EFFECTS OF ORAL SUPPLEMENTATION WITH CURCUMIN ON THE INSULIN SENSITIVITY IN SUBJECTS WITH PREDIABETES.

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Effects of oral supplementation with curcumin on the insulin sensitivity in subjects with prediabetes.

1. Background

The diabetes mellitus has grown to epidemic ranges, it is estimated that 425 million people live with diabetes around the world(1). In Mexico, diabetes mellitus type 2 (DM2) has a prevalence of 14.4%, which means that from the 112 millions of Mexicans, according to the last population census, more than 16 million are affected by the disease and half of them do not know it (2). Nonetheless improvements in treatment, DM2 is the main cause of blindness, terminal kidney disease, debilitating neuropathies, members amputation, myocardial infarction and embolisms (3). This generates a very important economic burden, besides the social charge associated to the pathologies generated by this disease. It is important to notice that the clinical definition of diabetes makes reference to a late relative state in the process of the disease. Significant defects in the glucose homeostasis and in the energy metabolism can be detected long time before the diabetes take place (4).

The above leads to the exhaustive search of prevention strategies to reduce the DM2 incidence, as it is an incurable disease. Being able to limit the number of new cases that develop diabetes would be an excellent measure to reduce its incidence.

One of the recommended strategies in recent years is the timely identification of prediabetes and the establishment of an effective treatment to prevent diabetes or comorbidities from progressing (5).

Prediabetes, risk factor for the development of type 2 diabetes mellitus

The term prediabetes is used for people with impaired fasting glucose and glucose intolerance. According to the American Diabetes Association (ADA), prediabetes is diagnosed under the following criteria (3):

a) Fasting serum glucose: 100-125 mg/dL

b) Glycosylated hemoglobin (HbA1c): 5.7-6.4%

c) Post-prandial glucose: 140-199 mg/dL after 2 hours of an oral load of 75 g of glucose.

The therapeutic strategies for prediabetes to this day are based on the change of habits, mainly food and exercise plans. It has been advice, in specific circumstances, to grant a pharmacological regimen. Studies sustain that the execution of a restrictive plan of exercise and food quality reduces the risk of DM2 between 40 al 70%, regardless of age, sex and racial condition (6). Pharmacotherapy (metformin and pioglitazone, mainly) is reserved for the treatment of patients with prediabetes who meet the following conditions: Body mass index > 35 kg/m^2, Women with previous gestational diabetes and patients under 60 years of age that meet any of the previous criteria (7). Pharmacotherapy represent a higher cost for the health sector, patients usually leave treatment due to secondary reactions and poor clinical management of doses (8, 9). The approach now is to identify new effective

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therapeutic agents, with a relatively low cost and toxicity, that can be used regularly to control DM2 progression in the pre-diabetic population.

Sensitivity and insulin resistance.

Insulin resistance is the initial characteristic of metabolic alterations, that lead to the development of prediabetes and type 2 diabetes mellitus.
The hyperinsulinemic euglycemic clamp technique (clamp) is the gold standard for measuring insulin resistance. However, it is only used in the field of scientific research due to its complexity, probable adverse effects and economic cost.
Among the indirect methods, most commonly used to measure insulin resistance, is the homeostatic model assessment of insulin resistance (HOMA-IR), which is derived from a mathematical evaluation, and is used to generate an estimate of insulin sensitivity through the measurement of fasting plasma glucose and insulin levels. (10). The correlation between the estimates of IR derived from HOMA and the euglycemic impingement is described in different studies (Rs 0,88, P <0,0001(10); Rs 0,85, P < 0,0001(11)).
The equation is simplified to:

HOMA-IR: (FPI)(FPG) /405

Where FPI is the fasting plasma insulin concentration (mU/l) and FPG is the fasting plasma glucose concentration (mmol / l)(10).

Other indirect methods for measuring insulin resistance use data derived from the oral glucose tolerance curve, which is a simple, non-invasive, physiological and inexpensive test, widely used in clinical practice to diagnose intolerance and diabetes mellitus type 2, as well as in the determination of insulin sensitivity in epidemiological, population and large-scale intervention studies. After a night of fasting, a 75g load of oral glucose is administered and the basal glucose and insulin concentrations are determined at 30, 60 and 120 minutes after the dose is applied. Derived from this information, various indices have been developed, among them the Matsuda index (12). Insulin sensitivity derived from these formulas correlates well with hyperinsulinemic euglycemic clamping.

Oral supplementation with Curcumin.

Curcumin or Curcuma Longa ((1E,6E)21,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is the main ingredient of the Hindu condiment, Turmeric, which is obtained from the Rhizome plant. In new studies, it has been documented that the oral consumption of curcumin (Curcuma longa) in pre-diabetic and diabetic patients has a positive effect as an antidiabetic agent thanks to its anti-inflammatory, antioxidant, antithrombotic, cardio and neuroprotective effects (13-15). In animal models, it has been shown that oral curcumin consumption is capable of increasing insulin sensitivity in liver, muscle and adipose tissue (16-18), increases glucose uptake in muscle (17) and insulin secretion (19,20), which is reflected in the reduction of hyperglycemia, glycosylated hemoglobin, decrease of the homeostatic model assessment of insulin resistance (HOMA-IR) and decrease of serum lipids (21). Many of these actions are performed by turning on the endogenous antioxidant battery and decreasing the pro-inflammatory proteins, thanks to its ability to modulate protein homeostasis.

In a variety of studies (in vitro, in vivo, or clinical) have been described for curcumin anti-inflammatory, antioxidant, anti-carcinogenic (22), anti-infective, neuroprotective and cardio protective properties. Recently, curcumin activity has been described as a regulator of homeostatic proteins that may have profound implications in the control of multiple molecular mechanisms involved in the prevention and/or pathophysiology of multiple chronic degenerative diseases and some types of cancer (23), Parkinson´s disease, Alzheimer´s disease, Huntington´s disease, depression, arthritis, cardiovascular disease, pancreatitis and those related to insulin resistance.

Regarding its anti-carcinogenic potential, some clinical trials have been described in humans and mice for multiple types of cancer, the most significant being stomach, skin, duodenum, breast and colon. Finding a decrease in the tumor induced expression through the diminish of molecules such as cytochrome b5, cytochrome P 450 and the raise of glutathione and the activity of glutathione S-transferase (24).

Curcumin has been included in the oriental diet since ancient times and is used in traditional medicine, which is why it is considered safe, since its consumption is approved by the FDA (Federal Drugs Administration). A 12g per day dose has shown no side effects in humans (25). Therefore, it is proposed that the consumption of curcumin in pre-diabetic patients can improve glucose tolerance and decrease insulin resistance parameters.

Multiple clinical trials have been conducted using curcumin in humans, specifically with population with similar characteristics to subjects with prediabetes, for example, Mohammadi et al, evaluated the effects of oral supplementation with curcuminoids in obese patients (n=30), using a dose of 500 mg of curcuminoids plus 5mg of bioperidine (total dose= 1g/day), during a follow-up period of 1 month, finding a statistically significant decrease in serum triglyceride levels (p = 0.009), without showing adverse events during the study period (26). Similarly, Ganjali et al, investigated the effects of curcumin on serum cytosines of obese subjects (n = 30), with a dose of 2 capsules of curcuminoids (500 mg/each per day), with a follow-up period of 1 month, finding in the difference of means of IL1β (P = 0.042), IL-4 (P = 0.008), and VEGF (P = 0.01) serum levels, significantly decreased with curcuminoids supplementation (27).

Chuengsamarn Set al, studied the effects of curcuminoids in the reduction of atherogenic risk in patients with diabetes mellitus type 2 (n = 213), with doses of 1.5 gr per day of curcuminoids, finding side effects in less than 1% of the sample, with a mean of 6-month follow-up, finding that intervention with curcumin significantly reduces pulse wave velocity, increases serum adiponectin levels and decreases leptin levels. As well as decrease in levels of triglycerides, visceral fat and total body fat (15).

Although follow-ups in similar studies with prediabetes have been performed at 6 months, finding significant differences, there are studies with 1 to 3 months follow-ups in obese patients or in metabolic syndrome, where significant differences have been found in lipid levels, bodyweight and inflammation markers. This is why, it is interesting to value the response of curcumin supplementation in less than 6 months, betting on a positive effect on insulin sensitivity after 3 months of intervention.

It has been noticed that the side effect of curcumin have not been reported when consumption is less than 12 g per day. At higher doses there may be presence of nausea and diarrhea. Without finding side effects when curcuminoids were used at doses of 1 to 1.5

g / day (15, 26, 27), this means that the 500 mg dose/12hrs is safe for curcumin supplementation.

2. Problem Statement

Due to the need to establish prevention and treatment schemes in stages prior to diabetes, the timely detection of prediabetes turns out to be one of the best schemes to use. In the diabetes prevention clinic, a prevalence of prediabetes of approximately 17% has been observed in subjects older than 18 years, who have been suggested to change their eating habits and increase their physical activity. However, the current labor and occupational demand is an important barrier in the implementation of a new lifestyle. Until now, drugs have not been an option in the treatment, since it raises the costs and increases the possibility of secondary reactions. In consequence, clinical intervention studies have been implemented based on the oral consumption of curcumin, supported by hundreds of basic and applied research on its benefits in health and diseases related to insulin resistance. Therefore, it is suggested that oral consumption of curcumin in pre-diabetic individuals with insulin resistance may be a good adjuvant that increases insulin sensitivity and improves the adverse metabolic state, characteristic of these patients.

3. Justification

Diabetes is a worldwide disease and recent research point to the importance of predicting its development in previous stages. It has been established that insulin resistance is one of the main factors that intervene in the development of diabetes. However, in these stages it has been noticed that the secretion of insulin by the β cells is increased, so these individuals can maintain the glucose homeostasis at normal levels. In later stages, the progressive decline of the function in the pancreatic β cells, promotes the deterioration of glucose homeostasis and the consequent development of hyperglycemia. This leads to focus on these two routes, to avoid the possible progression to diabetes.

Nowadays, the drugs used usually represent problems of treatment abandonment due to side effects and changes in lifestyle, since the disease manifestations are not evident. Therefore, the inclusion of parallel therapies that increase insulin sensitivity and prevent the deterioration of the β cells in the pancreas at the same time, could be considered as an excellent treatment.

Since curcumin has the ability to increase insulin sensitivity, improve β-pancreatic function and is considered a safe supplement by the FDA, it has been decided to include therapy based on oral consumption of curcumin in subjects with prediabetes who show resistance to insulin. This scheme will allow to attack metabolically the barriers previously presented, as well as overcome barriers due to the inability to adjust to lifestyle changes.

4. Hypothesis

Oral supplementation with curcumin will increase insulin sensitivity measured through homeostatic model HOMA-Beta and the Matsuda index.

5. Objectives

General: Determine the effects of oral supplementation with curcumin to improve insulin sensitivity through the homeostatic models HOMA β and Matsuda index.

Specifics
a. Determine the effect curcumin supplementation on the levels of: glucose, insulin (pre- and post-prandial), glycosylated hemoglobin, blood pleasure, insulin sensitivity, lipid level (e.g., cholesterol, triglycerides, high and low lipoproteins density) and anthropometric measures (weight, body mass index, waist-hip ratio).
b. Determine the effect of oral curcumin supplementation on models of insulin resistance measured through HOMA-IR and insulinogenic index.
c. Determine if the consumption of curcumin supplementation will decrease the levels of inflammation markers: PCR, IL1, IL-6, FNT α.
d. Determine the safety of curcumin supplementation by measuring the existence of possible side effects.

Methodology

Type and design of the study

It is a randomized, double-blind, placebo-controlled clinical trial.

Population and sample size.

142 pre-diabetic patients will be included, with prior informed consent, according to the criteria of the ADA [6]. The subjects will be randomly assigned to the treatment group with curcumin (n = 71) or the placebo group (control group, n = 71) using a fixed randomization scheme with assignment based on random numbers generated by a computer.

The calculus of the sample was performed with the statistical program Gpower 3.1, which resulted in 71 individuals per group, to obtain a statistical power of 80% in difference of means between two independent samples with an effect size of 0.5 in a two-tailed test, contemplating a 10% of losses during the study period.

Criteria of inclusion, exclusion and elimination.

Inclusion Criteria

- Men and women with age between 18 and 60 years old.
- With prediabetes:

   a)   Fasting serum glucose: 100-125 mg/dL

   b)   Glycosylated hemoglobin (HbA1c): 5.7-6.4%

   c)   Post-prandial glucose: 140-199 mg/dL after an oral dose of 75 g of glucose.

Exclusion Criteria

- Subjects with any type of diabetes.
- Subjects with body mass index $\geq$ 35 kg/m^2
- Pregnant Women.
- Volunteers who ingest drugs that alter blood glucose levels, antiplatelet agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, fibrates, statins.
- Subjects with serum creatinine > 2 mg/dL or in renal replacement therapy.
- Subjects that normally consume food supplements.
- subjects with acute infections or with chronical diseases (cancer, rheumatoid arthritis, etc.).

Elimination Criteria

- Patients that abandon treatment.
- Subjects that manifest any side effect (nauseas, diarrhea).
- Subjects that during the trial, show Diabetes mellitus diagnosis according to the ADA.

Definition of the variables to be evaluated and how to measure them

Nominals: Each variable is categorized and assigned a level (0 or 1) according to the information obtained in the questionnaires and the clinical results.

- Gender: Male (0) or Female (1)
- Treatment: placebo (0) or curcumin (1)
- Attachment to treatment: no (0), yes (1)
- Altered fasting glucose: no (0), yes (1)

Ordinals
- Body mass index. Is determined by measuring the weight (kg) and the size (m). It will be obtained dividing the weight by the squared size. It will consist of 5 levels: low weight (IMC <19), adequate weight (IMC: 19-24.9), overweight (IMC: 25-29.9), obese (IMC: 30-35), morbid obese (IMC >35).
- HbA1c. It will be determined in automatic equipment from a blood sample-EDTA in the central laboratory. Levels: low (<5.7), medium (5.8-6.4), high (>6.4).
- Fasting glucose and post-prandial glucose. It will be determined by evaluating the glucose tolerance curve after an oral dose of 75g of glucose. Every 30 min, for 2 hours, a peripheral blood sample will be obtained and the glucose concentration will be determined by automated equipment (Central Laboratory). The levels are the following:
Fasting Glucose (mg/dL): normal (<100), prediabetes (100-125), diabetes (<125).
Post-prandial Glucose (mg/dL) (2 horas): normal (<140), prediabetes (140-199), diabetes (<199).

Discontinue: Age, according to the given in the questionnaire.

Continues:
- Anthropometric measurements: weight, height, waist circumference, hip circumference, waist-hip circumference ratio and body fat percentage. They will be measured using an electric bio impedance scale and a measuring tape.

- Clinical: It will be determined in the Central Laboratory by standard methods and/or automated equipment, and includes the following:

a) Systolic blood pressure and diastolic blood pressure.

b) Blood chemistry: insulin, triglycerides, cholesterol, HDL cholesterol, LDL cholesterol, uric acid, creatine, urea, BUN, alanine amino transferase, alkaline phosphatase, glutamyl transferase, lactic dehydrogenase, glycosylated hemoglobin, direct bilirubin, indirect bilirubin, total bilirubin.

c) Blood count

d) Inflammation markers: PCR, IL 1, IL6, TNF-α.

e) Glucose tolerance curve: Fasting serum glucose and at 30, 60, 90 y 120 min after the oral dose of glucose (75 gr).

f) Parameters of insulin resistance and sensitivity under the following formulas

g) HOMA-IR: (Insulin µU/ml)(Glucose mg/dl)/405.

h) Matsuda index: 10,000/$\sqrt{}$[(basal glucose)(basal insulin)*(glucose)(insulin)]

i) Insulinogenic: Δ insulin/Δ glucose.

j) HOMA1-%B: (20)(FPI)/(FPG - 3.5)

Procedure

Intervention

Participants who meet the inclusion requirements and wish to participate in the study will sign an informed consent. 142 individuals will be included, who will be randomized to receive curcumin (n=71) or placebo (n=71).

•All participants will receive the same diet and exercise indications for a period of three months after enrollment (before randomization).

- Regarding the diet, all patients who enter the research protocol will be assessed and supervised. The feeding plan will be prepared by a nutritionist, individually for each patient, based on the recommendations of the American Diabetes Association 2018, with the following: Carbohydrates 55%, proteins 20% and lipids 25%.

According to the needs of the patient, the quantity of kilocalories/day is calculated. For weight reduction 20 kcal/kg/day, weight maintenance 25 kcal/kg/day. Follow-up appointments will be made by nutrition: at the beginning, 4, 8 and 12 weeks after the start of the intervention.

Individuals with the intervention will be administered 1g of curcumin in capsules per day deferred in two doses of 500 mg each. Each capsule should be taken orally at breakfast and lunch for 3 months. The dose of curcumin was extracted from previous studies with similar patients. Individuals in the placebo group will be given two capsules of starch (250 mg) daily at breakfast and lunch for 3 months. Due to curcumin having a characteristic yellow color, the placebo capsules will be the same color as curcumin capsules.

Data collection and measurements

During the intervention period: 3 measurements will be made by the research team: initial (week 0), intermediate (week 6) and final (week 12), as expressed in Table 1.

Table 1. Variables to be evaluated according to the measurement time during the intervention.

Variable	Initial	Intermediate	Final
Anthropometric measures	Yes	Yes	Yes
Biochemists and clinics	Yes	Yes	Yes
Glucose tolerance curve	**Yes**	**No**	**Yes**
Inflammation markers	Yes	No	Yes

Each participant will be given a format to record the consumption of capsules per day, which will deliver at each visit (intermediate and final) and the bottles must be returned to verify the information. They will be exhorted on the importance of acting truthfully and not alter the contents of the jars.

Double blind scheme
Both the randomization and the control of capsule consumption will be controlled by an investigator unrelated to data collection and sample processing. This researcher will be responsible for assigning each individual their corresponding treatment and giving them the capsules, which will be contained in a bottle of the same color, size and shape, for the curcumin and placebo capsules. Therefore, the researchers responsible for the project will not know during the intervention which individual receives placebo or curcumin.

Activities schedule
Since the entire study comprises 20 months, the activities will be carried out as shown in Table 2 after the project has been approved by the respective committees.

Statistical analysis
To achieve the goals of the study and the correct analysis of the data, the variables will be divided into two groups, with the primary ones being expected to be modified by the treatment in the first term, which will define the success or failure of the study. It is expected that the secondary variables may or may not be affected by the treatment. In addition, possible confounders that interfere with the response will be included in the analysis.

- *Primary variables*: post-prandial glucose (2 horas), HOMA-IR, HOMA-β, Matsuda index and insulinogenic.
- *Secondary Variables:* anthropometric measurements, serum lipids, each determination of blood chemistry.
- *Potential confounders:* age and gender.

To determine the statistical difference in the categorical variables between the group of curcumin and placebo, X^2 will be used. The continuous variables at the beginning and at the end between the two groups will be compared using t student test of independent samples and an analysis of covariance (ANCOVA), which will be adjusted by the initial values of the primary and secondary variables of interest. In addition, the percentage differences between the groups in the values of the primary variables will be analyzed, using values of adjusted covariates (including age, gender, BMI) such as 100 x (curcumin group-placebo group) / placebo group of each study variable.

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Table 2. Activities to be carried out during the study period.

Activity	1st Semester	2nd Semester	3rd Semester	Last bimester
Selection and recruitment of patients				
Intervention				
Anthropometric, clinical and biochemical determinations (markers of stress and inflammation)				
Opening of randomization keys				
Analysis and captured of results				
Results publication				

Ethical and biosecurity aspects

During the development of the project, all determinations and processes will be carried out under the norms and statutes pre-established, dictated by the Ethics and Biosafety Committee of this Hospital. The potential risks of the intervention will be made known to the volunteers before the intervention, which include:

a) From the sample taking. In each measurement period (initial, intermediate and final) blood sampling is required, which comprises approximately 60 ml, with the risks inherent to blood collection such as bruising and the elimination of contagion risk due to the use of disposable plastic material, new in each subject and in each shot.

b) Of the intervention. According to the FDA, there have been no reported adverse reactions to the consumption of curcumin less than 12 g per day. At higher doses there may be presence of nausea and diarrhea. This protocol includes the consumption of 1 g per day and no adverse reactions have been reported, however, an instrument sheet of adverse reactions will be granted and the participants will be instructed to stop treatment if they face any secondary reactions such as nausea, dizziness, vomiting and/or diarrhea.

Relevance and expectations

In the case that treatment is positive, safe alternatives for prediabetes can be established. In addition, derived from the results, an article will be published in a high impact magazine and presented at a congress.

Available resources

We count with the human resources required for the proper development of the project. Within the research group are Dr. César Leonardo González Aguilar, Resident doctor in the third year of the Internal Medicine specialty at the General Hospital of Mexico and student of a master's degree in Medical Sciences at the UNAM, and Dr. Silvestre de Jesús Alavez Espidio, Health Sciences Chief department at UAM-Lerma, who has extensive experience in the design of studies and with the necessary facilities for the processing of samples.

A professional in nutrition will be hired, who will be in charge of supervising the food plan during the intervention.

Regarding the material resources, curcumin and placebo capsules are available for patients and the necessary material for the processing of samples for the determination of markers of oxidative stress and inflammation.

Resources to request

The necessary for the glucose tolerance curve: trutol, catheters, syringes, gauze, three-way stopcocks, test tubes for blood collection, enzymatic assay for insulin determination and laboratory tests.

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