine lifestyle changes and herbal drugs with standard drugs for better quality of life and least complications. WHO recommends Metformin as a drug for the treatment of Type-2 DM, because it can reduce Obesity, lower Insulin resistance, hyperglycemia, and blood pressure, and can also decrease inflammation.[9] *Bhudhatryadi Yoga* is mentioned for the treatment of *Prameha* in *Ayurvedic* classical texts. The constituents of this formulation of *Bhudhatrikadi Yoga* are *Bhudhatri (Phyllanthus niruri) and Maricha (Piper nigrum). Bhudhatri* has *Tikta-Kashaya Rasa, Laghu-Ruksha Guna;* and acts as *Pitta-Kapha Shamaka,* and *Grahi.* So, can be used for the better management of DM. *Katu Rasa* of *Maricha* and its *Deepana-Pachana Guna* cause its *Kleda Shoshana, Meda Shoshana,* and *Kapha Harana* properties. It removes *Sroto Rodha* and thereby helps in alleviating *Kapha Prakopa* seen in *Prameha/Madhumeha Roga*.

Skimming through various studies on the action of P. niruri on diabetes, it was found to possess an anti-hyperglycemic effect, lower blood cholesterol, and triglycerides; it is anti-hypertensive; helps in the prevention and cure of degenerative disease or infection; improves insulin resistance and shows anti-apoptosis actions; it also inhibits inflammation and weight loss in Diabetic rats.[10] Its rich flavinoid and phenolic profile are responsible for its potent antioxidant properties. The oral consumption of P.niruri is considered to be safe, and the LD50 was higher than 5000mg/kg body weight.[11] Moreover, it is noteworthy that P. Niruri was clinically approved to be safely consumed by children.[12] Studies on this plant reported to have glucose-lowering activity and nephroprotective effect.[13] Piperine from *Maricha* has been validated as a bioavailability enhancer since 1979 and has been used in *Ayurvedic* medications since time immemorial.[14] Piperine can also provide additional benefits for Diabetes through its antioxidant and antiobesity properties.[15] In one of the studies it is used with Metformin as a bio enhancer.[16] Likewise physical activities reduce insulin resistance directly by promoting free fatty acid oxidation and reducing lipotoxicity in skeletal muscle and liver and indirectly by reducing visceral fat.[17] Furthermore, exercise seems to improve serum levels of adiponectin, a hormone that promotes insulin sensitivity.[18] Evidence suggests that a variable combination of β-cell mass loss and dysfunction are involved in diabetes pathogenesis.[19] Preliminary animal and human studies suggest that physical activities improve β-cell function by upregulating insulin signaling pathways and β-cell mass by stimulating proliferation and preventing apoptosis.[20] Evidence also shows that lifestyle changes may help mitigate the effects of genes on Diabetes risk. For instance, in the US Diabetes Prevention Program, the association between susceptible genotypes and progression to Diabetes was attenuated in individuals receiving a lifestyle intervention.[21] In light of the aforementioned facts it is expected that the trial with a combination of lifestyle changes and a potent monotherapy drug containing a bioenhancer in it, will show promising outcomes in managing the *Madhumeha* (Type-2 Diabetes Mellitus).

ACCESS TO DATA

As the study is a PhD research work, the concerned supervisor of the department will have access to the

final study data.

ANCILLARY AND POST-TRIAL CARE

No ancillary studies are proposed with this trial. The participants will be provided routine medical care after the completion of the study period if required.

DISSEMINATION

The outcomes of this study will be disseminated through original articles in a peer-reviewed medical/Ayush journal and presentations at national conferences.

CTRI REGISTRATION

The study is registered prospectively with the Clinical Trial Registry of India **CTRI/2022/07/043884 registered on 11/07/22.**

TRIAL STATUS

Recruitment of participants has begun for this study.

PROTOCOL NUMBER

UAU-PHD RC/KC-381-386/2021

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICTS OF INTEREST

There are no conflicts of interest

हिंदी सारांश

टाइप-2 मधुमेह मेलिटस में जीवन शैली संशोधन के साथ भूधात्रिकादि योग का एक मानक नियंत्रित नैदानिक परीक्षण": एक यादृच्छिक नियंत्रित परीक्षण का अध्ययन प्रोटोकॉल

पृष्ठभूमि- मधुमेह पूरी दुनिया में महामारी के अनुपात में बढ़ रहा है, जिसमें भारत अग्रणी है। ओरल हाइपो ग्लाइसेमिक एजेंट के प्रतिकूल प्रभावों के कारण डीएम टाइप 2 के लिए एक वैकल्पिक चिकित्सीय विकल्प खोजने की आवश्यकता है, जो तुलनीय प्रभावकारिता के साथ सुरक्षित, सहनीय हो।

उद्देश्य- यह क्लिनिकल अध्ययन मेटफॉर्मिन की तुलना में मधुमेह DM2 में भूधात्रिकादि योग की प्रभावकारिता और सुरक्षा निर्धारित करने के लिए डिज़ाइन किया गया है।

सामग्री और विधियां- यह संभावित, ओपन-लेबल, यादृच्छिक, सक्रिय नियंत्रण, समानांतर-समूह ट्रायल उत्तराखंड आयुर्वेद विश्वविद्यालय, ऋषिकुल परिसर हरिद्वार में आयोजित किया जाएगा। अध्ययन में कुल 60 प्रतिभागियों को नामांकित किया जाएगा, डीएम2 वाले 30-60 वर्ष की आयु के किसी भी लिंग के मरीज, जिनका फास्टिंग ब्लड ग्लूकोज लेवल 110 mg/dl और 250mg/dl के मध्य है। भोजन के बाद रक्त शर्करा स्तर 140 mg/dl और 350 mg/dl के मध्य को अध्ययन में मूल्यांकन के लिए माना जाएगा, नामांकित प्रतिभागी को यादृच्छिक रूप से दो समूहों में विभाजित किया जाएगा। ग्रुप ए के मरीजों को भोजन से पहले 5 ग्राम भूधात्रिकादि योग दो बार दी जाएगी। ग्रुप बी के मरीजों को 90 दिनों तक भोजन से पहले 500 मिलीग्राम दो बार मेटफॉर्मिन दिया जाएगा। परिणाम के उपाय रक्त शर्करा में परिवर्तन हैं – प्रागभुक्त रक्त शर्करा -

भोजन के बाद रक्त शर्करा, एचबीए1सी, मूत्र शर्करा, बीएमआई। प्रत्येक दौरे पर रोगी का श्रेणीबद्ध व्यक्तिपरक मापदंडों के लिए भी मूल्यांकन किया जाएगा। सुरक्षा का आकलन प्रतिकूल घटनाओं की घटनाओं और यकृत और गुर्दे के कार्य परीक्षणों में परिवर्तन के आधार पर किया जाएगा।

विमर्श- नियमित नैदानिक अभ्यास में मधुमेह के प्रबंधन के लिए आयुर्वेदिक फॉर्मूलेशन का उपयोग किया गया है, हालांकि जीवनशैली में संशोधन के साथ आयुर्वेदिक हस्तक्षेप का उपयोग कम है, इसलिए यह उम्मीद की जाती है कि इस परीक्षण के परिणाम मधुमेह डीएम2 के प्रभावी चिकित्सा की खोज में महत्वपूर्ण योगदान प्रदान करेंगे ।

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