Zinc supplementation in patients with cirrhosis and dysgeusia: Randomized Clinical Trial

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ABSTRACT

Background: Dysgeusia has been identified as part of liver cirrhosis (LC). Since zinc (Zn) is involved in taste and LC pathophysiology, this study aimed to evaluate the effect of zinc supplementation in patients with LC. **Methods**: Double-blinded randomized clinical trial, controlled with placebo in patients with LC. The intervention consisted of 100mg/day of Zn for six months. Improvement of dysgeusia was evaluated according to changes in perception (PT) and recognition (RT) thresholds of five flavors evaluated by ascending molar dilutions method. Differences were assessed by determining the size and the magnitude of effects, interpreted according to Common Language Effect Size, and determining the number needed to treat (NNT). **Results**: 50% (n=17) of patients were male, with a median age of 57 [51-63] years. After six months, 28 patients accomplished the follow-up; in patients who receive Zn, we observed a PT at a lower molar concentration in salty (1.0 [IQR 1.0-14.7] M vs. 12 [IQR 1.0-12] M, improvement probability 58% (NNT=6)), sweet (1.5 [IQR 1.5-3.5] M vs. 3.5 [IQR 1.5-4.0] M, improvement probability 57% (NNT=6)), sour (0.48 [IQR 0.48-0.48] M vs 0.48 [IQR 0.48-2.44] M, improvement probability 65% (NNT=3)) and umami (0.40 [IQR 0.40-0.40] M vs 0.70 [IQR 0.70-0.80] M, improvement probability 74% (NNT=2)) tastes compared to placebo group. With respect to RT, patients who received Zn, recognition of umami taste was observed at a lower molar concentration (0.70 [IQR 0.40-1.17] M vs 0.90 [0.70-1.1] M, improvement probability 59% (NNT=5)) compared to placebo. **Conclusion**: Patients supplemented with GZn show an improvement probability of PT higher than 55% for salty, sweet, sour, and umami tastes. Meanwhile, the improvement probability of RT for umami taste is 59%.

Key words: taste disorders; cirrhosis; zinc; liver.

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RESUMEN

Antecedentes: La disgeusia se ha identificado como parte de la cirrosis hepática (CH). Ya que el zinc (Zn) está involucrado en la fisiología del sabor y la CH, el objetivo de este estudio fue evaluar el efecto de la suplementación con Zn en pacientes con CH y disgeusia. **Métodos**: Ensayo clínico aleatorizado, doble ciego, controlado con placebo de 34 pacientes con CH. La intervención consistió en 100mg/día de gluconato de Zinc (GZn) durante 6 meses. La mejoría de la disgeusia fue evaluada con la concentración en que se detectaron los umbrales de percepción (UP) y reconocimiento (UR) de cinco sabores. Para evaluar las diferencias, se determinaron los tamaños de efecto y la magnitud de estos con interpretación de acuerdo con los Common Language Effect Size (expresado en porcentaje) y determinando el numero necesario a tratar (NNT). **Resultados**: El 50% (n=17) fueron hombres con mediana de edad de 57 [IQR 51-63] años. Posterior a los 6 meses, 28 pacientes cumplieron el seguimiento; en los pacientes que recibieron Zn se observó UP a menor concentración en los sabores salado (1.0 [IQR 1.0-14.7]M vs 12 [IQR 1.0-12]M, con una probabilidad de mejoría de 58% (NNT= 6)), dulce (1.5 [IQR 1.5-3.5]M vs 3.5 [IQR 1.5-4.0]M, probabilidad de mejoría de 57% (NNT=6)) , ácido (0.48 [IQR 0.48-0.48]M vs 0.48 [IQR 0.48-2.44]M, probabilidad de mejoría de 65% (NNT=3)) y umami (0.40 [IQR 0.40-0.40]M vs 0.70 [IQR 0.70-0.80]M, probabilidad de mejoría de 74% (NNT=2)) en comparación con el placebo. Los pacientes que recibieron Zn presentaron UR del umami en menor concentración respecto al placebo (probabilidad de mejoría 59% (NNT=5)). **Conclusión**: Los pacientes suplementados con GZn durante seis meses, presentan probabilidades de mejoría del UP de los sabores salado, dulce, ácido y umami mayores al 55%, mientras que la probabilidad de mejoría del UR del sabor umami es del 59%.

Palabras clave: alteraciones del gusto; cirrosis; zinc; hígado.

INTRODUCTION

Liver cirrhosis (LC) is the final stage of chronic liver diseases, characterized by four pathophysiological mechanisms independent of the initial cause of liver damage: necrosis of hepatocytes with loss of liver parenchyma and inflammation, fibrogenesis, changes in cell growth and vascular alterations.[1] The epidemiology of LC is challenging to estimate due to the multifactorial etiology and access to health systems according to the economic development of each country; on the other hand, the prevalence may be underestimated due to the asymptomatic phase of the disease. According to 2021 published data, LC is the 11th cause of death worldwide, with 1.32 billion deaths per year.[2]

Dysgeusia is defined as an impairment in perception (PT) or recognition (RT) thresholds of basic flavors (salty, sweet, sour, bitter, and umami),[3] and it has been associated with a direct impact on quality of life (QoL), weight loss and malnutrition.[4] Despite the importance of dysgeusia, its effect is commonly underestimated until its presentation.[5] Dysgeusia is recognized as part of the natural history of liver diseases, with a prevalence of 40%;[6-8] taste disorders are associated, majorly, with zinc deficiency, although the cause of LC and pharmacological treatment could have a role in the presence of dysgeusia in patients with cirrhosis.

Since the 1970s, zinc has been identified as a key player in human taste perception,[9] however, its physiology has not been fully described. Zinc is also implicated in liver function, therefore, hepatic injury is related to zinc liver function impairments, including taste perception and recognition.

Despite the clinical relevance of dysgeusia and zinc deficiency in LC patients, evidence related to epidemiology and clinical impact needs to be clarified; the reported prevalence of dysgeusia comes from small studies with variable methodology and performed in single cirrhosis etiology.[10-13] Therefore, this clinical trial aims to evaluate zinc supplementation in improving dysgeusia in patients with cirrhosis.

MATERIAL AND METHODS

Trial design

This is a double-blinded randomized clinical trial controlled with a placebo of two parallel groups with a 1:1 allocation ratio.

Eligibility criteria of participants

Adult patients (18-70 years old) with an LC diagnosis who attended Medica Sur Foundation for hepatic disease surveillance, patients with and without comorbidities, were

included. Exclusion criteria: patients with hepatic encephalopathy at the time of evaluation, patients with zinc supplement consumption, patients with neurological impairment, patients with common cold, allergic rhinitis or buccal infections, and patients with active alcohol consumption. After clinical confirmation of LC diagnosis, eligible patients were invited to participate in this trial. Patients who presented adverse effects higher than grade 214 related to supplementation and patients who did not accomplish a six-month follow-up were eliminated.

Setting

Recruitment was made by an open invitation to patients diagnosed with LC who attended medical surveillance at Fundación Clínica Médica Sur.

Interventions

Once LC was confirmed, dysgeusia was evaluated by ascending dilutions method15 at baseline and after six months to identify PT and RT of five basic tastes: salty, sweet, sour, bitter, and umami. The substances used for the five tastes were dissolved in distilled water in eight ascending concentrations (Supplementary 1). The solutions were prepared every week and stored at 4ºC; at the time of testing, 5 ml of each solution was poured into a Falcon tube at room temperature, and each box was labeled with a letter and number according to concentration taste. The order in which eight solutions for each taste were presented was identical for all subjects. PT was identified as the number of dilutions in which the patient tasted dilution different from water; meanwhile, RT was defined as the number of dilutions in which the patient could identify the taste. For diagnosis of dysgeusia, dilutions were compared with normal values previously established in the Mexican population [16]; patients who perceive or recognize tastes in different dilutions of these values were diagnosed with dysgeusia.

Patients diagnosed with dysgeusia were randomized into two groups: Zinc supplementation (100mg of Zinc Gluconate (ZnG)) and Placebo (100 mg of dextrose), and they were provided a bottle with 30 capsules, then instructions for consumption of capsules were explained (1 capsule/24 hrs). In both groups, patients received nutritional consulting adequate to LC (including adequate protein and fiber consumption), at baseline. Patients were evaluated monthly to identify possible adverse effects and clinical evaluation of liver disease. At baseline and after six months, serum zinc was determined.

Nutritional risk was evaluated by Subjective Global Evaluation16 and Royal Free Nutrition Priorizating Tool17 at baseline and after six months. Quality of life was assessed by the Liver Disease Quality of Life Questionnaire (Spanish version)18 at baseline and after six months. Macro and micronutrient consumption were evaluated with the SNUT19 questionnaire at baseline and after six months.

Outcomes

The primary outcome was the improvement of PT and RT according to the difference in the number of dilutions identified at baseline and after six months. Nutritional risk, liver decompensation, quality of life, macro and micronutrient consumption, and serum zinc levels were secondary outcomes.

Sample Size

After twelve months of population analysis, the prevalence of dysgeusia in patients with cirrhosis was determined at 80%. This intervention aims to decrease the prevalence of dysgeusia in LC patients, considering 85% of statistical power and 5% alpha two-sided, with 1:1 proportion between groups, 13 patients were required in each group for reject the null hypothesis of failure ratio in intervention and control group are equal. Considering a 10% loss, we obtained a final sample size of 29 patients.

Randomization

A random sequence table was generated using a computer-based- number generation. A study external person generated the sequence. Capsules and bottles were identical, placed in two boxes, and allotted in an external office. At the inclusion moment, treatment was assigned according to a random sequence for an external person not involved in the clinical evaluation of patients. At every monthly assessment, the patient delivered the monthly bottle, and at this moment, leftover capsule counting was made.

Blinding

During inclusion and evaluation, all researchers and patients were blinded to the group assigned to each patient.

Statistical analysis

Only patients who accomplished the six-month follow-up were considered for statistical analysis. Variable distribution was determined by the Shapiro-Wilks test, resulting in non-parametric distribution; therefore, descriptive analysis for continuous data was presented as median and interquartile ranges. Meanwhile, categorical data were presented as numbers and percentages. A p-value <0.05 was considered statistically significant.

For the primary outcome, median differences of dilutions were evaluated by the Mann-Whitney U test and the Cohen d test calculated effect sizes. Differences in LC decompensation and nutritional risk after six months were evaluated by the Chi-square test. Median differences in macro and micronutrient consumption, quality of life domains, and Zn serum levels were evaluated by the Mann-Whitney U test and effect sizes (Cohen d).

Ethical considerations

All procedures were performed according to the Helsinki Declaration; all patients signed a Consent Informed Form. The protocol was approved by Comité de Ética en Investigación de Médica Sur S.A.B. de C.V. (2013-EXT-16) and by Comité de Investigación de la Universidad Anáhuac.

RESULTS

A total of 34 patients were randomized, sixteen in the ZnG group and eighteen in the placebo group. Figure 1 presents the study flow diagram. 50% (n=17= of patients were male, with median age of [IQR 51-63] years. Hepatitis C Virus infection was the primary etiology of LC (41.2%, n=14), followed by abuse of alcohol consumption (26.5%, n=9). According to LC status, the median of MELD was 11 [IQR 9.7 – 12.2]; at baseline, the presence of ascites was the most prevalent decompensation. There were no differences in baseline characteristics of patients (Table 1).
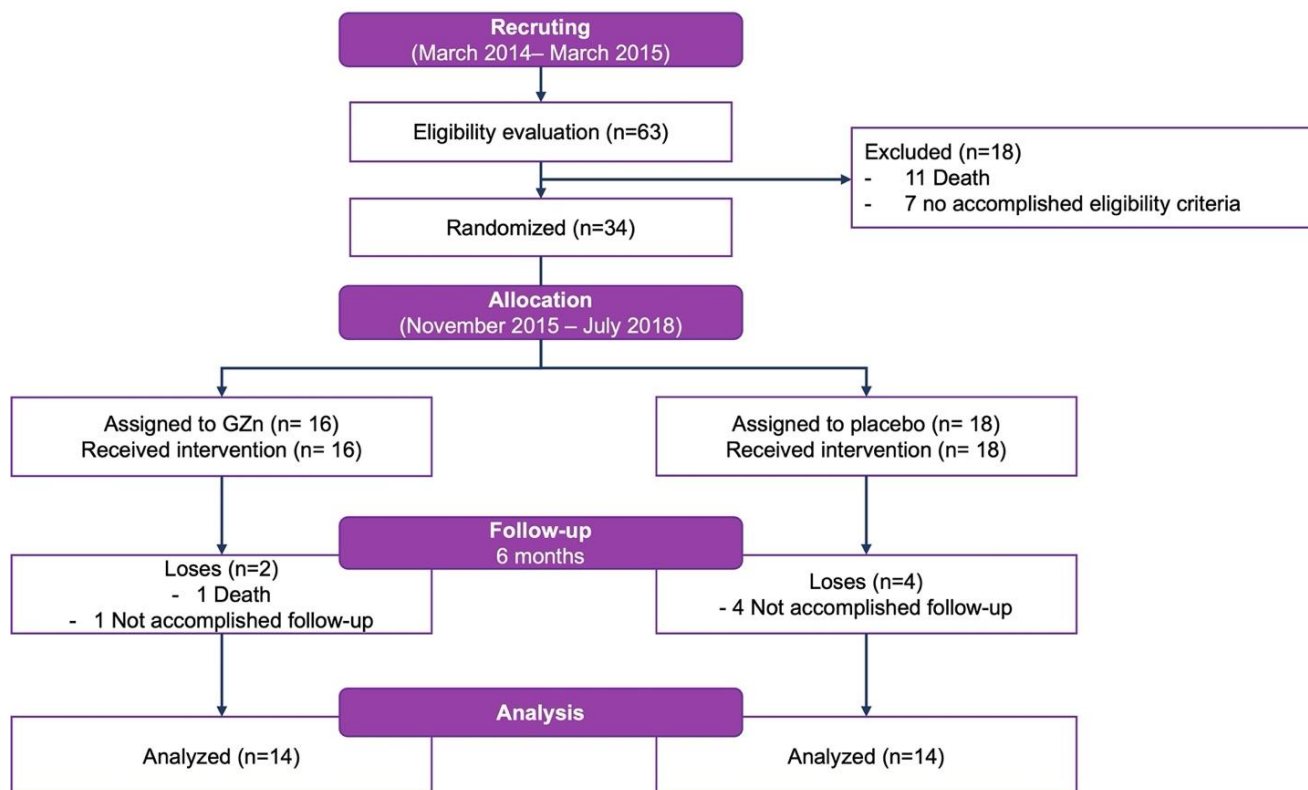

FIGURE 1. Study Flow Diagram.

TABLE 1. General characteristics of patients included

Characteristic	General n=34 % (n)/M [IQR]	ZnG n=16 % (n)/M [IQR]	Placebo n=18 % (n)/M [IQR]	p*
General				
Male	50% (17)	50% (8)	50% (9)	1.00
Age (years)	57 [51-63]	55[49-64]	57[54-61]	0.48
BMI (kg/m²)	27[24.-28.8]	27.1[23.9-28.7]	26.4[23.6-31.1]	0.41
DM	41.2% (14)	25% (4)	55.6% (10)	0.92
Hypertension	20.6% (7)	25% (4)	16.7% (3)	0.68
Smoking	41.2% (14)	50% (8)	33.3% (6)	0.48
Serum Zn	60.5 [46.7-70.2]	61[44.5-70.7]	58.5[47-70.2]	0.73
Liver cirrhosis characteristics				
Etiology				
Alcohol	26.5% (9)	18.8% (3)	33.3% (6)	
NAFLD	8.8% (3)	0	16.7% (3)	
HCV	41.2% (14)	50% (8)	33.3% (6)	0.30
Autoimmune	17.6% (6)	25% (4)	11.1% (2)	
Other	5.9% (2)	6.3% (1)	5.6% (1)	
MELD	11 [9.7 – 12.2]	10 [9.2-11-7]	11 [9.5-13]	0.41
Ascities	38.2% (13)	31.3% (5)	44.4% (8)	0.49
Variceal Bleeding	20.6% (7)	6.3% (1)	33.3% (6)	0.09
Taste disorders				
PT Dysgeusia	76.5% (26)	68.8% (11)	83.3% (15)	0.42
RT Dysgeusia	85.3% (29)	75% (12)	94.4% (17)	0.16

* p value represents difference significance between ZnG group and placebo group. BMI body mass index; DM diabetes mellitus; Zn zinc; NAFLD non-alcoholic fatty liver disease; HCV Hepatitis C virus; MELD Model of End-stage Liver Disease; PT perception threshold; RT recognition threshold.

76.5% (n=26) of the patients presented at least one dysgeusia in PT, while 85.3% (n=29) presented dysgeusia in RT. Regarding nutritional risk, according to SGA, most patients were malnourished or at risk of malnutrition (61.8%, n=21). On the other hand, the risk of malnutrition measured by the Royal Scale was (41.2%, n=14). Zinc consumption was within the recommended daily intake ranges for Mexican patients.[20]

Regarding QoL, the global median was 4.7 [IQR 4.2-5.3], with the lowest scores observed in the domains of fatigue 4.2 [IQR 3.4-5.4] and worry 4.3 [IQR 3.4-5.8]. Regarding the median consumption of the intervention, the overall median consumption was 17,700 [IQR 17,250 – 17,900] mg, with no differences between the group that received the supplement (17,600 [IQR 17,350 – 17,925] mg) and

the placebo group (17,800 [IQR 17,000 – 17,850] mg) (p=0.44, Mann-Whitney U).

Dysgeusia improvement

According to the evaluation of the PT of each flavor, after six months of intervention, patients who received ZnG perceived sweet, sour, and umami tastes at a lower concentration.; That is, they needed a smaller amount of the stimulus to be able to perceive it; however, the effect size of the salty and sweet flavors was small, while the sour and umami flavors presented intermediate and large effect sizes respectively. According to the interpretation of the magnitude of the effect sizes, after six months of intervention

with ZnG, the probability of improvement in the UP of salty tastes is 58.1%, and sweet taste is 57.8%, with an NNT of 6 patients, while the probability of improvement in the UP of the acid taste is 65.3% and 74.4% for the umami taste, with NNTs of 3 and 2 patients, respectively. No significant diffe-

rences were observed in bitter taste (Table 2). In RT evaluation, differences were only observed in RT of the umami taste, similarly at a lower concentration in the patients who received ZnG, with a small effect and probability of improvement of 59.5% (NNT=5). (Table 2)

TABLE 2. Differences in perception and recognition thresholds after six months of intervention

Taste	ZnG M [IQR]	Placebo M [IQR]	p*	Effect size	CLEs	NNT
Perception Threshold						
Salty	1.0 [1.0-14.7]	12 [1.0 - 12]	0.59	0.29	58.12%	6.1
Sweet	1.5 [1.5-3.5]	3.5 [1.5-4.0]	1.00	0.28	57.85%	6.3
Bitter	89 [89-89]	89 [89-93]	0.07	-0.31	41.32%	NA
Sour	0.48 [0.48-0.48]	0.48 [0.48-2.44]	0.32	0.56	65.39%	3.2
Umami	0.40 [0.40-0.40]	0.70 [0.70-0.80]	0.59	0.93	74.46%	2.0
Recognition Threshold						
Salty	1.0 [1.0-23]	12 [9.2 - 12]	0.16	-0.07	58.12%	6.1
Sweet	3.5 [2.5-7.5]	3.5 [3.0-4.0]	0.67	-0.42	57.85%	6.3
Bitter	89 [89-93]	93 [89-93]	0.25	-0.02	41.32%	NA
Sour	0.48 [0.48-0.96]	0.48 [0.48-2.44]	1.00	0.17	65.39%	3.2
Umami	0.70 [0.40-1.17]	0.90 [0.70-1.1]	0.44	0.34	74.46%	2.0

* p value represent significance of median difference. Effect size was evaluated by Cohen d. M median IQR interquartile range. CLES Common Language Effect Size. NNT number needed to treat.

Liver cirrhosis decompensation

After six months of intervention, MELD did not show significant differences between the ZnG group (10.0 [IQR 9.7-10] and placebo (10.0 [IQR 9.2-12.2]), p=0.64 (null effect size). Regarding LC decompensations, 35.7% (n=5) of patients in the placebo group presented variceal bleeding (p=0.04), and 50% (n=7) developed hepatic encephalopathy (p=0.005). Only one patient (2.9%) died after six months of follow-up (ZnG group).

Nutritional risk

Regarding nutritional risk evaluation by SGA, patients who received ZnG did not show significant differences after six months of intervention; on the contrary, patients in the placebo group significantly improved nutritional status according to this indicator, increasing the proportion of

well-nourished patients compared to the baseline evaluation (14.2% vs. 54.2%, p=0.01). The nutritional risk assessment using the Royal Free Tool did not show significant differences in any groups.

Macro and micronutrient consumption

Regarding the consumption of macro and micronutrients, no significant differences were observed in the consumption of kilocalories, proteins, carbohydrates, and lipids. According to micronutrient consumption, in patients who received ZnG, lower consumption of fiber (19.2 [15.8-21.3] vs. 22.8 [18.8-23.2]) and vitamin B6 (1.5 [1.3-1.5] vs. 1.7 [1.4-1.7]) was observed, with a small effect size and a probability of change of 60% and NNT of 4 patients for both cases. Sucrose (17.9 [16.8-27.1] vs. 30.1 [22.7-33.3]) and vitamin C 120 [72.4-152.4] vs. 168.9 [143.4-169.3]) consumption also showed a reduction in patients receiving

ZnG, with an intermediate effect size and a probability of change of 66.6% (NNT=2) for sucrose and 64.8% (NNT=4) for sucrose consumption of vitamin C.

Quality of life

According to QoL, after six months of intervention, statistically significant differences were observed in the worry domain, obtaining a higher score in patients who received GZn (6.0 [IQR 5.2-6.4] vs. 4.4 [IQR 2.9-5-5], p=0.007). However,

the effect size was -1.01 (Adverse). Global QoL did not show significant differences.

Serum Zinc levels

Regarding the effect of ZnG supplementation on serum Zinc concentration, this was significantly lower in patients who received placebo compared to those who received ZnG (52 [IQR 45.5-58.2] mg vs. 64 [IQR 60- 76.2] mg, p=0.007), however, when evaluating the effect size, it had a value of -1.08 (Adverse). (Figure 2)
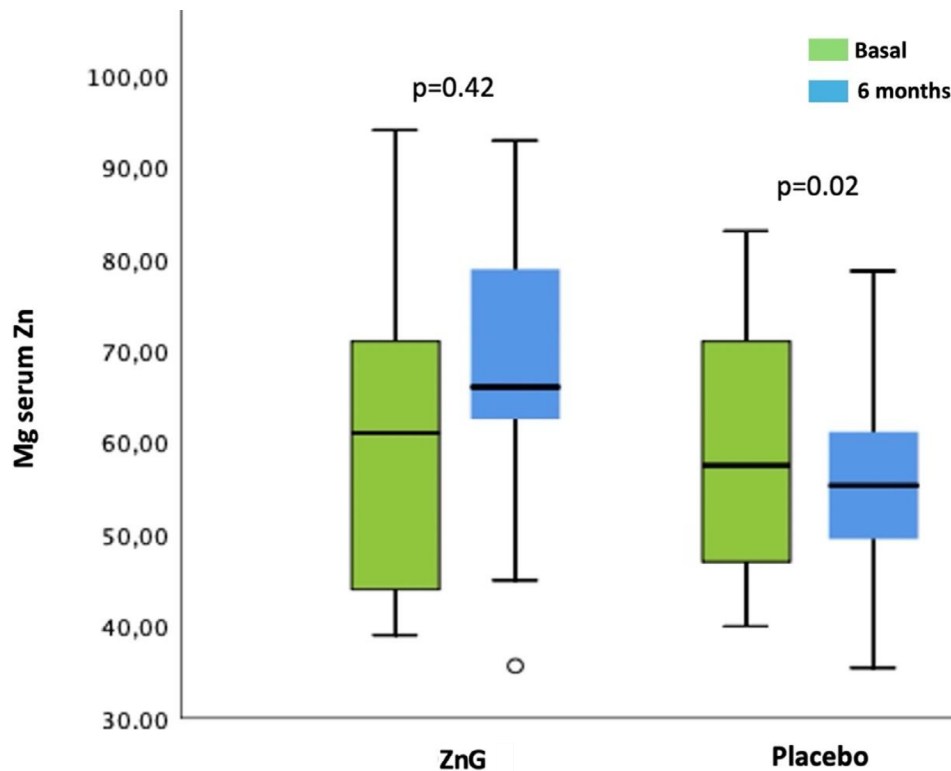

FIGURE 2. Differences in serum levels of Zinc.

Adverse effects

The presence of fatigue (71.4% (n=20), nausea (57.1% (n=16)), and skin rash (53.6% (n=15) were the most frequent; no significant differences were observed between groups. Only in one patient, the intervention was suspended for one month due to the presence of nausea > grade 2. This patient was assigned to the placebo group.

DISCUSSION

To our knowledge, this is the first study that objectively evaluates taste perception and recognition changes in patients with cirrhosis and proposes a therapeutic intervention. In patients who received supplementation with 100 mg/day of ZnG for six months, it was observed that at the end of the follow-up, they presented earlier PT in salty, sweet, sour,

and umami tastes compared with patients who received placebo. Regarding RT, this early detection of the umami taste was only observed in patients who received ZnG.

The importance of these changes lies in the fact that sweet, bitter, and umami tastes are the most important for the acceptance of foods since they are responsible for pleasant taste sensations, which is why monosodium glutamate is increasingly used as an additive in Western food.[21] However, in this study, no significant differences were observed in bitter taste. Improvement in taste perception is directly related to the individual's well-being since it has been shown that the organoleptic properties of foods represent the primary reason individuals desire to eat.[8,22]

Even dysgeusia in patients with LC has been observed as part of the disease; it is an underdiagnosed entity, and few studies evaluate this condition despite being reported in more than 30% of patients.[8] In our population, at baseline, the prevalence of dysgeusia was higher in salty and umami tastes, which showed changes after supplementation. These observations coincide with the study carried out by Madden *et al*.,[23] in which it was observed that patients with cirrhosis perceived and recognized the salty taste at higher concentrations compared to healthy volunteers (UP 16 [IQR 1-50] mMol vs 11[IQR 1-60] mMol, p=0.004; UR 72 [IQR 1-800] mMol vs. 60 [IQR 1-800], p=0.009). The umami taste was not evaluated in this study. Although they assessed dysgeusia with different dilutions of each flavor, the standardized method published by Amerine & Pangborn[15] was not used. Another important observation of this study was that those patients who needed higher concentration to taste perception or recognition were patients with restrictive diets, mainly in sodium. Hyponatremia is common in patients with cirrhosis, and it has been identified that the main factor is the deficiency in the consumption of this micronutrient due to excessive or unnecessary restrictions, as well as changes in fluid consumption.[24]

According to cirrhosis decompensation, most patients were in decompensated stages at baseline, mainly due to a history of ascites, variceal bleeding, or second decompensation events; no patient presented hepatorenal syndrome. Regarding the average MELD score (11.3), our patients had a three-month mortality risk of less than 6%. When the effect of ZnG supplementation on liver decompensation was evaluated, patients who did not receive ZnG had a higher prevalence of hepatic encephalopathy. Zn supplementation has been considered as an intervention for hepatic encephalopathy. According to a meta-analysis, which evaluated a total of 233 patients, it was observed that Zn supplementation improves the score of neuropsychometric tests for the evaluation of hepatic encephalopathy (standard difference

from the mean: –0.62; 95% CI –1.12 to –0.11).[25] In another meta-analysis, it was observed that when Zn supplementation is combined with lactulose for more than three months, this intervention could also improve the scores of the tests used for diagnosis (standard difference of the mean: -0.97; 95% CI: - 1.75 to - 0.19). Supplementation with ZnG could be why only seven patients presented episodes of encephalopathy over six months in the group that received this intervention. Although the consumption of nutrients has been associated with decompensation of the disease, [26] supplementation with ZnG did not show significant differences in the frequency of consumption of macro and micronutrients; on the other hand, the supplementation of a single nutrient is insufficient to improve the nutritional status of patients and the decompensation of cirrhosis that is dependent on HVPG.

Since most patients were in decompensated stages of liver disease, the prevalence of malnutrition is expected to be high. The risk of malnutrition, like dysgeusia, is an entity considered part of the natural history of the disease, but it is also underdiagnosed due to the variability of methods to identify it. Therefore, prevalence data varies between 10 to 100% of patients, depending on the diagnostic instrument and stage of the disease.[26] In our population, after six months of intervention, the proportion of well-nourished patients increased in the placebo group, with no significant differences observed in the group of patients who received ZnG; despite this favorable result, although not related to the ZnG group, prevalence of patients at risk or malnutrition was higher than 10%, this in combination with the decompensated stage of our patients, increases the risk of infections, delay in the list of transplantation for potential candidates, prolonged hospital stays and mortality.[27] However, it must be considered that malnutrition in these patients is due to different factors such as long fasting periods, inflammation, dysbiosis, malabsorption, alterations in nutrient metabolism, and hypermetabolism of the disease; on the other hand, the decrease in food intake is related to the presence of ascites, sodium restriction, micronutrient deficiency, loss of appetite and portal hypertension.[26]

QoL in patients with LC is associated with the presence of malnutrition and decreased food consumption, as well as the stage of the disease and the presence of dysgeusia.[28-30] As mentioned above, hyponatremia is common in patients with LC. Ahluwalia *et al*. evaluated the effect of correcting hyponatremia on the QoL of patients with LC after 14 days of supplementation, demonstrating that the correction of hyponatremia improved the global quality of life scores (3.4±1.1 vs 3.8 ±1.2, p=0.04) according to specific questionnaire for chronic liver diseases.[31] Hyponatremia is associated with the characteristics of the diet and food perception,

so improving the perception of salty taste could contribute to improving or correcting hyponatremia with a direct impact on quality of life.

Regarding serum Zn levels, patients who received ZnG maintained serum levels in normal ranges at the end of the intervention, while patients in the placebo group significantly decreased serum Zn levels; once again, when evaluating the effect size, this change was not clinically relevant. Serum Zn levels in both groups remained in the range of 54 to 70 mg/dL, in which it has been shown that the manifestation of symptoms associated with deficiency is mild to moderate.[32]

In adverse effects evaluation, these were lower than those reported in studies of Zn supplementation in patients with liver diseases,[11-13] demonstrating the safety of supplementation with 100 mg/day of ZnG. Although these symptoms were higher than 50%, it cannot be determined if the intervention is the cause since both the pharmacotherapy and the natural history of the disease are strongly associated with these symptoms.

Despite our favorable results in the primary outcome, the secondary objectives did not show significant changes. On the other hand, patient losses during follow-up were high. This may be due to the medical care scheme for these patients which was by open invitation without being a captive population with strict follow-up. According to decompensation, it is essential to highlight that at the end of the intervention, the patients who presented episodes of encephalopathy were not eliminated from the study, which could affect the result of the perception and recognition of flavors. However, at the time of final evaluation, it was ensured that no patient presented overt encephalopathy. Although mortality was low, the outcome of patients who did not complete follow-up is unknown. On the other hand, pharmacological treatment and LC etiology could be related to the presence or severity of dysgeusia.

CONCLUSION

Patients supplemented with ZnG show an improvement probability of PT higher than 55% for salty, sweet, sour, and umami tastes. Meanwhile, the improvement probability of RT for umami taste is 59%. The probability of decreased sucrose, fiber, vitamin C, and B 6 consumption is higher than 60% in patients supplemented with ZnG. There are no significant differences in QoL and plasma Zn levels in patients receiving ZnG compared to placebo.

CONFLICT OF INTERESTS

None.

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