“Effect of Propolis or Metformin Administration on Glycemic Control in Patients With Type 2 Diabetes Mellitus”

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INTRODUCTION

Type 2 Diabetes Mellitus (DM2) is a health problem that has reached alarming levels, as currently, about half a billion people suffer from it around the world. For 2019, a total of 463 million was estimated and an increase of 51% is expected by 2040.[1] It is a disease characterized by dysfunction of beta cells, hepatic glucose metabolism and peripheral insulin resistance, a state in which tissues sensitive to it show a decreased response to normal insulin levels.[2]

The first-line treatment in newly diagnosed patients is metformin, mainly due to its efficacy in reducing glycemic control, safety profile, and weight neutrality.[3,4] However, this depends on factors such as treatment compliance, access to medicines, counseling, regular monitoring of blood sugar levels, access to health care services, and quality of management. To date, a significant number of people around the world use complementary and alternative medicine (CAM) to treat chronic diseases, with reports of 64%. Of these, 35.5% use CAM for DM2.[5]

Propolis, is a natural product produced by the bee *Apis mellifera* by adding salivary secretions (β-amylase) and wax to the balsamic resinous material, which they collect from shoots, exudates of trees and other parts of the plants as lipophilic materials in the leaves, mucilages, gums, resins, latex, etc. Etymologically the term propolis, comes from the Greek and means in "defense of the city (or beehive)".[6–9] It has been known and used since ancient times by offering options such as antimicrobial, anti-inflammatory, antioxidant, antitumor, antiulcer, anesthetic, hepatoprotective and healing therapy.[6,10,11] It is composed of flavonoids, terpenes, phenolic acids, as well as proteins, sugars, vitamins and abundant minerals.[10,11]

Recent studies have shown the efficacy of propolis on the reduction of fasting glucose and glycated hemoglobin,[9,12,13] insulin resistance[13,14] and postprandial glucose.[14] However, there is a controversy between some results, as Fukuda et al. indicated that there was no significant difference in the parameters of glycemic control and insulin resistance.[15] Likewise, Zakerkish et al. found no relevant reduction in fasting glucose after propolis supplementation.[14]

Therefore, there is a need for further studies, as there is no evidence from studies evaluating the effect of propolis on glycemic control in newly diagnosed patients without drug treatment. In addition to this, it has not been compared to the gold standard, metformin. Our hypothesis is that the administration of propolis or metformin modifies glycemic control in newly diagnosed patients without pharmacological treatment. The objective of this study is to evaluate the effect of propolis or metformin administration on glycemic control in recently diagnosed patients without pharmacological treatment.

MATERIAL AND METHODS

Selection criteria

Patients with a diagnosis of DM2 less than 5 years old and without pharmacological treatment for at least 3 months before entering the study, 30 to 60 years of age, mild to moderate physical activity, stable body weight for at least 3 months before the study, body mass index (BMI) of 25.0 to 34.9 kg/m^2, fasting serum glucose <13.88 mmol/L and postload serum glucose >11.10 mmol/L, will be criteria for entering the study. For the selection of individuals diabetes detection campaigns will be carried out in the metropolitan area of the City of Guadalajara. Women in the reproductive stage at risk of pregnancy, subjects who consumed drugs or supplements that modify the behavior of DM2, personal history of cardiovascular, kidney, pancreatic or thyroid disease and/or uncontrolled systemic arterial hypertension, known allergies to bee's sting or its derivative products, intolerance to metformin, total cholesterol (TC) ≥6.20 mmol/L, triglycerides (TG) ≥4.48 mmol/L will be excluded. Individuals with lack of tolerability to propolis, metformin and/or placebo, with adherence to treatment <80%, in the presence of a serious adverse event and/or who withdrew informed consent will be eliminated.

Study design

A randomized, double-blind, placebo-controlled clinical trial of three pharmacological groups will be carried out, with the participation of 34 patients with a recent diagnosis of DM2 according to the criteria of the American Diabetes Association.[16] The propolis capsules

will be obtained from NOW® of Chicago, Illinois (USA), containing 300 mg of propolis powder. Calcined magnesia will be used for the placebo. The allocation will be done by simple randomization using a list of numbers. All patients will receive for 12 weeks one capsule before the first bite of breakfast and another before the first bite of dinner. 12 of them took propolis (300 mg twice a day), another 12 received metformin (850 mg twice a day) and 12 more, placebo in the same pharmacological presentation. Each participant will receive medical nutritional therapy and will be instructed to continue with their normal physical activity.

Clinical and laboratory measurements

The medical history of each patient will be taken and anthropometric indices will be measured that included: height, weight, BMI, waist circumference (WC) and percentage of fat mass. In addition to blood pressure. Five visits will be completed during the study and a 2-h oral glucose tolerance test (OGTT) will be performed at the beginning and end of the intervention to calculate the areas under the curve (AUC) of glucose and insulin, total insulin secretion (insulinogenic index), first phase of insulin secretion (Stumvoll index) and insulin sensitivity (Matsuda index). For this, the individuals will take a solution with 75 g of anhydrous glucose dissolved in 300 ml of water in 5 minutes. After that, blood samples will be taken through a heparinized catheter before and at 30-min intervals (30, 60, 90 and 120 minutes) for 2 hours. At each visit, the presence of adverse events will be verified through the diary and compliance through the capsule count.

Laboratory tests will be performed at 8:00 a.m. after an overnight fast from 10 to 12 h. Body weight will be evaluated by bioimpedance with a digital scale (Tanita®), with the participant in a standing position and wearing light clothing, without footwear and with the bladder evacuated before the measurement. For height, subjects will be asked to remove their shoes and stand with their feet together; measurements will be rounded to the nearest centimeter. WC will be taken at the midpoint between the highest point of the iliac crest and the lowest rib on the midaxillary line to the nearest centimeter. Percentage of fat mass will be evaluated through bioimpedance. BMI will be calculated as weight (kg) divided by height (m^2). A digital sphygmomanometer (Omron Hem-907 XL®) will be used to determine blood

pressure, and the mean value of three measurements will be recorded after a 5-min rest period.

Venous blood samples will be obtained and kept at room temperature for 30 min. The samples will be centrifuged and the serum will be placed in three aliquots; one will be used immediately for the measurement of fasting glucose, glycated hemoglobin A1c (A1C), TC, TG, high-density lipoprotein cholesterol (HDL-c), uric acid and creatinine, and the rest will be frozen at -20 °C for the determination of insulin. All biochemical measurements will be calculated with enzymatic colorimetric methods on an automatic analyzer (Erba XL-100®) with BioSystems S.A. reagents. Insulin concentrations will be measured with the enzyme-linked immunosorbent assay (ELISA) technique using the kit (DRG, Inc).

To calculate low-density cholesterol, the Friedewald formula will be used: LDL-c (mmol/L)= TC (mmol/L) - HDL-c (mmol/L) - [TG (mmol/L) / 2.2], while for very low density cholesterol (VLDL) the ratio of TG (mmol/L) / 2.2 will be used. With a liquid chromatography the percentage of A1C will be calculated. The AUC of glucose and insulin will be calculated with the polygonal formula. Total insulin secretion will be assessed with the insulin index: (ΔAUC of insulin) / (ΔAUC of glucose). With the Matsuda 10000 / √ ([(Glucose 0^ '· Insulin 0 ^') (Average of the PTOG · Average of the insulin in the PTOG)]) index the insulin sensitivity will be estimated, while with the index from Stumvoll 1283 + 1.829 × insulin 30' - 138.7 x glucose 30’ + 3.772 × insulin 0', the first phase of insulin secretion.

Sample size

For this study, the sample size it’s calculated using a formula for mean difference[17] with a statistical confidence of 95%, a statistical power of 80%, a standard deviation (SD) and an expected difference for fasting glucose, A1C and 2-h glucose of 0.6 mmol/L[12] and 1.0 mmol/L[9], 0.5% and 0.8%[12], 2.3 mmol/L[18] and 3.9 mmol/L[19], respectively. While for metformin it’s of 2.4 mmol/L[20] and 3.0 mmol/L[21], 1.0% and 1.5%[22], 3.5 mmol/L[23] and 5.5 mmol/L[24], respectively. A total of 12 patients is obtained for each group, including 20% of the expected loss.

Security measures

All patients will be informed about the possible adverse effects of propolis and metformin; they will have the emergency telephone numbers of the responsible and associated investigators.

STATISTIC ANALYSIS

The study will be designed to demonstrate the effect of propolis and metformin relative to placebo in terms of the outcome variables of effectiveness. Assuming there are no differences in propolis and metformin versus placebo regarding effectiveness in reducing glycemic control, it's calculated that approximately 36 randomized patients will provide ~80% power to demonstrate superiority.

All statistical analyzes will be performed by intention to treat, which will be included randomized patients who receive at least 1 dose of study treatments and for whom there has a baseline value on measurements. First, with the Kruskal-Wallis test, it will be tested whether the baseline data group of primary and secondary variables come from the same population, that is, whether the 3 groups are comparable as no statistically significant differences are found.

Then, using the Kruskal-Wallis test, the final data will be evaluated and with those that will be significant a post-hoc test (Mann Whitney U) will be performed, comparing propolis versus metformin, propolis versus placebo, and metformin versus placebo. Differences between baseline and final measurements for primary and secondary variables will be calculated with the Wilcoxon test. Statistical comparisons will be made using a comparative type 1 error of 5% (two-tailed).

The safety profile analysis will include patients who receive at least 1 dose of study medication; safety data will be summarized using descriptive statistics.

FINANCING

The financing will be by own resources of the University of Guadalajara.

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