

**IMPAIRED GLUCOSE INTOLERANCE AND PREVENTION OF
DIABETES MELLITUS TYPE 2 BY POLYHERBAL FORMULATION OF
EASTERN MEDICINE**

Official Title: Impaired Glucose Tolerance and prevention of diabetes mellitus type 2 by polyherbal formulation of Eastern Medicine

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Responsible Party: Principal Investigator

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IMPAIRED GLUCOSE INTOLERANCE AND PREVENTION OF DIABETES MELLITUS TYPE 2 BY POLYHERBAL FORMULATION OF EASTERN MEDICINE

Title: Impaired glucose tolerance and prevention of type 2 diabetes mellitus by polyherbal formulation of Eastern Medicine.

Target population: Model Town A, B of Bahawalpur, City area Khairpur Tamewali

Introduction

Diabetes mellitus is a severe concern of mankind in the recent years and is a global health situation irrespective of the socioeconomic profile and geographic location of the population. A variety of statistics across the globe has been clearly representing that diabetes mellitus has attained a pandemic form(1). World Health Organization (WHO) has indicated that more than 80% of the diabetes deaths occur in low and middle revenue countries. It has also been expected that diabetes will be the seventh important cause of death in 2030(2). According to International Diabetic Foundation (IDF), throughout 2012, more than 371 million people suffer from diabetes. The number of people with diabetes is rising in every country and about 4.8 million citizens die every year. More than 471 billion USD were used up on healthcare for diabetes (3). The increase in type 2 diabetes is related to lifestyle changes that have resulted in overweight, obesity, and decreased physical activity levels. These environmental changes, superimposed on genetic predisposition, increase insulin resistance, which, in concert with progressive- β -cell failure, results in rising glycemia in the nondiabetic range. In addition to the risk for diabetes, insulin resistance and impaired insulin secretion are accompanied by a host of major cardiovascular disease (CVD) risk factors including hypertension and dyslipidemia. Further reduction in insulin secretion over time results in increasing glycemia and the development of diabetes, which in turn is associated with the development of microvascular and cardiovascular complications.

In the last few years, there has been an exponential increase in the field of herbal medicinal study which is ahead of popularity both in the developing and developed countries for the reason of their natural origin and less side effects (4). Despite extensive progress in the treatment of diabetes by oral hypoglycemic agents, the exploration for newer drugs continues because of the several restrictions found in the usage of synthetic drugs. Medicinal plants supply a potential source of hypoglycemic drugs possessing the dynamic compounds which have been used in the treatment of diabetes and they are highly praised for their therapeutic properties in the traditional medicine system(5).

Diabetes prevention

The transition from the early metabolic abnormalities that precede diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years; however, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes (6-7). During the pre-diabetic state, the risk of a CVD event is modestly increased (8-11). With the development of diabetes, however, there is a large increase in risk for CVD, as well as for long-term complications affecting the eyes, kidneys, and nervous system. The complications of diabetes, which are the cause of major morbidity and mortality, are related to its duration, chronic level of glycemia, and other risk factors. Although clinical trials have demonstrated the effectiveness of intensive glycemic and blood pressure control to reduce the long-term complications of diabetes. The public health burden of the disease remains enormous. The magnitude of the epidemic, coupled with complex treatment requirements that are difficult and costly to implement, make the prevention of diabetes a critical public health goal. (12) Between 1997 and 2006, eight major clinical trials examined whether lifestyle or pharmacologic interventions would prevent or delay the development of diabetes in populations at high risk by virtue of having IFG and/or IGT(13-15)

Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT)

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. IFG is now defined by an elevated fasting plasma glucose (FPG) concentration (≥ 100 and < 126 mg/dl) (29). IGT is defined by an elevated 2-h plasma glucose concentration (≥ 140 and < 200 mg/dl) after a 5-g glucose load on the oral glucose tolerance test (OGTT) in the presence of an FPG concentration < 126 mg/dl. (16-17)

Objectives:

1. To assess Glucose Intolerance in the targeted population
2. To assess the screened population for prevention of Diabetes Mellitus Type 2.
3. To assess / screened pre-diabetics and potential benefits attained by the polyherbal / test formulation in Pre-diabetics and diabetics.
4. To evaluate the safety profile for use of polyherbal formulation by assessing the effect on various blood markers and to assess its acceptability to proceed for further progress to develop preventive phytotherapy (test).
5. To evaluate the preventive efficacy of polyherbal formulation(test) by assessing the effect on Glucose intolerance.
6. To evaluate effect of polyherbal formulation (test) on the insulin.

7. To evaluate the potential preventive effect of polyherbal formulation for developing a preventive strategy for prevention of DM.

Material and Method:

Chemicals:

Liver function test kit

Renal function test kit

Lipid profile kit

Insulin kit

Glucose Reagent Kit

Glucose (pharmaceutical grade)

Polyherbal formulation:

In the last few years, there has been an exponential increase in the field of herbal medicinal study which is ahead of popularity both in the developing and developed countries for the reason of their natural origin and less side effects (4).

Despite extensive progress in the treatment of diabetes by oral hypoglycemic agents, the exploration for newer drugs continues because of the several restrictions found in the usage of synthetic drugs. Medicinal plants supply a potential source of hypoglycemic drugs possessing the dynamic compounds which have been used in the treatment of diabetes and they are highly praised for their therapeutic properties in the traditional medicine system.(5) Polyherbal formulation of Eastern Medicine used in this research is popularly utilized in traditional medicine in various countries to control and treat diabetes. These herbs are used extensively. Four important herbs among these are selected for the preventive effect of these products. These includes Colosynth seed, Occimum tenuiflorum seed, Holarrhena antidysenterica seeds, Gymnemia Sylvester leaves. These herbs have proved to produce anti-diabetic effect by modulating beta-cell in pancreatic islet cell, enhanced insulin secretion, hypoglycemic, anti-hyperlipidemic, anti-Cholesterolic effects on CVS and diabetes. (18-21)

Study Design:

Three arm parallel Observational Cross-Sectional and Case-Crossover clinical trial (Phase 1)

Groups:

Groups and Interventions

| Groups/Cohorts | Interventions |
|--|--|
| Group A Pre-diabetic placebo Group of pre-diabetics receiving placebo BD for six weeks | |
| Group B Pre-diabetic test Group of Pre-diabetic receiving polyherbal / test candidate 900mg in two divided doses for six weeks | Dietary Supplement: Polyherbal formulation Test candidate will be administered per oral before / with meal in two divided doses |
| Group C Diabetic test Early onset of Diabetes mellitus receiving polyherbal formulation 1800mg in two divided doses for six weeks | Dietary Supplement: Polyherbal formulation Test candidate will be administered per oral before / with meal in two divided doses |

Study Description:

Brief description:

Primary protocol to this study is to develop a natural remedy to prevent diabetes mellitus in pre-diabetic state and elaborate the effectiveness of polyherbal formulation for carrying out Phase-II, III and IV. It also aimed at to see the level of difference of glucose tolerance and impaired fasting glucose and impaired glucose tolerance between pre-diabetic and diabetic to evaluate the potential benefit for treatment of insulin resistance and sensitivity. To see the for prevention of Diabetes Mellitus (DM) and stopping / delaying the onset of DM.

Detailed description:

This study is a clinical trial study to evaluate the potential of prevention in pre-diabetics and to prevent onset of diabetes mellitus. For this purpose, volunteers will be enrolled in the study by observing the Helsinki Declaration for clinical trials.

volunteers will be screened for the impaired glucose tolerance or impaired fasting glucose or at risk to develop diabetes mellitus type 2.

On screening, pre-diabetics and early onset diabetics with no previous history of treatment etc will be grouped into A and B.

Biochemical evaluations will be carried out at base line and followed by three weeks intervention and evaluation of biomarkers and at sixth week for further evaluation.

Collected data will be evaluated for primary out comes and secondary out come. statistical analysis will be done.

Method:

Step 1: Consent, observation of Ethical Principles of Declaration of Helsinki, questionnaire and screening of targeted population for impaired fasting glucose (IFG) and impaired glucose tolerance(IGT), (16-17)

State FPG Level 2-h plasma glucose

In OGTT (mg/dl)

Impaired Fasting Glucose = 100-125 <200

Isolated IFG = 100-125 <140

Impaired Glucose Tolerance = <126 140-199

Isolated IGT = <100 140-199

Step 2: Individuals with IFG & IGT evaluated for age, family history of diabetes in first degree relation, BMI = 35 kg/m³ will be evaluated for following profiles on two week basis with baseline

1. Lipid profile for elevated triglycerides, low HDL, Cholesterol
2. Hepatic functions: SGPT, SGOT, ALT,
3. Renal Function test for Creatinine, Urea
4. Insulin level

Step 3: At high risk population with impaired FG & IGT and underlying or corresponding diseases ,(8-11) population will be given oral polyherbal formulation of Eastern Medicine for six weeks.

Step 4: data collected and interpreted with statistical significance

Eligibility Criteria:

| | |
|-----------------------------|---|
| Study Population: | <ul style="list-style-type: none">• community samples will be obtained from the area of Bahawalpur• Model Town A, B, and• remote areas of district Bahawalpur consisting of Khairpur Tamewali city population |
| Sampling Method: | Probability Sample |
| Minimum Age: | 18 Years |
| Maximum Age: | 59 Years |
| Sex: | All |
| Gender Based: | No |
| Accepts Healthy Volunteers: | Yes |
| Criteria: | Inclusion Criteria: <ul style="list-style-type: none">• Age: 18-59• Impaired Fasting Glucose (100-125mg/dl) |

- Impaired Glucose Tolerance (140-199mg/dl) 2h-75gm OGTT
- History of Diabetes in first degree relation with one condition
- At high risk with BMI > 35%
- Early onset diabetic / accidental on screening (glucose >200mg/dl)

Exclusion Criteria:

- on renal dialysis;
- an acute or terminal illness or serious mental illness;
- history of recent coronary event within the last 12 months;
- a recent history of acute medical problem or admission to hospital;
- any other severe medical conditions that need intervention / treatment
- has poor short-term prognosis (expected death in <2 years);
- is planning to travel for longer than 6 weeks during the 6-week intervention period; or
- is with compromised liver / kidney / cardiac function
- older patients of DM taking any form of medication / intervention

Out Comes:

Study outcomes will be measured by various biomarkers and beneficial effects / toxic effect will be assessed by certain blood biomarkers as followed.

Primary outcomes:

1. Enhancement of Glucose Tolerance
2. Enhancement of Impaired Fasting Glucose Tolerance
3. HbA1c level of reduction

Secondary Outcomes:

1. Lipid Profile including
 - a. Level of Cholesterol
 - b. Triglycerrhides
 - c. Low density lipid (LDL)
 - d. High density lipid (HDL)

Unspecified Outcomes:

1. Liver Function
 - a. Serum Glutamate Oxaloacetate Transaminase (SGOT) level
 - b. Serum Glutamate Pyruvate Transaminase (SGPT) level
 - c. Alkaline Phosphatase level

2. Kidney Function
 - a. Serum Creatinine level
 - b. Blood Urea Nitrogen level

Noting of Adverse events:

Any adverse event /effect observed during study will be categorized by the version of Medical Dictionary for Regulatory Activities.

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Machines :

Centrifuge,
Microlab,
Chemistry Analyser
Weighing machine

Analysis: Statistical Analysis

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