“Effects of dapagliflozin on blood pressure variability in patients with prediabetes and prehypertension without pharmacological treatment: a randomized”

NCT03006471

June 9, 2016

Introduction

There is a reciprocal relationship between the possibilities of developing arterial hypertension (HT) and diabetes mellitus type 2 (DM2). The probability of developing HT in patients with DM2 is 40% in the first 5 years of diagnosis and 12% in the development of DM2 in HT. The prevention or timely detection of these conditions can reduce the risk of the development of cardiovascular disease (1). Prediabetes and prehypertension are defined as metabolic states that lead to the appearance of DM2 and HT, respectively.

Approximately 12 million people suffer from prediabetes in Mexico according to the report of the International Diabetes Federation (IDF) in 2017 (2). In 2015, a global prehypertension prevalence of 37.5% will be reported according to the 8th report by the Joint National Committee (JNC8) (3).

Ambulatory blood pressure monitoring (ABPM) is superior to office BP to predict cardiovascular mortality and its most potent component is the alteration in nighttime blood pressure variability (BPV) compared to daytime (4).

Sodium-glucose cotransporter inhibitors type 2 (iSGLT-2) are oral antidiabetics that improve glycemic control. Dapagliflozin promotes natriuresis and osmotic diuresis, which decreases plasma volume and decreases blood pressure (BP) in patients with DM2; however, until now it is unknown whether this effect could modify BPV in individuals with prediabetes and prehypertension without pharmacological treatment (5,6).

Methods

A clinical study, double-blind, randomized and placebo control group in 30 patients. Men and women (30-60 years) diagnosed with prediabetes according criteria of the American Diabetes Association (ADA) with fasting plasma glucose (FPG) 5.6-6.9 mmol/L (>2 occasions) or the 2 h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test 7.8-11.0 mmol/L, or both (7) and prehypertension according criteria of the JNC8 with BP of 120-139 / 80-89 mmHg (3).

All subjects will be sedentary, non-smokers, without HT, kidney, heart, thyroid or liver disease; pregnant or breastfeeding women will be excluded. They had not consumed any medication during the previous 6 months and all individuals had a stable body weight for at least 3 months prior to the study. Withdrawal of informed consent, loss of follow-up, therapeutic adherence <80% and the presence of serious adverse effects from treatment will be considered criteria for elimination. Dapagliflozin (Forxiga ®Bristol-Myers Squibb, Humacao, Puerto Rico) wa given at a dose of 10 mg per day before breakfast for 6 months to 15 patients, while the remaining 15 patients received placebo in the same dose, which will be randomly assigned to one of the intervention groups using a table of numbers. All patients received general nutrition recommendations, as suggested in the ADA guidelines for patients with prediabetes (7), and will be instructed not to modify their usual physical activity.

The enrolled subjects underwent an evaluation at 8:00 a.m. after an overnight fast from 10 to 12 h, will be instructed to avoid strenuous physical activity before clinical and laboratory tests. The body weight and height will be measure with light clothes

and after having evacuated the bladder with digital scale Tanita® TBF-215 A (Corportation of American Inc.)

The body mass index (BMI) wil be calculated as body weight (kg) divided by the square of the body height (m^2).

Office BP will be assessed after a period of rest with the subject sitting for 15 minutes with a digital sphygmomanometer Omron 907-E (Healthcare, Inc.), the suitable cuff for the circumference of the non-dominant arm will be used (> 80% of the size of the circumference of the cuff) (8). The mean of three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be determined.

The FPG and 2-h PG (mmol/l) will be quantified from the serum obtained from a 5 ml sample of venous blood centrifuged at 2500 rpm and the amount of glucose will be determined by colorimetric methods with the automatic clinical chemistry analyzer Erba XL 100™ (Mannheim, Germany), and with an intra- and inter-assay coefficient of variability of < 1% and 2%, respectively. The hemoglobin glycated A1c fraction (A1C) (%) will be measured using high-performance liquid chromatography (HPLC) (Bio-Rad Laboratories, Hercules, CA, USA) with an intra- and inter-assay coefficient of variability of 0.4% and 1.6%, respectively.

ABPM will be recorded during 24 h using an oscillometric method with the Microlife WatchBP O3 (Microlife AG, Widnau, Switzerland). BP measurement will be scheduled every 15 minutes during the day (8 a.m. to 11 p.m.) and every 30 minutes during the night (11 p.m. to 8 a.m. of the next day) (8). Patients will be instructed to continue with the usual activities during the ABPM and they will be advised to remain calm when they felt the pressure increase in the cuff. The

method will be considered reliable if more than 70% of valid measurements will be met.

The BPV will be calculated: 24-h BP; daytime and nighttime BP; BP weighted standard deviation (SD) (the average of the daytime and nighttime BP SD each weighted for the duration of the respective day or night period), this method has been proposed as a method of excluding day to night BP changes from the quantification of overall 24 h SD, without discarding either daytime or nighttime values; the coefficient of variation (CV) of 24-h, daytime and nighttime (the average SD of SBP divided by the corresponding mean BP and multiplied by 100); the mean real variability (AVR) of SBP and DBP (the average of the absolute differences between consecutive BP measurements); and identify the dipper circadian BP pattern (BP nightly decline between 10-20% of the BP day, this is normal), Non-dipper (night decrease in BP <20% compared to the BP of the day), dipper reverse (increase in night-time BP compared to day BP), dipper extreme (BP nightly decline between >20% of the BP day) which are relevant to cardiovascular prognosis (9).

Also, will be identified through the ABPM by 24-h: mean arterial pressure (MAP), daytime and nocturnal hypertensive load.

Adherence to treatment and the presence of adverse events will be assessed with an attachment diary that will be given to the patient at study entry, as well as a record of medications and returned by patients at each visit.

The formula for clinical trials will be used to determine the sample size (10), with a statistical confidence of 95% and a power of 80%, as well as the SD and the expected difference for each of the primary variables (11), a total of 8 and 12

patients will be obtained for the SBP and the DBP, respectively. The highest n obtained will be taken into account, to which 20% will be added for possible losses. A total of the 15 patients per group will be estimated in this calculation.

Analysis

Data will be analyzed with the software IBM SPSS Statistics V21.0 software (SPSS, Inc., Chicago, IL, USA)..

The Mann-Whitney U test (non-parametric test for quantitative variables) is used to evaluate the differences between the intervention groups expressed in means and SD; Wilcoxon (non-parametric test for quantitative variables) will be used to evaluate the differences between the baseline and final evaluation of each group expressed in means and SD; and Pearson's Chi2 or Fisher's exact test (non-parametric test for qualitative variables) will be used to evaluate the differences between the intervention groups expressed in frequencies and percentages.

A $p \leq 0.05$ is considered statistically significant.

The present study will be consistent with the Helsinki declaration and will be approved by the Local Committee of Ethics and Research of the University with this register number CEI/357/2016 and Clinical Trials NCT03006471. The informed consent will be obtained from the participants before performing any intervention or evaluation. The principal investigator explained to each participant the nature, risks and benefits of the study.

Financing

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

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