ScieniQ Publishers

Japan Journal of Medical Science

Research Article

Behavior of Acidemia in Two Nutritional Interventions: A Double-Blind Comparative Study

Corresponding author
Gabriela Enriqueta Saldaña-Davila L.N. Academia ZéléMexico

Received: 11 Nov 2024
Accepted : 15 Nov 2024
Published: 26 Nov 2024

Gabriela Enriqueta Saldaña-Davila L.N[1], Francisco J. Nachón- García MD. MSci. PhD[2]

[1]*Academia ZéléMexico*
[2]*Instituto de Ciencias de la Salud Universidad Veracruzana Xalapa*

Abstract

Introduction: The ketogenic diet, characterized by very low carbohydrate intake, promotes fat catabolism, leading to ketone body formation. High levels of nutritional ketogenesis support weight loss; however, excessive ketone levels may induce oxidative stress, inflammation, and insulin resistance. Current studies are investigating a low-calorie, low-fat KetogenicDietvariant to assess the impact of ketonemia on pH and blood lactate in the context of weight loss.

Materials and Methods: In a double-blind, randomized clinical trial, we compared two nutritional interventions effects on blood pH, beta-hydroxybutyrate, lactate levels, and weight loss.

Results: Very low-calorie low fat ketogenic dietpatients experienced significant weight loss (12.39 ± 2.8 kg) compared toLow-Calorie Diet participants (6.95 ± 1.96 kg, $p < 0.001$). A positive correlation was found between ketone body levels and weight loss, with 3BHB levels of 0.776 mmol/L associated with ≥1 kg/week weight loss ($p < 0.0001$). No significant differences were observed in pH or lactate between groups (pH: $p = 0.933$; lactate: $p = 0.104$), indicating stable acid-base status.

Conclusion. The findings suggest that very low-calorie low fat ketogenic diet effectively promotes weight loss without altering blood pH or lactate levels, supporting its use as a safe option for obesity management under professional guidance.

Key words: Diet. pH. Lactic Acid. Ketoacidosis. Weight loss diet. Acidemia

Abbreviations

3BHB	3-β-hydroxybutyrate
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CHO	Carbohydrate
DKA	diabetic ketoacidosis
GGT	Gamma-glutamyl transferase
ICM	Indirect Calorimetry Method
KD	Ketogenic Diet
LCD	Low Calorie Diet
MCTs	medium-chain triglycerides
VLCLFKD	very low-calorie low-fat ketogenic diet

Introduction

Over 100 years ago, it was first reported [1], that in healthy individuals, acetone and beta-hydroxybutyric acid are produced after fasting. A similar finding was observed following a low-carbohydrate, high-fat diet, known as the Ketogenic Diet (KD) [2], In response to carbohydrate (CHO) restriction, the body activates fat catabolism; mitochondria in hepatocytes oxidize free fatty acids released by adipose tissue into acetic acid, which then conjugates with Coenzyme A to form Acetyl-CoA. The excess Acetyl-CoA facilitates the formation of Acetoacetyl-CoA, which quickly loses the CoA to form acetoacetic acid. This, in turn, leads to the production of acetone, 3-β-hydroxybutyrate (3BHB), and acetoacetate, energy-rich metabolites [3, 4].

Under normal conditions, the reference range for ketone body concentration in healthy adults is between 100 and 250 µmol [5]. Ketone levels increase during prolonged fasting, exercise, ketogenic diet usage, and even during pregnancy and lactation [6]. Recent studies have established that a safe and effective nutritional ketosis range for weight loss is between 0.5 and 3.0 mmol/L. In contrast, in pathological conditions—including cases

of hyperemesis gravidarum, diabetic ketoacidosis (DKA), alcoholism, and various metabolic disorders—ketone levels can reach up to 20 mmol [5].

As previously mentioned, a ketogenic diet (KD) mimics the fasting state, thereby altering metabolism to primarily utilize fats as an energy source [7]. Several variations of KDs exist, differentiated by their macronutrient composition. Generally, KDs reverse the typical dietary macronutrient pyramid by promoting restricted CHO intake while allowing more liberal consumption of proteins and fats. Traditionally, a KD is a stringent nutritional regimen that must be closely monitored by healthcare professionals [8]. These diets emphasize the consumption of medium-chain triglycerides (MCTs), as these fats yield a greater amount of ketone bodies per gram compared to long-chain triglycerides.

The modified Atkins diet is less restrictive, permitting ad libitum intake of fats, proteins and CHO [9]. In contrast, the diet based on the Low Glycemic Index pattern focuses on maintaining stable blood glucose levels through adherence to a KD, allowing for approximately 10% of total energy expenditure to come from CHO [10]. Recently, KDs have been integrated into medical nutrition therapy (MNT) for treating overweight and obesity [11–13]. In N-of-1 trials, patients with overweight and obesity often prefer this type of intervention over traditional hypocaloric diets [14]. This preference may be attributed to the appetite-suppressing effects of KDs, which also serve as a weight loss tool [15,16].

Consequently, although not traditionally included in classic ketogenic diets, our group is investigating a variation characterized by a very low-calorie, low-fat, and normal-protein content (VLCLFKD), which initially provides less than 800 total kcal, with 1.2 g of protein per kg of ideal body weight, 50 g of CHO, and 20 g of fats, primarily from medium-chain triglycerides. This regimen gradually transitions to a normal diet, as previously described by the **Zélé Method** [17].

Considering the myths surrounding KDs and the assumption of their ability to modify blood pH, a comparative study was conducted between two nutritional interventions: a low-calorie diet (LCD) and a very low-calorie low-fat ketogenic diet (VLCLFKD). This study aimed to assess whether the level of ketone bodies produced results in changes in blood lactate and pH levels over a 12-week treatment period. Additionally, the research sought to establish the ketonemia threshold at which patients could achieve a weight loss of one kilogram or more per week.

MATERIALS AND METHODS

This is a prospective, longitudinal, randomized, double-blind clinical trial registered atwww.clinicaltrial.gov under NCT06275347. The study compared levels of beta-hydroxybutyrate (3BHB), blood pH, and lactate in Mexican patients with a body mass index (BMI) between 30 and 34.9 kg/m² undergoing two metabolically distinct nutritional interventions: a very low-calorie low-fat ketogenic diet (VLCLFKD) and a low-calorie diet (LCD).

The primary outcome was to establish baseline pH and ketone body levels and then track their behavior at peak ketonemia and after 12 weeks of nutritional intervention in patients following a VLCLFKD. The secondary outcome focused on determining the ketone body levels necessary for patients on a VLCLFKD to achieve a weight loss of one kilogram or more per week. Finally, the study aimed to compare the changes in blood pH and lactate levels between patients on a VLCLFKD and those on an LCD.

PARTICIPANTS

Eligible participants included individuals of both sexes, aged 18 to 60 years, with a BMI ranging from 30 to 34.9 kg/m². To ensure the integrity of the results, patients who had received weight loss treatment within the previous 6 months were excluded. Recruitment was conducted in Mexico City through an open call on Zélé®'s (Agustin González de Cossío 806 Colonia del Valle Centro, AlcaldíaBenito Juárez 03100 CDMX, México) social media channels.

Exclusion criteria encompassed pregnant or breastfeeding individuals, those with severe eating disorders, alcoholism, or substance abuse issues, as well as individuals with severe psychiatric disorders such as schizophrenia or bipolar disorder. Patients with liver disorders were excluded if their alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) levels exceeded three times the reference value. Furthermore, individuals with endocrine, metabolic, cardiovascular, or renal diseases who were undergoing treatment and had been diagnosed prior to the study, or those taking blood glucose control medications—including insulin, GLP-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors—were also excluded.

SAMPLE SIZE

The sample size was determined based on resource availability and the need for population representativeness, with a target of 95% power and a 95% confidence interval. A 3:1 ratio of cases to controls was selected to accommodate up to 35% attrition. Sample size calculations were conducted using Fleiss' equation, with results derived from EPI Info STATCALC, leading to the inclusion of 56 cases and 32 controls.

RANDOMIZATION

The first 100 individuals deemed eligible for the study were invited for an interview with the researchers. During this interview, participants received detailed information about the project's characteristics and conditions, and their consent was obtained through the signing of an informed consent form. This form was reviewed and approved by the Research Ethics Committee of the Centro de Alta Especialidad "Dr. Rafael Lucio" of the Ministry of Health of the State of Veracruz. Each participant was assigned a number randomly through a computerized process, which was then sent to the food production and distribution facility. A blind selection process was conducted for both the researchers and the participating patients. It is important to note that participants did not receive nutritional treatment until their baseline laboratory analyses had been reviewed and interpreted.

NUTRITIONAL INTERVENTION

All participants underwent a nutritional intervention program that included a standardized physical activity plan and psycho-emotional support over a 12-week period. Additionally, they received nutritional supplements containing vitamins and trace elements, such as sodium chloride, magnesium oxide, and calcium carbonate, to meet daily recommended requirements throughout the study.

Participants assigned to the VLCLFKD group progressed through four stages

1. **Frank Ketosis:** In this initial stage, caloric intake was limited to 650 to 730 kcal per day, divided into five meals based on Zélé® commercial preparations and low-glycemic-index vegetables. Patients received an average of 1.2 g of protein per kilogram of ideal body weight daily, 20 g of lipids based on essential fatty acids, and less than 60 g of absorbable carbohydrates. Thisstagelasted 4 weeks.
2. **Mixed Ketosis:** During this stage, two meals based on commercial preparations were gradually replaced with animal proteins (meat, fish, eggs, etc.), increasing caloric intake by 100 to 150 kcal per day without causing patients to exit ketosis. Thisstagealsolasted 4 weeks.
3. **Transition Stage:** In this phase, simple carbohydrates from fruits and some complex carbohydrates in the form of grains were introduced. This allowed patients to exit ketosis and transition to a hypocaloric diet with an intake of 1300 to 1500 kcal per day. Macronutrient proportions were adjusted to 30-35% protein, 25% fat, and 40-45% carbohydrates. This stage lasted 2 to 3 days.

4. **Integral and Maintenance Phase:** In this phase, patients were provided with a hypocaloric diet tailored to their energy expenditure, as measured by the Indirect Calorimetry Method (ICM), with caloric intake ranging from 1300 to 2250 kcal per day. Macronutrient proportions were adjusted to 50% carbohydrates, 25% protein, and 25% fat, following the Diogenes study.

Conversely, participants assigned to the LCD group followed a balanced low-calorie diet, with caloric intake reduced by 20% relative to basal metabolic expenditure, calculated via Multifrequency Bioelectrical Impedance Analysis and verified using the FAO/WHO/UNU formula (FAO/WHO/UNU, 1985). Caloric intake ranged from 1200 to 1400 kcal per day, with a macronutrient distribution of 50% carbohydrates, 25% proteins, and 25% fats, following the Diogenes study.

FOOD DELIVERY DURING THE STUDY

Throughout the study, all participants received, free of charge, all the products needed to complete their meals according to each phase of the study. They were only required to add fresh vegetables to complete their meals. Each participant received a weekly food package during their consultation, containing everything necessary to meet the meal requirements for their assigned stage of nutritional intervention. It is important to note that this process was conducted while maintaining double-blinding criteria.

ANTHROPOMETRIC AND METABOLIC DATA

Anthropometric measurements were taken at the same time and under the same conditions each week. Height was measured at the beginning of the study using a Seca wall stadiometer with 0.1 cm precision. Weight and body composition were recorded with participants wearing light clothing and no shoes, using an InBody 570 body composition analyzer with 0.1 kg accuracy. Fasting blood samples were collected at a medical laboratory by specialized personnel trained in phlebotomy and arterial puncture.

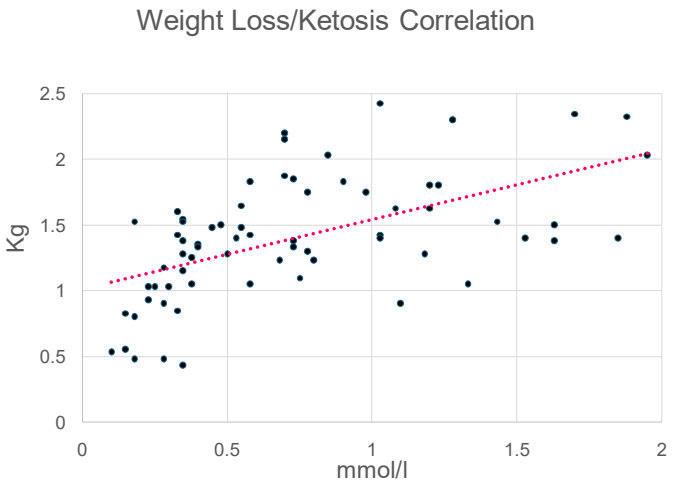
STATISTICAL ANALYSIS

The initial demographic and clinical characteristics of the participants are summarized in tables, with descriptive statistics presenting n (%) and mean (SD) for categorical and continuous variables. To evaluate the differences in each variable between the two groups, a t-test and repeated measures ANOVA were conducted for continuous variables, while Chi-square (χ^2) tests and one-way ANOVA were performed for categorical variables. Bivariate Pearson correlation was calculated between weight loss and ketone body levels. A ROC curve analysis was conducted to determine the optimal ketone body level for achieving a weight loss of at least 1.0 kg per week during the ketosis phases. A p-value of ≤ 0.05 was considered statistically significant in all cases. The primary outcome was the percentage and/or absolute change in ketone body values, pH, and lactate levels.

RESULTS

A total of 88 patients were included in the study, with 56 randomly assigned to the VLCLFKD group and 32 to the LCD group. The dropout rate during the first stage of the study was 12.5%, so the analysis was conducted only on the patients who completed the protocol, resulting in 51 and 26 patients, respectively.

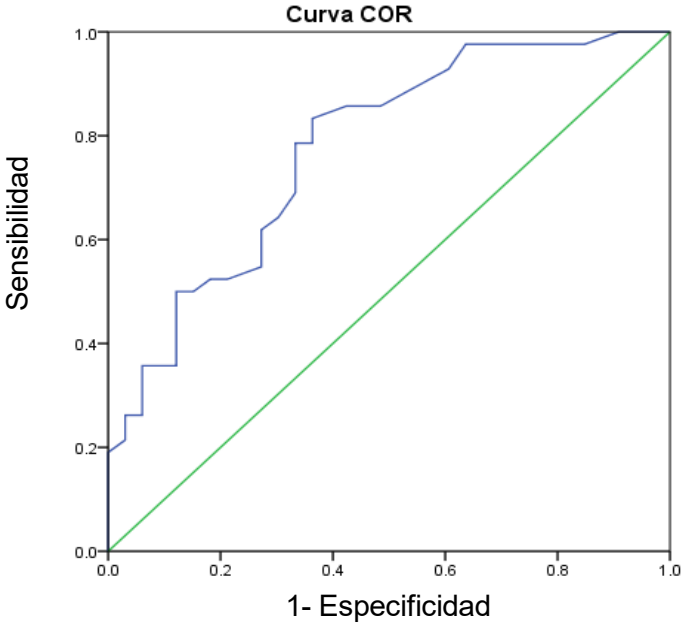
To establish the correlation between weight loss and ketosis, the mean weight in kg and levels of 3BHB were obtained during the first 4 weeks of treatment, corresponding to the strict ketosis period of the Zélé method. A bivariate Pearson correlation was performed using the mean values of these variables for each patient, resulting in r=0.558, p<0.0001, as shown in Graph 1.



Graph 1. Correlation between Weight Loss and Blood Ketone Levels

Subsequently, the levels of 3BHB were analyzed to calculate the optimal level of β-Hydroxybutyrate. All patients who lost between 1 and 1.5 kg per week were included, and their blood ketone levels were used to construct a ROC curve, indicating that a value of 0.776±0.054 mmol/L corresponds to a weight loss of at least 1 kg per week (p< 0.0001), as illustrated in Graph 2.

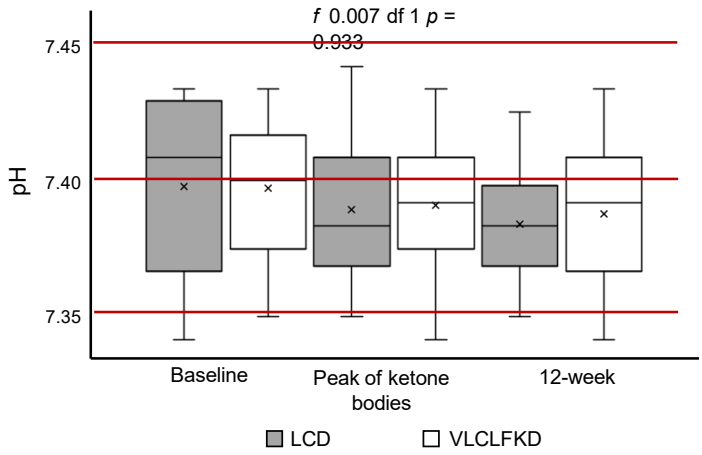
Optimal level of β-Hydroxybutyrate



Graph 2. ROC curve to achieve a loss equal to or greater than 6 kg in 4 weeks, it is necessary to reach the figure of 0.776 ± 0.054 mmol/l p < 0.0001

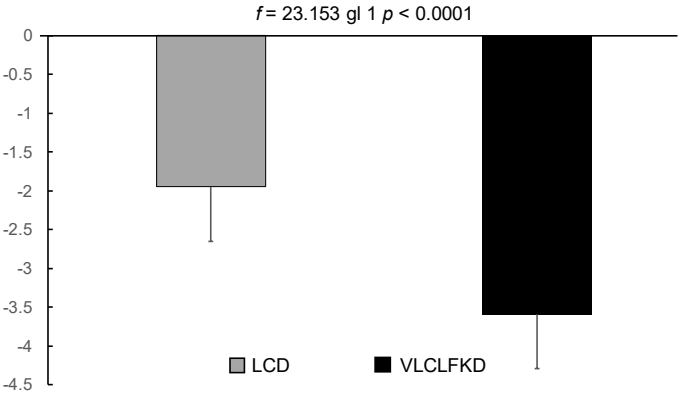
Next, baseline results for arterial pH and ketone bodies were analyzed, focusing on the peak elevation of ketone bodies achieved in the second week of treatment with VLCLFKD, compared to the results from LCD patients during the same week and the values at the end of the 12-week treatment period. A general linear model for repeated measures was employed, which showed no significant differences in pH levels between patients on VLCLFKD and those on LCD (f=0.007, df=1, p=0.933), as illustrated in Graph 3. The lactate levels at the study's onset had a mean of 1.02±0.241.02 \pm 0.241.02±0.24 mmol/L for VLCLFKD and 1.18±0.401.18 \pm 0.401.18±0.40 mmol/L for LCD patients. The intermediate measurement was 0.97±0.30and 0.96±0.20 mmol/L, respectively, and at the end of the study, 0.92±0.30mmol/L, which showed no differences in repeated measures tests (f=3.01df=1, p=0.104p), as shown in Graph 4.

pH Levels



Graph 3. pH levels remained within normal ranges even when expanding all dispersion measures and showed no differences between the nutritional interventions.

Visceral Fat Index Decrease



Graph 4. Reduction in Visceral Fat Index

Finally, to complement the study, the weight loss in patients subjected to VLCLFKD was 12.39±2.81kg for the VLCLFKD group and 6.95±1.96kg for the LCD group (t=9.16df=76, p<0.001). The reduction in the visceral fat index was 3.59±1.2 in patients with VLCLFKD and 1.95±1.2for LCD (t=−4.81df=76, p<0.0001).

DISCUSSION

Conducting case reports and nutritional intervention studies in humans presents challenges due to high variability among participants, a common issue faced by many researchers. This study aimed to control most variables, and with the participation of the manufacturing plant, randomization and blinding were successfully implemented.

Recently, the term "nutritional ketosis" has been used, with experts such as Jeff S. Volek, Timothy Noakes, and Stephen D. Phinney recommending ketone levels between 0.5 and 3.0 mmol/L [18]. In our study, we found that to achieve a weight loss of 1.5 kg per week, a ketone level of 0.8 mmol/L was sufficient. Additionally, we demonstrated a directly proportional correlation between weight loss and the concentration of 3BHB.

Finding articles that measure acidemia and lactate levels in patients undergoing ketogenic diets is not easy. The hypothesis that acidemia production has therapeutic potential in treating epilepsy was proposed in 1931 [19]. Several years later, this theory was challenged when an animal study showed that a ketogenic diet did not alter cerebral acidosis levels. More recent reviews exploring the mechanism of action of ketosis in epilepsy treatment also assert that there are no changes in the pH of patients undergoing these nutritional interventions [19].

Focusing on weight loss, our study demonstrates that there is no significant change in arterial pH or lactate levels in patients undergoing VLCLFKD, and the behavior of these variables is consistent with those in patients on an LCD. We found only one study measuring pH values during weight loss treatment; although not a comparative study, its results were nearly identical to those of our study [20].

An experimental study comparing Wistar rats on a ketogenic diet and a hypocaloric diet for 60 days found that the hypocaloric diet group concluded the experiment with a pH of 7.52±0.177.52 \pm 0.177.52±0.17, while the ketogenic diet group had a pH of 7.36±0.277.36 \pm 0.277.36±0.27. The authors concluded that the animals in ketosis exhibited acidosis; however, normal blood pH values range from 7.35 to 7.45, suggesting that the control diet animals may have tended toward alkalosis [21]. The most recent study published regarding pH determination in patients on a ketogenic diet relates to nutrition in patients with sepsis hospitalized in intensive care units, which also demonstrated no changes in acidemia values secondary to this type of nutrition [22].

Conclusion

The ketosis state induced by the very low-calorie, low-fat ketogenic diet (VLCLFKD) promotes safe weight loss, achieving a reduction of at least 1 kg per week when ketone body levels are maintained around 0.776 mmol/L. Additionally, the study confirms that VLCLFKD does not cause significant changes in acidemia nor does it induce lactate elevation, indicating an acid-base stability comparable to that observed in a conventional hypocaloric diet.

References

1. Wilder RM. (1921) The effects of ketonemia on the course of epilepsy. Mayo Clin Proc. 2: 307–8.
2. Woodyatt RT. (1921) OBJECTS AND METHOD OF DIET ADJUSTMENT IN DIABETES *. Arch Intern Med [Internet]. 28: 125–41. Available from: http://archinte.jamanetwork.com/
3. Laffel L. (1999) Ketone Bodies: a Review of Physiology, Pathophysiology and Application of Monitoring to Diabetes. Diabetes Metab Res Rev. 15: 412–26.
4. Mezhnina V, Ebeigbe OP, Velingkaar N, Poe A, Sandlers Y, Kondratov R V, et al. (2022) Circadian clock controls rhythms in ketogenesis by interfering with PPARα transcriptional network. PNAS [Internet]. 119: 1–11. Available from: https://doi.org/10.1073/pnas.2205755119
5. Puchalska P, Crawford PA. (2017) Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. Vol. 25, Cell Metabolism. Cell Press. 262–84.
6. Qian M, Wu N, Li L, Yu W, Ouyang H, Liu X, et al. (2020) Effect of elevated ketone body on maternal and infant outcome of pregnant women with abnormal glucose metabolism during pregnancy. Vol. 13, Diabetes, Metabolic Syndrome and Obesity. Dove Medical Press Ltd. 4581–8.
7. Rho JM, Anderson GD, Donevan SD, White HS. (2002) Acetoacetate, acetone, and dibenzylamine (a contaminant in L-(+)-β-hydroxybutyrate) exhibit direct anticonvulsant actions in vivo. Epilepsia. 43: 358–61.
8. Armeno M, Caraballo R, Vaccarezza M, Alberti MJ, Ríos V, Galicchio S, et al. (2014) Consenso nacional sobre dieta cetogénica [Internet]. Vol. 59, Rev Neurol. Availablefrom: www.neurologia.com
9. Atkins RC. Dr. Atkin' (1972) diet revolution. . New York: David McKay Company.
10. Pfeifer HH, Thiele EA. (2005) Low-glycemic-index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy [Internet]. Available from: www.neurology.org

11. Choi YJ, Jeon SM, Shin S. (2020) Impact of a ketogenic diet on metabolic parameters in patients with obesity or overweight and with or without type 2 diabetes: A meta-analysis of randomized controlled trials. Nutrients. 1;12: 1–19.
12. Malhotra V, Sawal A. (2023) Metabolic Effects of Ketogenic Diets and Their Utilization in Obesity Management: A Systematic Review. Cureus. 27.
13. Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, et al. (2023) Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. BMC Med. 1: 21-1.
14. Grammatikopoulou MG; GKK; GK; BDP; EAG; GDG. (2022) The Niche of n-of-1 Trials in Precision Medicine for Weight Loss and Obesity Treatment: Back to the Future. Curr Nutr Rep. 11: 133–45.
15. Gibson AA, Seimon R V., Lee CMY, Ayre J, Franklin J, Markovic TP, et al. (2015) Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. Obesity Reviews. 1;16: 64–76.
16. Roekenes J; MC. (2021) Ketogenic diets and appetite regulation. Curr Opin Clin NutrMetab Care. 24: 359–63.
17. Nachón-García Francisco, Saldaña-Davila Gabriela. (2023) Participation of a Low-Fat Controlled Ketogenic Diet in the Regulation of Blood Pressure in Mexican Women with Type I Obesity [Internet]. Vol. 3, Int J Diabetes Metabolic Synd. Available from: www.asrjs.com
18. Volek JS, Noakes T, Phinney SD. (2015) Rethinking fat as a fuel for endurance exercise. Eur J Sport Sci. 2;15: 13–20.
19. Nylen K, Likhodii S, Mcintyre Burnham W. (2009) The Ketogenic Diet: Proposed Mechanisms of Action.
20. Gomez-Arbelaez D, Crujeiras AB, Castro AI, Goday A, Mas-Lorenzo A, Bellon A, et al. (2017) Acid–base safety during the course of a very low-calorie-ketogenic diet. Endocrine. 1;58: 81–90.
21. Arsyad A, Idris I, Rasyid AA, Usman RA, Faradillah KR, Latif WOU, et al. (2020) Long-Term Ketogenic Diet Induces Metabolic Acidosis, Anemia, and Oxidative Stress in Healthy Wistar Rats. J NutrMetab.
22. Rahmel T, Effinger D, Bracht T, Griep L, Koos B, Sitek B, et al. (2024) An open-label, randomized controlled trial to assess a ketogenic diet in critically ill patients with sepsis. SciTranslMed. 10: 16-755.

Cite this article: Gabriela Enriqueta Saldaña-Davila L.N. Francisco J. Nachón- García. (2024) Behavior of Acidemia in Two Nutritional Interventions: A Double-Blind Comparative Study. Japan Journal of Medical Science 5 (1): 208-212.