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KEY WORDS: Pre-Diabetes, Mother tincture, Homoeopathy, Randomized trial

AN OPEN RANDOMIZED TRIAL IN PRE-DIABETES EVALUATING EFFECTIVENESS OF ADD-ON PLANT EXTRACTS USED IN HOMEOPATHY AS MOTHER TINCTURES: A RESEARCH PROTOCOL

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ABSTRACT

Background: Pre-diabetes can be termed as at risk of developing diabetes. Targeting pre-diabetes in the population may be considered as having immense value in preventing much adversity of diabetes. Keeping this in mind we intend to evaluate the effectiveness of add-on plant extracts used in homeopathy as mother tinctures in pre-diabetes.

Methods/Designs: In this open randomized trial evaluating effectiveness of add-on plant extracts used in homeopathy as mother tinctures on patients diagnosed with pre-diabetes will be randomized in 1:1 ratio to one of the two interventions- Individualized homoeopathy or mother tincture as an add-on to Individualized homoeopathy. The outcome measure are being used in this study, Fasting Blood Sugar (FBS), Post-Prandial Blood Sugar (PPBS), Glycated Haemoglobin (HbA1C) as primary and Revised Diabetes Symptom Checklist (DSC-R) as secondary, will be taken at baseline, after 3 months and 6 months. Trial will require 140 patients, keeping in mind 90% power, level of significance at 0.05 and 5% drop-out. All the collected data will be analysed on intention to treat approach following CONSORT guidelines.

Discussion: This trial will evaluate the effectiveness data of add-on mother tincture therapy to individualized homoeopathy. Trial registration: CTRI/2018/08/015319

INTRODUCTION:

Type 2 diabetes mellitus (DM2) is one of the most costly diseases due to the size of the population at risk and the fact that diabetes is a risk factor for almost all other chronic diseases [1]. Globally, about 382 million individuals are diagnosed with DM, and this number will increase to over 430 million by 2030 [2]. It is expected that the burden of disease will increase primarily in developing countries [3]. Studies have reported higher diabetes prevalence in Asians, Africans and their descendants compared to whites [4]. Over a 10-year period, the estimated risk to progress from pre-diabetes to diabetes was 50% [5]. It is associated with the simultaneous presence of insulin resistance and β-cell dysfunction-abnormalities that start before detectable glucose changes. A handful of studies have shown that a quarter of those with confirmed pre-DM will develop diabetes within 3 to 5 years of detection [6]. Observational evidence suggests that there is an association between confirmed pre-DM and complications of diabetes such as early nephropathy, small fibre neuropathy, early retinopathy, and risk of macrovascular disease [7]. Recent Indian studies reported one of the highest global rates of pre-diabetes progression to DM2, ranging between 71.52 and 78.9 per 1000 persons year [8-10]. In terms of annualized incidence rates, these translate to 15-19% annual risk of progression to DM2, which is much higher than 2.5% observed in the Diabetes Prevention Program (DPP) study [11]. This may be reflective perhaps of a more aggressive diabetes pathophysiology, where progression to DM2 from pre-diabetes is just a matter of time. Lifestyle intervention is the first line intervention and should be aggressively implemented in individuals with pre-diabetes. But implementing lifestyle intervention has been challenge across the globe, has poor long term compliance, and involves extensive use of human resources. These challenges are perhaps far greater in countries with limited population awareness like India. Hence, use of metformin in pre-diabetics for DM2 prevention has been proposed, especially in high-risk ethnic groups like Asian Indians with multiple risk factors, till better alternatives are made available in future. Additional use of metformin is proposed to be encouraged in the subset of pre-diabetics with multiple risk factors, e.g. presence of strong family history of DM2, central obesity, history of gestational diabetes; occurrence of both impaired fasting glucose and impaired glucose tolerance [12].

Individuals with diabetes are 1.6 times more likely to use complementary and alternative medicine (CAM) including homeopathy than individuals without diabetes [13, 14]. A large variety of interventions have been tried for prevention of DM2 in pre-diabetes, both in human trials and experimental rat models – e.g. curcumin [15], mulberry leaf extract [16], aloe vera [17], almonds [18], black chokeberry fruit extract [19], Jiangtang Xiaozhi [20] and Qiyao Xiaoke Capsule [21] (Chinese herbal formula), Vitis vinifera grape seed extract [22], herbal food supplements (Emblica officinalis or gooseberry, fenugreek, green tea, Momordica charantia or bitter melon, and cinnamon) [23], Propolis glandulosa (Honey mesquite tree) [24], enhanced physical activity [25], and community-based yoga intervention [26]. However, their use in clinical practice has been limited by lack of concrete clinical evidence. Positive outcomes have been observed only in small specific subset of individuals with pre-diabetes, often with significant adverse effects, evaluated in small ethnic groups or have suffered from lack of adequate reproducibility of observations in different populations.

Background and justification: After extensive searches into different electronic and bibliographic databases and hand searches in hard copies up to 2016, different journal research papers and conference proceedings were identified regarding homeopathic treatment of diabetes. Majority of the

research database was contributed by Central Council for Research in Homoeopathy (CCRH). In an open, observational, non-randomized trial conducted by CCRH on 2325 patients of DM, no conclusive result was obtained; only in 201/2325 cases, treatment was assessed as effective [27]. In another parallel arm trial of CCRH, efficacy of add-on Cephalandra indica mother tincture to standard therapy was tested in DM; however, the study remained under-reported [28]. Following this, role of Cephalandra indica mother tincture as an add-on medicine along with conventional anti-diabetics was further evaluated by CCRH in the management of DM with promising outcomes [29]. Homeopathy was found to be useful in management of diabetic foot ulcer in yet another observational study by CCRH [30] and one case report [31]. Few more papers were also traced mentioning about few lesser known homeopathic drugs in successful treatment of DM, including Cephalandra indica and Rhus aromaticus [32-35]. A randomized double-blind placebo-controlled clinical trial testing efficacy of homeopathic treatment for diabetic distal symmetric polyneuropathy is ongoing by CCRH [36]. In a recent retrospective cohort study in Hong Kong on 27 adults suffering from DM2 with 40 patients under standard conventional treatment as control, add-on individualized homeopathic treatment for 1 year was associated with better glycaemic control in terms of fasting plasma glucose and glycated hemoglobin compared with standard conventional treatment alone [37]. In a multicentric parallel arm but relatively under-reported trial of homeopathic complex R40, it was found superior to placebo [38]. In a non-randomized, observational study on 41 patients suffering from DM2, Gymnema sylvestre and Cephalandra indica mother tincture was used. Treatment had a significant effect in patients with very high blood glucose levels only [39]. In a single blind, randomized, parallel arm, placebo-controlled trial, efficacy of individualized homeopathy was tested on 78 patients suffering from DM. Mean HbA1c decreased 6.1% in homeopathy patients and 0.5% in placebo patients [40]. In another double blind, parallel arm, placebo-controlled trial, efficacy of Selenium C7 was tested on 27 diabetic patients. Selenium C7 did not reduce the production of free radicals; but decrease in albumin concentration, uric acid, ferritin and HbA1c could be demonstrated [41]. In experimental male albino rat models also, promising hypoglycemic effects of Cephalandra indica and Syzygium jambolanum were elicited [42, 43].

Homeopathic clinical research evidence in pre-diabetes remains seriously compromised in spite of ever-growing basic/experimental researches in DM. With an aim to explore this relatively under-researched area, the investigators intends to uptake an efficacy trial of most frequently used add-on plant extracts used in homeopathy as mother tinctures in treatment of pre-diabetes.

METHOD/DESIGN:

Study Design: Open, prospective, randomized, two parallel arm, clinical trial with 6 months duration for each patient.

Trial registration: The trial is registered in Clinical Trial Regestry- India (CTRI) having reg. no. CTRI/2018/08/015319

Study setting: Out-patients of Mahesh Bhattacharyya Homoeopathic Medical College &Hospital

Selection of Samples: Samples will be selected as per below mentioned eligibility criteria from the patients visiting the outpatient departments of the said institutions. Absence of any relevant paper reporting mean and standard deviation of pre-diabetic population of India or West Bengal and further absence of any paper reporting effect size (standardized difference) of homeopathy treatment in pre-diabetes hindered formal sample size calculation. Hence, keeping α (type I error) 0.05, power $(1 - \beta)$ 90%, approximate relative sample size becomes 134 (IH: 67; IH+MT: 67) [46]. Accounting for assumed 5% drop-outs, target sample size becomes 140 (IH: 70; IH+MT: 70).

Inclusion Criteria:

1. Age above 35 yrs
2. Both sexes
3. Indian diabetic risk score (IDRS) ≥ 60 [47]
4. Impaired glucose regulation [48]; i.e. Fasting plasma glucose concentration of 100-125 mg/dL (impaired fasting glucose; IFG); and 2 hrs. post 75 gm glucose load plasma glucose value of 140-199 mg/dL (impaired glucose tolerance; IGT)
5. Voluntary written consent to participate

Exclusion Criteria:

1. Unwilling to take part in the study
2. Cases with other systemic unevaluated or uncontrolled diseases or systemic infections affecting quality of life or on other treatment therapies
3. Psychiatric illness
4. Patients with any vital organ failure
5. History of homeopathic treatment for any chronic disease within last 6 months
6. Self-reported immune-compromised states
7. Alcohol and /or drug addiction or dependence
8. Pregnancy and lactation

Randomization: Computer generated random number list [Appendix 10] was used to generate random sequence. The list was generated using restricted 14 blocks of size 10 (14x10 = 140) to maintain equal distribution between groups and 1:1 ratio easily; i.e. Individualized Homoeopathy, IH: 70 and Individualized Homoeopathy +Mother tincture, IH+MT: 70.

Intervention:

I. All medicines and vehicles in this project will be procured from GMP certified firm. All the patients will be treated with individualized homoeopathic medicines in both centesimal and 50 millesimal potencies as per need of the case. In centesimal potencies, each dose shall consist of 4 cane sugar globules medicated with a single drop of the indicated medicine, preserved in 88% v/v ethanol. In 50 millesimal potencies, a single medicated cane sugar globules of poppy seed size (no. 10) shall be dissolved in 50 ml distilled water with addition of 2 drops of 88% v/v ethanol, 10 doses marked on the vial, each dose of 5 ml to be taken after 10 uniformly forceful downward strokes to the vial in 45 ml normal water in a clean cup, to stir well, to take 5 ml of this liquid orally, and to discard rest of the liquid in the cup. Repetition 24, 12 or 8 hourly or even oftener, depending upon the individual requirement of the case.

II. Among different plant extracts used as mother tinctures in homeopathy, Cephalandra indica, Gymnema sylvestre, and Syzygium jambolanum are the most frequently used as per their indications as mentioned in Boericke's Materia Medica. These 3 medicines will be used as add-on to individualized homeopathic medicines in empirical dosage – 10 drops in ½ cup of water twice daily after meals.

III. Irrespective of the groups, all the patients will be advised to take low calorie and high fibre diet, do regular physical exercise for at least 30 minutes, and to avoid physical and mental stress.

Brief of procedure: Patients suffering from pre-diabetes will undergo phase I preliminary screening using IDRS. Patients

scoring ≥60 will proceed to phase II preliminary screening, i.e. blood sugar testing. Following that, the patients will go through detailed screening as per the mentioned inclusion and exclusion criteria. The eligible participants will be recruited in the trial. Baseline investigations will be performed. After that, the patients will be randomized, either to individualized homeopathy (IH) treatment or individualized homeopathy plus mother tincture (IH+MT), as per computer generated random number list. The randomization chart will be made available to the prescribing doctors and pharmacists. Outcomes will be measured at baseline, after 3 months and after 6 months. Follow-up will be given every month or as and when necessary. All the data will be recorded in specially designed data collection forms.

Outcome assessment:

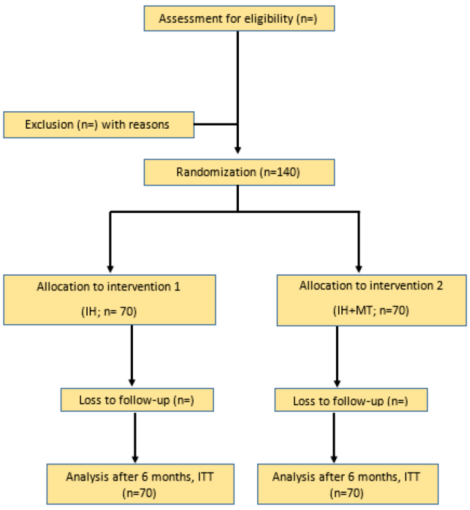
i. Primary – Fasting plasma glucose (FBG), 2 hrs. post 75 gm glucose load plasma glucose(PPBG), blood glycosylated haemoglobin % (HbA_{1C});
ii. Secondary – Revised Diabetes Symptom Checklist (DSC-R) [49]

All the outcome measures will be taken at baseline, after 3 months and 6 months. A specially designed Microsoft MS Office Excel 2007 spread sheet (master chart) will be used for data extraction and shall be subjected to statistical analysis.

Statistical techniques and data analysis: All the collected data in the standardized format will be subjected to data extraction in a specially designed excel spreadsheet. That will be subjected to statistical analysis – both descriptive and inferential. Intention-to-treat (ITT) population will be analyzed in the end. Missing values will be calculated using last value carried forward (LVCF) method. Data distribution will be examined using skewness, kurtosis, and Kolmogorov-Smirnov test. Descriptive statistics will be presented in terms of absolute values, percentages, mean, standard deviations, 95% confidence intervals, median, inter-quartile ranges etc., as appropriate. Parametric or non-parametric tests will be used as inferential statistics as per normality or non-normality of data distribution respectively. The groups will be checked for comparability of socio-demographic characteristics at baseline using independent t test (for continuous normal data) or Wilcoxon rank sum (Mann Whitney) test (for for continuous non-normal data) or chi-square or Fisher exact test (for categorical data). Baseline differences, if any, will be adjusted using analysis of covariance (ANCOVA) models. Changes in categorical outcome between groups will be compared using chi-square or Fisher's exact test. Dependent observations of continuous outcomes at baseline and at different points of time will be compared using paired t test or Wilcoxon signed rank test. For continuous data, changes in outcomes obtained longitudinally at different points of time will be tested using post hoc repeated measure analysis of variance (ANOVA) or Friedman test, as appropriate. Bonferroni-Holm correction will be used to adjust for multiple testing. P values will be set at less than 0.05 two-tailed as statistically significant.

Ethical issues: Ethical clearance will be obtained from the institution prior initiation of the study. Neither any new drug is being investigated nor is any placebo control arm being used. Patients will be provided information sheet in local language and written informed consent will be obtained subsequently. Confidentiality of the individual patients will be maintained throughout. Even when the paper is published, no patient can be recognized by name. Adverse event(s), if any, will be managed by appropriate homeopathic medicines or proper referral, as appropriate, irrespective of the code allocated. The study will be registered prospectively in international trial registers.

Study flow diagram:



DISCUSSION &CONCLUSION:

Diabetes is going to be a pandemic in few years and keeping in mind the disease burden and complications it's better to prevent in pre-stage. Rigorous researches are definitely needed in multispectral field to find a way out of it. Although homoeopathy is long been in controversy for its therapeutic efficacy. Despite this, patients are being treated with Individualized homoeopathic treatment (IH) which is very much patient centred. But whether this Individualized treatment along with plant extract processed in certain way, called mother tincture(MT) is more or less effective than only IH therapy is the matter of question. May be this study will have a significant impact because no amount of research or trial have taken place till now on this concerned topic. And for future therapy it can contribute the seed of evidence based thought.

The protocol is based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [50] and TIDieR (Template for Intervention Description and Replication) checklist [51]. Reporting of the study results will adhere to the RedHot (homoeopathy specific CONSORT) statement [52] and model validity of homoeopathic treatment (MVHT)[53] specific for homoeopathicity of a trial.

We have planned to publish the results in Peer-reviewed and indexed journal and other scientific meetings.

Trial status: The trial was started in Aug 2018 and presently going on; intended to complete it by 2020.

Conflict of Interest: There is no conflict of interest.

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