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Research Article

Participation of a Low-Fat Controlled Ketogenic Diet in the Regulation of Blood Pressure in Mexican Women with Type I Obesity

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ABSTRACT

The World Health Organization has labeled the global obesity epidemic as "globesity," highlighting its critical impact on health, particularly through the rise of obesity-related diseases like cardiovascular conditions, the leading cause of death worldwide. Obesity is closely linked to hypertension and cardiovascular diseases, with 65% to 78% of hypertension cases attributed to obesity. Effective prevention and treatment strategies, including lifestyle modifications such as diet and exercise, are essential to manage this growing health concern.

This study aimed to analyze the impact of weight loss and body fat reduction on blood pressure in Mexican patients with grade I obesity using the Zélé Method, a low-fat controlled ketogenic diet (VLCLFKD). Conducted as a longitudinal, randomized, double-blind clinical trial, the study involved 27 Mexican women aged 18 to 60 years. Over 12 weeks, participants followed a four-stage VLCLFKD program, coupled with exercise and emotional support.

Results showed significant reductions in both systolic and diastolic blood pressure, correlating with weight loss and decreased waist circumference. Specifically, systolic blood pressure dropped from 126.45 mmHg to 108.58 mmHg, and diastolic pressure from 92.51 mmHg to 75.29 mmHg. Participants also experienced an average weight loss of 12.64 kg, with a significant reduction in fat mass and waist circumference.

The study concluded that the Zélé Method effectively reduced blood pressure, weight, and waist circumference, presenting a promising adjunctive nutritional intervention for hypertension treatment. These findings suggest that targeted dietary interventions can play a crucial role in managing obesity-related hypertension, contributing to overall cardiovascular health improvements.

Keywords

Hypertension, Obesity, Ketogenic Diet, Weist Circumference, Blood Pressure.

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Introduction

The World Health Organization (WHO) coined the term "globesity" to describe the worldwide obesity epidemic that continues to rise. This situation is critical because obesity-related diseases are becoming increasingly common, particularly cardiovascular diseases, which are the leading cause of death globally [1]. Obesity is associated with life-threatening health problems such as hypertension, type II diabetes mellitus, increased risk of coronary heart disease, unexplained heart failure, hyperlipidemia, infertility, and an increased prevalence of colon, prostate, endometrial, and breast cancers [1].

As the prevalence of obesity continues to rise, so will hypertension and associated cardiorenal diseases unless more effective strategies are developed to prevent and treat obesity [2]. It is estimated that between 65% and 78% of hypertension cases can be attributed to obesity [3]. Lifestyle modifications, including diet, reduced sedentary behavior, and increased physical activity, are generally recommended for patients with obesity [2]. The relationship between obesity and hypertension is well established [4]. Factors such as the activation of the sympathetic nervous system (SNS), the amount of intra-abdominal and intravascular fat, sodium retention leading to increased renal reabsorption, and the renin-angiotensin system play important roles in the pathogenesis of obesity-related hypertension [4,5].

Additionally, adipose tissue, besides the liver, is a source of angiotensinogen (AGN), which is subsequently converted by the kidney into angiotensin I and then, by the action of the angiotensin-converting enzyme (ACE), into angiotensin II, a potent vasoconstrictor. The angiotensin II Type 1 receptor (AR-1) is expressed in adipocytes and interferes with the differentiation of preadipocytes, contributing to the formation of large and dysfunctional adipocytes. These dysfunctional adipocytes increase the expression of AGN, creating a vicious cycle between the Renin-Angiotensin System (RAS) and dysfunctional adipose tissue, which partially explains hypertension associated with obesity [6].

It is also known that large adipocytes produce elevated levels of leptin, reactive oxygen species, and pro-inflammatory interleukins [7]. The accumulation of ectopic fat, mostly composed of large adipocytes, is often infiltrated by macrophages that have reciprocal communication with fat cells. This interaction releases free fatty acids that condition the expression of higher amounts of TNF by macrophages and IL-6 by adipocytes [8,9], promoting insulin resistance and improper handling of excess energy due to a chronic low-grade inflammatory process [10].

Achieving a body weight loss of between 5% and 10% leads to reductions of 5 and 4 mmHg in systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, and a weight loss of 10 kg can reduce SBP by 5 to 20 mmHg [2].

In treating hypertension, managing obesity constitutes a therapeutic strategy. The Mediterranean diet [11] and the DASH diet [12] have been tested and provided benefits in treatment. Therefore, in this study, we analyzed the effect of weight loss and body fat reduction obtained with a low-fat controlled ketogenic diet (Zélé Method) on blood pressure levels.

Material and Methods

Based on the results obtained from the Zélé 2021 study, registered on the clinicaltrials.gov platform as a prospective, longitudinal, randomized, double-blind clinical trial under the code NCT06275347, the behavior of blood pressure (BP) was analyzed in a group of Mexican patients with grade I obesity [13] during the weight loss process with a low-fat controlled ketogenic diet (VLCLFKD).

All patients underwent weekly BP measurements, preferably in the early morning hours, on the right arm. Measurements were taken with the patient seated, after 3 minutes of rest. The average of 3 readings taken at 1-minute intervals was recorded. If the BP reading was above 160/90 mmHg, a 5-minute rest was given before repeating the measurement. A Welch Allyn digital sphygmomanometer, Series H-BP100SBP 1700i, was used for this purpose. Body composition data were obtained using multifrequency bioelectrical impedance (BIEM) with the DSM-BIA Multifrequency Segmental Body Composition Analyzer InBody 270, with both measurements taken weekly. Additionally, samples obtained at the beginning of the project were used to establish the correlation between biochemical parameters and hypertension.

Sample Size

The original sample size was determined firstly by resource availability and secondly by population representativeness with a power of 95% and a 95% confidence interval (CI), using a 3:1 ratio of cases to controls and accepting a dropout rate of up to 35%. Fleiss' equation was used for the calculation (calculated with EPIinfo STATCALC for sample size), including 56 cases and 32 controls.

Participants

Among the patients included in the study and assigned to VLCLFKD, female patients with BP disorders were selected, resulting in 29 female patients. All were Mexican women aged 18 to 60 years with Type I obesity who agreed to participate by signing an informed consent form reviewed and approved by the ethics committee of the Centro de Alta Especialidad of the Secretary of Health of the State of Veracruz. It should be noted that the assignment to the nutritional intervention was random.

Nutritional Intervention

In addition to the nutritional intervention, a standardized exercise plan and emotional support were implemented for 12 weeks. During the intervention, patients received vitamin and trace element supplements (sodium chloride, magnesium oxide, calcium carbonate) to meet the recommended daily needs throughout the study period.

The VLCLFKD program consisted of four stages:

1. **Frank Ketosis:** Patients consumed between 650 and 730 kcal/day in 5 meals based on commercial Zélé® preparations and low-glycemic-index vegetables. They received an average of 1.2 g of protein per kg of ideal body weight per day, 20 g/day of lipids based on essential fatty acids, and less than 60 g/day of absorbable carbohydrates. This stage lasted for 4 weeks.
2. **Mixed Ketosis:** In this stage, two meals of commercial preparations were gradually replaced by animal protein sources (meat, fish, eggs, etc.), increasing the intake by 100 to 150 kcal/day without the patient leaving the state of ketosis. This stage also lasted for 4 weeks.
3. **Transition Stage:** Simple carbohydrates from fruits and some complex carbohydrates from cereals were added to the previous program, allowing patients to exit the state of ketosis and enter a controlled hypocaloric diet of approximately 1300 to 1500 kcal/day. This was to metabolically readapt to macronutrient consumption in an approximate proportion of 30 to 35% proteins, 25% fats, and 40 to 45% carbohydrates. This stage lasted for one or two days.
4. **Integral and Maintenance Phase:** Patients received a

hypocaloric diet adapted to their energy expenditure measured by IBMF, which could vary between 1300 and 2250 kcal/day, with a macronutrient ratio of 50% carbohydrates, 25% proteins, and 25% fats, according to the Diogenes study [14].

Food Delivery During the Study

Participants received, free of charge, the products necessary to prepare meals and snacks for each phase of the study, only needing to add fresh vegetables to complete their diet. Meals were delivered once a week with menu items for 7 days at the time of their clinical review. Participants received the necessary elements to design their weekly menu for the nutritional intervention to which they were assigned following a blinding process. All necessary nutritional advice was provided weekly throughout the study, including suggestions for integrating menu elements.

Statistical Analysis

The demographic data and initial clinical characteristics of the participants are summarized in tables, presenting (n), mean, and measures of dispersion (SD and 95% CI) for the variables. Subsequently, bivariate Pearson correlation tests were performed between the biochemical and anthropometric variables and BP measurements to establish, through this regression test, the contribution of each variable to the determination of SBP or DBP. A generalized linear model with repeated measures ANOVA was used to evaluate changes in BP values, assuming significant differences with P values ≤ 0.05. The primary outcome was the percentage and/or absolute change in systolic blood pressure and diastolic blood pressure values.

Results

Initially, baseline conditions were established in the study group.

Twenty-nine women were included in the study; two were excluded as they dropped out before completing the first 4 weeks of the study, none for reasons attributable to the nutritional intervention. Table 1 presents the general anthropometric and biochemical characteristics of the 27 patients. As a first analysis, bivariate Pearson correlation tests were conducted between all study variables and systolic and diastolic blood pressure readings. It was found that muscle mass, fat mass, and total body water percentage significantly correlated with systolic blood pressure (SBP) with p-values of 0.017, 0.027, and 0.02, respectively. Heart rate correlated with diastolic blood pressure (DBP) with a p-value of 0.05. The only variable that significantly correlated with both blood pressure readings was waist circumference, with p-values of 0.0024 for SBP and 0.037 for DBP (Table 1).

To rule out the influence of age on elevated blood pressure levels, despite not finding a correlation between these variables, patients were divided by decades, and a one-way ANOVA was conducted to determine whether age could be a factor influencing blood pressure levels. No differences were found in systolic and diastolic blood pressure among the different age groups. The significant correlation between waist circumference and blood pressure persisted until both blood pressure and waist circumference were

		Confidence Interval (95%)			Correlation *p* val	
	Mean	Lower	Upper	SD	Sys BP	Dias BP
Age (years)	37.68	34.44	40.92	8.83	0.094	0.692
Weight (kg)	86.79	83.45	90.12	9.08	0.051	0.764
Height (cm)	162.96	160.28	165.64	7.17	0.051	0.838
Systolic Blood Pressure (mmHg)	125.61	119.8	131.42	15.83		
Diastolic Blood Pressure (mmHg)	92.13	88.85	95.41	8.95		
Heart Rate (bpm)	80.09	75.11	85.08	13.59	0.697	0.05
Body Mass Index (BMI) (kg/m^2)	32.67	31.98	33.37	1.89	0.394	0.721
Muscle Mass (%)	27.79	25.73	29.85	5.61	0.017	0.714
Fat Mass (kg)	42.16	39.9	44.41	6.13	0.027	0.895
Visceral Fat (index)	14. 56	13.39	14.98	2.31	0.749	0.999
Total Body Water (kg)	36.59	34.12	39.05	6.71	0.02	0.069
Waist Circumference (cm)	102.01	98.8	105.21	8.72	0.024	0.04
Hip Circumference (cm)	108.83	101.68	105.99	19.49	0.979	0.784
Glomerular Filtration Rate (ml/min)	100.66	94.95	106.38	17.62	0.489	0.276
Creatinine (mg/L)	0.77	0.71	0.83	0.15	0.414	0.207
Sodium (Eq/L)	138.91	138.05	139.77	2.12	0.469	0.678
Total Cholesterol (mg/dL)	195.64	181.84	209.44	34.16	0.377	0.175
HDL Cholesterol (mg/dL)	49.72	43.88	55.56	14.46	0.892	0.928
LDL Cholesterol (mg/dL)	117.71	105.84	129.57	29.38	0.351	0.125
VLDL Cholesterol (mg/dL)	32.13	25.85	38.41	15.54	0.157	0.289
Triglycerides (mg/dL)	145.16	119.98	170.35	62.34	0.108	0.814

Table 1: The means of the analyzed variables are presented along with their measures of dispersion, as well as the correlation found between these variables and the (S) systolic and (D) diastolic blood pressure readings. Significant correlations are shown in red.

within normal parameters, specifically up to week 12 (Figure 1).

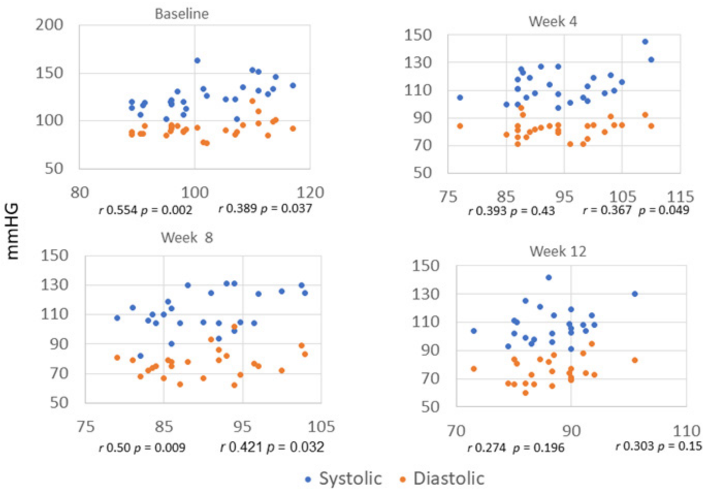

Figure 1: Correlation between waist circumference at baseline, and at 4, 8, and 12 weeks of VLCLFKD. A significant correlation is maintained while the mean systolic and diastolic blood pressure readings and waist circumference in cm are altered. This correlation is lost when the variables enter normal ranges.

A significant reduction was observed in both systolic blood pressure (SBP) from 126.45 ± 16.04 mmHg to 108.58 ± 12.27 mmHg (t = 4.47, df = 26, p < 0.001) and diastolic blood pressure (DBP) from 92.51 ± 9.13 mmHg to 75.29 ± 8.7 mmHg (t = 6.981, df = 26, p < 0.001) (Figure 2) during this period. This reduction was associated with an average weight loss per patient of 12.64 ± 2.96 kg (t = 5.52, df = 26, p < 0.001), corresponding to 14.5 ± 2.69% of total body weight. According to body composition measurements, the average fat loss per patient was 6.27 ± 2.66 kg (95% CI: 5.17 to 7.23 kg), a significant loss in the repeated measures analysis (F = 1054, df = 26, p < 0.001). The reduction in waist circumference was proportional to the loss of weight and body fat, with an average reduction of 11.96 ± 4.71 cm (95% CI: 9.20 to 14.72 cm), which was also significant in the repeated measures analysis (F = 58.61, df = 26, p < 0.0001) (Figure 3).

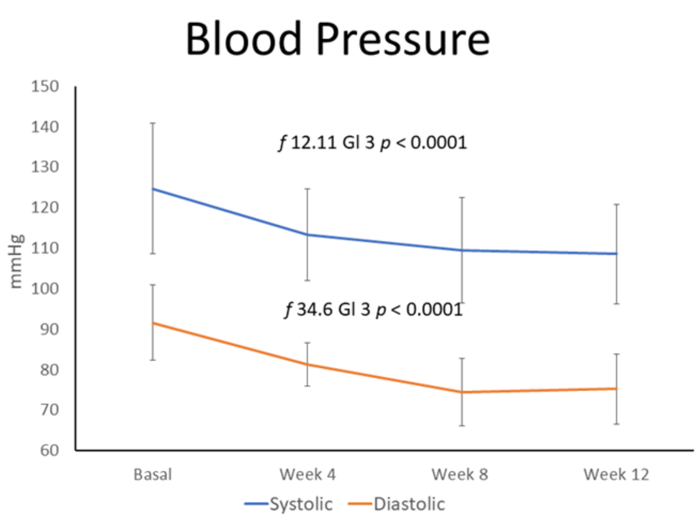

Figure 2: Blood Pressure. The behavior of systolic and diastolic blood pressure is compared using a generalized linear model of repeated measures.

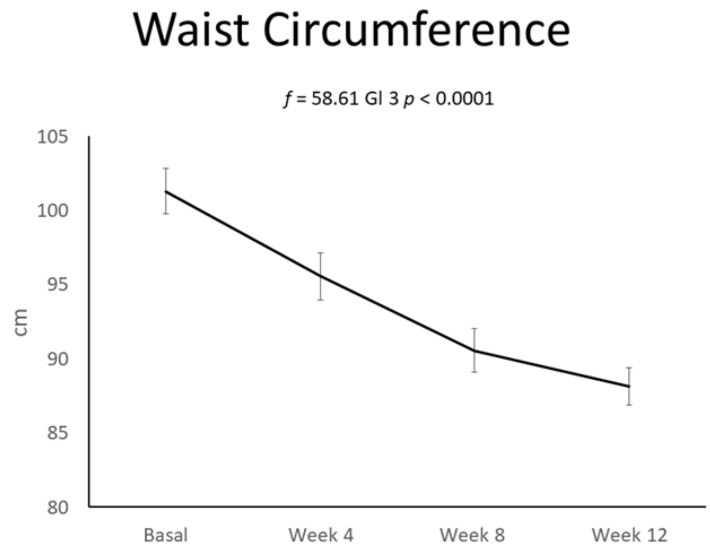

Figure 3: Waist Circumference. Significant decrease in waist circumference between the beginning and the end of the nutritional intervention.

From a biochemical perspective, although no correlation was found, the behavior of blood lipid levels was analyzed. The mean total cholesterol at the beginning of the study was 197.37 ± 38.6 mg/dl (95% CI: 181.44 to 213.31 mg/dl) and at the end of the study was 173.9 ± 30.37 mg/dl (95% CI: 161.37 to 186.45 mg/dl) (t = 2.22, df = 52, p = 0.031). HDL cholesterol decreased non-significantly, from 48.4 ± 14.5 mg/dl to 43.61 ± 20.05 mg/dl. LDL cholesterol levels decreased from 117.05 ± 35.84 mg/dl (95% CI: 104.34 to 129.76 mg/dl) to 98.41 ± 26.7 mg/dl (95% CI: 88.94 to 107.89 mg/dl) (t = 2.88, df = 52, p = 0.005). Finally, VLDL cholesterol changed from 30.49 ± 12.01 mg/dl (95% CI: 25.41 to 35.56 mg/dl) to 19.7 ± 7.5 mg/dl (95% CI: 16.52 to 22.88 mg/dl) (t = 2.52, df = 52, p = 0.011). The rest of the variables were not relevant to this article.

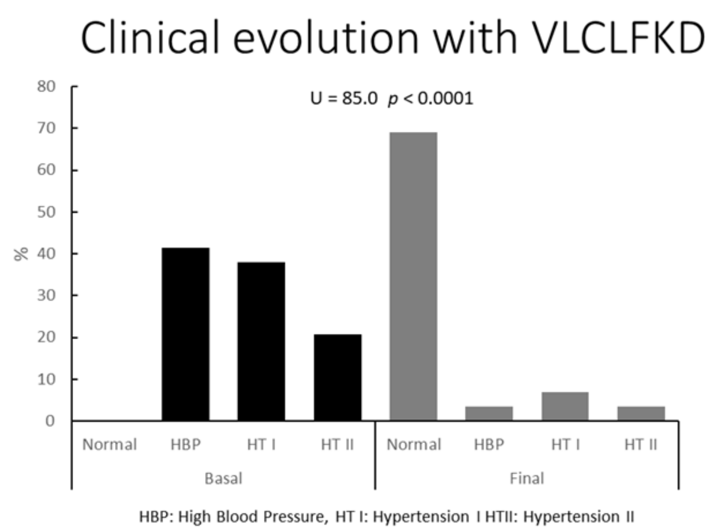

Figure 4: Clinical Evolution of Blood Pressure Alterations. According

to the American Heart Association classification, there was a significant change in the clinical condition across the 4 stages of blood pressure at the end of the study.

Of the 27 patients with blood pressure abnormalities according to the American Heart Association classification, after 12 weeks on a VLCKLFD, 69% normalized their blood pressure readings. Among the 41.4% of patients with high blood pressure, only 3.4% remained in this range. The percentage of patients with Stage 1 Hypertension decreased from 37.9% to 6.9%, and those with Stage 2 Hypertension decreased from 20.7% to 3.4% (Figure 4).

No adverse effects attributable to the nutritional intervention were reported.

Discussion

Obesity has a higher prevalence in patients with obesity compared to those with a normal BMI. It has been demonstrated that up to 79% of patients with type I obesity have hypertension, compared to 45% of patients with a normal BMI [15]. In this study, which proposes a new nutritional intervention to help control hypertension, a very low-carbohydrate and low-fat diet was successfully maintained for 12 weeks in this group of patients. The measurements taken established a significant correlation between both diastolic and systolic blood pressure and waist circumference, which is an easily obtainable indirect measure of visceral fat in clinical practice. It was observed that when patients achieved normal blood pressure levels and a significant reduction in waist circumference, this correlation was lost.

Various types of nutritional interventions have been proposed to aid in the treatment of hypertension, such as the Mediterranean diet or the DASH diet, which appear to provide more solid blood pressure-lowering effects [2]. However, some studies claim that there is not enough evidence to be certain of this result, and it is unclear if following a weight loss diet could reduce cardiovascular diseases [16]. In this study, a significant reduction in both systolic and diastolic blood pressure was demonstrated, which translated into a decrease in the number of patients diagnosed with high blood pressure or hypertension. By the end of the study, 69% of the 27 patients had normal blood pressure levels.

The study showed a fat loss of 6.27 ± 2.66 kg with minimal muscle mass loss, which resulted in a reduction in systolic blood pressure of 16.2 ± 14 mmHg (95% CI: 10.3 to 22.9 mmHg) and in diastolic blood pressure of 18.1 ± 12.9 mmHg (95% CI: 12.6 to 23.6 mmHg), differing from the findings of James A. Blumenthal, who reported a reduction in systolic blood pressure of 5.79 mmHg (95% CI: 3.54–8.05) and 3.36 mmHg (95% CI: 1.93–4.75) in diastolic blood pressure [12]. It is difficult to establish that the reduction was directly related to the decrease in visceral fat since no direct correlation was found between visceral fat measured by IBMF and blood pressure, but there was a correlation with the indirect measurement obtained by waist circumference.

Conclusion

The study demonstrated that the VLCKLFD led to significant improvements in systolic blood pressure (SBP), diastolic blood pressure (DBP), as well as in body weight and waist circumference over the 12 weeks of the study. The reduction in fat mass, which resulted in a decrease in waist circumference, was significantly correlated with the reduction in SBP and DBP, maintaining this correlation until waist circumference and blood pressure reached normal values. Age was not an influencing factor in blood pressure levels. The Zélé method for weight reduction could be included in the arsenal of adjunct nutritional interventions for the treatment of hypertension.

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Author Contributions

The following statements should be used "Conceptualization, J. Nachón García and Gabriela E. Saldaña-Dávila.; methodology, Francisco J. Nachón García; software, Gabriela E. Saldaña-Dávila; validation, Francisco J. Nachón García and Gabriela E. Saldaña-Dávila; formal analysis, Francisco J. Nachón-García.; investigation, Francisco J. Nachón-García; Gabriela E. Saldaña-Dávila; Francisco J. Nachón García; writing-review and editing, Gabriela E. Saldaña Dávila, Francisco J. Nachón García; supervision, Franciso J. Nachón García; project administration, Gabriela E. Saldaña-Dávila; funding acquisition, Gabriela E. Saldaña-Dávila. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work re-ported.

Institutional Review Board Statement

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics committee of the CAE of the Secretary of Health of the State of Veracruz (protocol code CONBIOETICA-30-CEI-001-20170221, ID 1/114/2021 CI-ICS approved at September 21st, 2021. And Protocol Registration in ClinicalTrials.gov ID NCT06275347.

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