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Original Research Article (Clinical)

Ayurvedic polyherbal combination (PDBT) for prediabetes: A randomized double blind placebo controlled study

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ABSTRACT

Background: Increasing prevalence of type 2 diabetes mellitus (DM) has become alarming, burdening health care systems throughout the world. Prediabetes is an intermediate step before manifestation of full blown DM. Effective intervention at this step would help stop/slow progression to DM.
Objective: This study aimed at use of a polyherbal combination (PDBT — constituted of *Tinospora cordifolia*, *Pterocarpus marsupium*, *Gymnema sylvestre*, *Zingiber officinale* and *Momordica charantia*) along with life style modification compared to a placebo in prevention of DM among prediabetic individuals.
Materials and Methods: The study was a double blinded, placebo controlled randomized clinical trial. Participants were divided in to a group on PDBT and life style management (LSM) and second on placebo and LSM. Participants in the intervention group received 2 gm/day of PDBT. All participants received the intervention for a period of 6 months.
Results: One hundred and fourteen participants were enrolled in the study, 57 each in intervention and control group. At the end of the study, 8 participants from the intervention group, compared to 15 participants in the control group had converted to DM. There was a 47% risk reduction in the intervention group. Participants in the intervention group showed statistically significant decrease in their blood glucose level (fasting and PP), HbA1c, fasting serum insulin and HOMA-IR values. There was no significant change in BMI. No adverse effects were reported by any participants.
Conclusion: PDBT along with LSM in prediabetic participants was associated with reduction in conversion to DM than placebo along with LSM without any adverse effects.
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1. Introduction

Increase in prevalence of diabetes mellitus (DM) has reached alarming proportions putting burden on healthcare systems around the world. There were a total of 382 million patients estimated to be living with DM worldwide in 2013. The World Health Organization (WHO) estimated that 422 million adults were living with diabetes worldwide in 2014 which costs the world US$ 827 billion [1]. The International Diabetes Federation has estimated that there will be 642 million diabetics till 2040 worldwide [2]. In India, the prevalence of diabetes is estimated to be 8.7 % [3].

Prediabetes, also called as intermediate hyperglycemia, is a stage which is characterized by blood glucose levels which are above normal but below the threshold defined for diabetes or having impaired glucose tolerance [4]. Studies have reported a higher likelihood of progression of prediabetes to type 2 diabetes mellitus [4,5]. Early intervention at Prediabetic stage would help to slow/stop progression towards diabetes.

Various studies conducted on Prediabetic individuals for prevention of progression to diabetes include metformin, life style modification (LSM) and various other medicines like orlistat, acarbose, pioglitazone [6–8]. However, adverse reactions of medicines and continuation of LSM were reported to be the major hurdles in long term sustainability of these interventions. Hence, global interest is increasing towards search for safe and effective remedies for preventing progression from prediabetes to diabetes which we believe *Ayurveda* can provide [9].

Various herbs mentioned in the *Ayurveda* literature have been found to be useful for reduction in blood sugar, decrease in insulin resistance, and improvement in beta cell activity [10,11]. Fenugreek seeds have been reported to be associated with lower conversion from prediabetes to DM [12]. Etiology of diabetes is multifactorial and multi targeted herbal drugs would be comparatively safer than modern drugs and may be used in management of prediabetes and prevention of progression to diabetes.

Therefore, this study aimed to see whether a Polyherbal combination for prediabetes (PDBT) along with life style modification can reduce the conversion from prediabetes to type 2 diabetes mellitus compared to placebo along with life style modification.

2. Methodology

This study was a prospective randomized double blinded placebo controlled trial. Participants were enrolled from after ethical approval; at OPD of R.A. Podar Ayurvedic College, Mumbai. India. Participants were recruited through OPD and various camps. They were screened and enrolled after taking consent.

2.1. Polyherbal combination (PDBT)

The polyherbal combination for prediabetes (PDBT) contained aqueous extracts of stem of *Tinospora cordifolia* (Thunb.) Miers, bark of *Pterocarpus marsupium* Roxburgh., leaves of *Gymnema sylvestre* R. Br., rhizome of *Zingiber officinale* Roscoe. *and* fruit of *Momordica charantia* L. in equal proportions. All these drugs have previously been shown to have hypoglycemic properties [10,13–19]. As per the *Ayurvedic* principles they are *Medoghna, Kledghna, Kaphaghna, Pramehghna with Tikta Katu Ras* dominant *and Katu Vipak* dominant with *Ushna Virya* [20,21].

After identification, powdered stem of *T. cordifolia* (Thunb.) (Batch no AHTC 1147/ext 10:1), bark of *P. marsupium* Roxburgh. (Batch no AHPM 1112/ext 15:1), leaves of *Gymnema sylvestrie* R. Br. (Batch no AHGS1127/ext 10:1), rhizome of *Zingiber officinale* Roscoe. (Batch no AHZO1156- 6:1), *and* fruit of *M. charantia* L. (Batch no AHMC1128/ext 10:1) were purchased and sent to Amrita Herbals, Indore for preparation of capsules containing extracts. This combination (PDBT) was initially tested for its safety and hypoglycemic activity and its results are published elsewhere [9].

2.2. Trial participants

Initially persons with presumptive prediabetes or willing for screening were screened on the basis of Indian Diabetes Risk Score (IDRS) [24] and if the score was more than 50 then individuals were asked for fasting blood sugar and oral glucose tolerance test. People with a IDRS score of more than 50 were selected they have been reported to be at a higher risk of progressing to diabetes [22].

2.3. Inclusion and exclusion criteria

People with age 18 years or more, newly diagnosed with prediabetes (fasting blood glucose between 100 and 125 mg/dL and glucose tolerance between 140 and 199 mg/dL), who were able and willing to give informed consent were included in the study.

Exclusion criteria included people currently using oral hypoglycemic agents (OHAs); those reporting prior use of medication to treat diabetes mellitus (except gestational diabetes); those who were diagnosed with DM (Fasting Plasma Glucose (FPG) >/ = 126 mg/dL, Postprandial glucose > 200 mg/dL, HbA1c > 7.0); had abnormal liver function studies; had symptoms of kidney failure (microalbuminuria, serum creatinine > 2.0 mg/dL) or on renal dialysis; reported having received any medications for DM or

prediabetes in the preceding one month; pregnancy or breast-feeding; had previously participated in any studies of investigational drugs within 1 month before this study or patients with any other major illness.

2.4. Sample size

A sample size of 57 was calculated with hypothesis that PDBT + LSM will be 45–50 % better than placebo + LSM (20.5 %) [23] in reducing conversion to type 2 diabetes mellitus, with 95 % confidence interval and power of 80 %, binary end point, keeping continuity correction using the method described by Julious [24]. Randomization was done with lottery method.

2.5. Trial protocol

Participants first underwent general and systemic examinations. Clinical symptoms of prediabetes were assessed and recorded in the case record form (CRF). *Prakruti* was assessed on the basis of a *Prakriti* format by Maharashtra University of Health Sciences, Nashik. Then baseline investigations which included Hemogram, ESR, urine routine and microscopic, HbA1c, fasting serum insulin, liver function tests, renal function tests and lipid profile were done.

Then homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment - beta cells (HOMA-B) was calculated using the formula described by Matthews et al. to assess insulin resistance and beta cell function [25,26].

Participants were then randomized to either PDBT or placebo group by lottery method. Those in PDBT group were given PDBT in a dose of two capsules (500 mg each) twice daily, to be taken orally (after breakfast and before dinner) with lukewarm water for 180 days. The time for when drugs are to be taken was decided based on *Sushrut Samhita*, which states that *Prameha* is caused due to vitiation of *Vyana* and *Apana vayu* [27]. Participants in placebo group were given excipients. All participants were guided to continue with their routine diet whilst excluding direct sugar intake and to undertake moderate physical activity (150 min walking in a week for at least 5 days in a week in equally divided span). One month's stock of trial medicine was provided to every participant at a time.

For follow-up, participants were called to M.A. Podar Hospital, Worli, Mumbai, every month after the baseline visit (i.e. on 30th, 60th, 90th, 120th, 150th and 180th days). On each follow up visit, participants underwent general and systemic examinations followed by clinical symptoms assessment. Fasting and post prandial glucose was done every month. HbA1c was done at baseline and after 180 days. End points for the study were completion of the trial period or conversion to type 2 diabetes mellitus during the trial period. FPG >125 mg/dL, post prandial glucose >200 mg/dL [28].

Tolerability of the PDBT and placebo was assessed by the investigator at the end of the study. All participants were closely monitored for any adverse events/adverse drug reactions. All the investigations performed at the screening visit were done on 180th day of the treatment. Based on the above study procedures, observations were being made and recorded in the CRF for each participant at every follow up. Participants were assessed for improvement in clinical and pathological parameters of prediabetes at the end of the study.

To assess participant characteristics as per Ayurveda, an index was prepared which used *Shithilangta*, (~Laxness of body) *Swedatipravrutti*, (~Excessive Sweating) *Angagandha* (~Excessive body odor), *Shayyasanswapnrati*, (~Desire sit and Sleep), *Pipasavrudhhi*, (~Excessive thurst), *Danatadimaladhyata*, (~Oral Diseases), *Hasta pad daha*, (~Burning in hands and feet), *Ghanagata*, (~Heaviness of body), *Kshudavruddhi*, (~increased eating desire), *Madhurasyata*, (~feeling of sweet taste in mouth), *Mutrlikaepipilika* (~Presence of

sugar in urine) and *Chimchimayan* (~tingling) The score had a range between 0 and 36. Each symptom had a score between 0 and 3. The lower the score, better the clinical parameters.

After the completion of study period, blinding was opened to know which group was placebo and which group was getting PDBT.

2.6. Statistical analysis

Categorical variables among the socio-demographic characteristics of the study participants were described using numbers and proportions, while continuous variables were described using means and standard deviations. Kruskal Wallis H was used to analyze the difference between the groups at the end of the trial. A p-value of 0.05 or below was considered statistically significant. Statistical analysis was done using IBM SPSS V20.

2.7. Ethics

Informed written consent was provided by all participants. The study was approved by the Institutional Ethics Committee, R.A. Podar Ayurved Medical College, Worli, Mumbai (approval number 2314/31-03-2011). The trial was registered with Clinical Trials Registry - India (CTRI/2015/01/005471). Good Clinical Practice guidelines issued by Central Drug Standard Control Organization

and ethical guidelines for Biomedical research on Human subjects, issued by Indian Council of Medical Research were followed.

3. Results

3.1. Study population

Two hundred participants having IDRS more than 50 were screened for assessing eligibility; twenty-six withdrew their consent and were excluded. Forty-four met the exclusion criteria. Among 130 found eligible, 114 participants were randomly selected and equally allocated to intervention and control groups. Participant distribution is shown in the CONSORT flowchart (Fig. 1). Socio-demographic and baseline clinical characteristics of these are described in Table 1. Clinical characteristics at end of trial are described in Table 2.

3.1.1. Baseline characteristics

Overall median age was 48 years (Inter quartile range [IQR] — 43.25—55) and 40.4 % were male. Sixty-six percent had a family history of diabetes. In *Prakriti* analysis, 58 % patients had *Kapha-Pitta Prakriti*, while 38 % participants had *Mandagni*. Baseline fasting glucose was similar between the 2 groups (Table 2). Mean levels of glycated hemoglobin at baseline was 6.4 % (SD — 0.3).
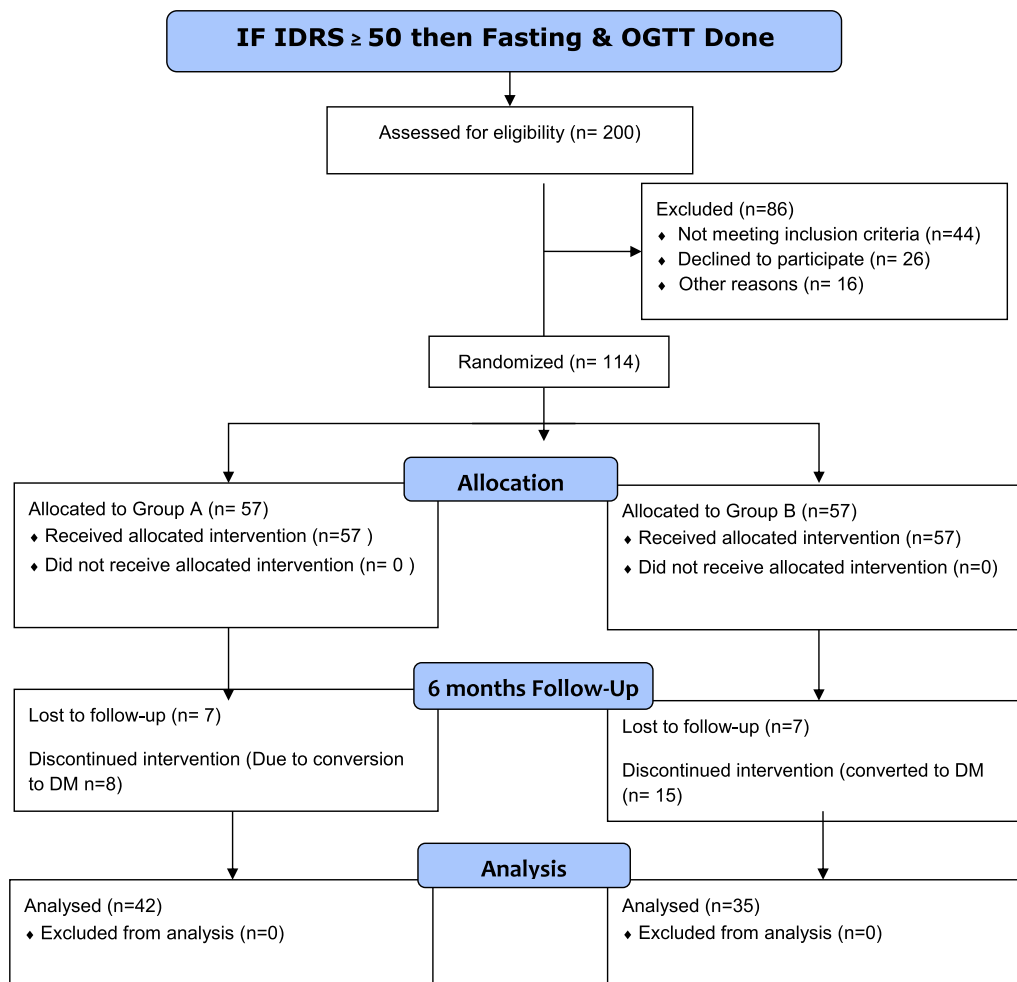

Fig. 1. CONSORT flowchart.

Table 1

Socio-demographic characteristics of pre-diabetic participants on PDBT in Mumbai, India.

Variables	PDBT (n = 57)	Placebo (n = 57)
Median age (IQR)	51 (46–59)	45 (39–52)
Male: Female (%)	19: 38 (37–73)	27-30 (47–53)
Family history of diabetes (%)	44 (77)	31 (54)
Mean Fasting blood glucose (mg/dl) (SD)	107 (13.8)	109.4 (8.8)
Mean glucose tolerance test (SD)	162.7 (24.1)	164.8 (19.1)
Mean HbA1c (SD)	6.5 (0.4)	6.3 (0.2)
Mean fasting serum insulin (μIU/ml) (SD)	19.3 (35.6)	14.1 (4.8)
Mean HOMA-IR (SD)	4.1 (3.7)	3.8 (1.4)
Mean HOMA-B (SD)	201.8 (438.2)	112 (47.1)
Mean BMI (SD)	27.5 (2.9)	29.1 (3.9)
Mean hip to waist circumference (SD)	1.0 (0.03)	0.9 (0.2)
Mean Ayurvedic score (SD)	14.9 (2.5)	12.4 (2.4)
Ayurveda variables		
Prakriti		
Kapha Pitta	29 (51)	37 (65)
Kapha Vata	18 (32)	13 (23)
Pitta Vata	10 (18)	7 (12)
Agni		
Manda	8 (14)	29 (51)
Sama	21 (37)	1 (2)
Tikshna	13 (23)	12 (21)
Vishama	15 (26)	14 (25)
Koshtha		
Krur	18 (32)	24 (42)
Madhya	30 (53)	26 (46)
Mrudu	9 (16)	7 (12)

Seven participants dropped out of the study each from placebo and PDBT groups.

3.2. Effect analysis

Eight participants in the PDBT group converted to diabetes mellitus, while 15 participants from the placebo group converted during the study period. The relative risk of conversion was 0.53 for the intervention group (95 % CI: 0.25–1.14) compared to controls, which is 47 % risk reduction. The median time for conversion to diabetes mellitus was 4 months for placebo while it was 4.5 months for PDBT.

Mean fasting glucose at the end of study period was 90.25 mg/dL (SD: 12) which was a decrease of 15.7 mg/dL in the PDBT group. On the other hand, at the end of study, placebo group had a mean fasting blood glucose of 110.9 mg/dL (SD: 8.24), which is an increase over the baseline. This difference was statistically significant (χ^2 (1) = 30.595, p < 0.001) with mean rank score of 34.46 for PDBT group and 66.54 for placebo group. Monthly follow-up of fasting blood glucose is shown in Table 3, which shows a decreasing trend after 4th month of treatment with PDBT. Difference between

HbA1c, fasting serum insulin and HOMA-IR were also statistically significant and are described in Table 2. There was an increase in HOMA-IR for both the groups. However, the increase in control groups was higher in magnitude than in intervention group.

Ayurveda clinical index showed significant decrease in score at the end of the study in the intervention group while the control group showed an increase in the score, suggesting symptomatic relief in the intervention group.

3.3. Adverse events

No participants reported any adverse events from medicine during the study.

4. Discussion

This study shows that a Polyherbal drug combination (PDBT) along with life style modifications decreased the progress from pre-diabetes to diabetes when compared to placebo with life style modification. Participants in the PDBT group also reported symptomatic relief. A decrease in HOMA-IR and fasting serum insulin was also seen in PDBT group which suggests that a decrease in insulin resistance among the participants. No adverse drug reactions were reported by any of the participants during the entire course of the trial.

The herbal medicines used in this study have previously been studied separately to have been effective as hypoglycemic agents, and decrease insulin resistance. However, we have not found studies which have used a combination of herbal drugs used to impede the progression of pre-diabetes to diabetes. Gaddam et al. have studied the effect of fenugreek as a single herbal drug intervention in prevention of type 2 diabetes mellitus in prediabetes. They report that daily dietary supplementation with 10 gm fenugreek was associated with a lower conversion to diabetes [12]. The study showed an increase in serum insulin levels which resulted in lower blood glucose levels. However, in current study, we see a decrease in blood glucose levels and serum insulin levels, which might suggest a decrease in insulin resistance. Increase in Insulin resistance causes hyperinsulinemia and is the basic cause of early beta cell fatigue and rapid progression to diabetes [29] and hence, PDBT might be more appropriate in halting the progression from pre-diabetes to Diabetes.

LSM has been an important suggestion given to Prediabetic individuals. However, in this trial, we found out that only walking 150 min/week was not sufficient for prevention of DM, especially in the case of a city like Mumbai where persistent pollutants might also be a contributing cause [30].

According to the principles of *Ayurveda*, *Prameha* is one of the *Astamahagada*, i.e. diseases which are difficult to treat [31]. Hence,

Table 2

Baseline and end of trial clinical characteristics of pre-diabetic participants on PDBT in Mumbai, India.

	End of study		p
	Intervention mean (SD) (n = 42)	Control mean (SD) (n = 35)	
Fasting blood glucose (mg/dL)	90.3 (12.0)	110.9 (8.2)	< 0.001
Glucose tolerance test	126.1 (28.4)	184.2 (14.1)	< 0.001
HbA1c	6.2 (0.9)	6.8 (0.6)	< 0.001
Fasting serum insulin (μIU/mL)	15.5 (20.3)	17.1 (6.9)	< 0.001
HOMA-IR	4.9 (10.1)	4.97 (2.5)	< 0.001
HOMA-B	181.8 (452.2)	108.2 (53.0)	0.537
BMI	29.0 (3.7)	27.5 (2.9)	0.1
Hip to waist circumference	1.0 (0.02)	0.8 (0.1)	< 0.001
Ayurvedic score	8.3 (4.6)	16.0 (3.0)	< 0.001

Table 3
Baseline and monthly blood glucose (in mg/dL) follow-up of pre-diabetic participants on PDBT in Mumbai, India.

	Follow-up period	Baseline	1 month	2 months	3 months	4 months	5 months	6 months
Intervention	Fasting	106.0 ± 14.0	99.2 ± 11.3	100.2 ± 10.4	97.5 ± 13.5	93.9 ± 14.8	95.1 ± 11.7	90.3 ± 12.0
	Post Prandial	166.1 ± 22.7	145.5 ± 14.6	139.5 ± 24.8	133.9 ± 27.1	130.8 ± 26.0	133.2 ± 27. 2	123.2 ± 22.1
Control	Fasting	105.8 ± 8.1	107.1 ± 7.9	108.0 ± 8.1	107.8 ± 8.7	109.2 ± 8.1	110.5 ± 7.6	110.9 ± 8.3
	Post Parandial	159.5 ± 15.9	160.3 ± 13.6	162.2 ± 13.7	165.6 ± 12.8	167.3 ± 14.3	167.3 ± 18.1	172.1 ± 14.8

it has been suggested that the disease may be treated in its *Purvarupawastha* [32]. Hence, treating at prediabetes stage, which may be considered as the *Purvarupawastha*, will be more beneficial and PDBT is seen to be effective in doing this.

We believe this is the first study to use a polyherbal combination to decrease conversion from prediabetes to diabetes with no reported adverse events. The polyherbal combination (PDBT) used in this study has also shown positive effects on lipid profile which has been described elsewhere [9]. However, the study has some limitations, which include a small sample size, which precluded us from undertaking multivariate modeling. The timeframe with this study was conducted was also a limitation and studies with a longer duration using PDBT should be undertaken to study the long term effects of the combination on progression from prediabetes to diabetes. Another limitation was the inability to use newer markers such as C reactive proteins and serum adiponectin owing to cost restrictions.

This study shows that a Polyherbal combination (PDBT) using stem of *T. cordifolia* (Thunb.) Miers, bark of *P. marsupium* Roxburgh., leaves of *G. sylvestre* R. Br., rhizome of *Zingiber officinale* Roscoe. *and* fruit of *M. charantia* L. along with Life Style Management can be used to decrease the conversion from pre-diabetes to type 2 diabetes mellitus. The use of this PDBT along with life style modification was seen to be more effective than only life style modification to decrease the number of patients being converted to diabetes. Along with hypoglycemic effects, PDBT is also seen to decrease hyperlipidemia. Long term clinical study using this PDBT would provide us with more evidence regarding efficacy of this combination.

5. Conclusion

Polyherbal formulation, PDBT, was seen to be effective and safe method for management of pre-diabetes and reduce conversion to type 2 diabetes mellitus by positively altering blood glucose levels, serum insulin and lipid profiles. *Ayurveda* parameters like *Agni*, *Aahar*, *Nidra* in short *Dincharya* also plays very important role in conversion from prediabetes to diabetes and proper recording of these parameters is also necessary.

Conflict of interest

None.

Source of funding

None.

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