ORIGINAL ARTICLE

Hypozincemia in Mexican patients with diabetic foot ulcer treated out of hospital

Hipozinquemia en pacientes mexicanos con úlcera de pie diabético tratados en el primer nivel de atención

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Abstract

Objective: *To know the frequency of people with hypozincemia in a group of Mexican patients with Diabetic Foot Ulcers (DFU) m and its relationship with metabolic and clinical profile.* **Material and methods:** *Cross-sectional, analytical, and observational study in patients with and without DFU, treated in Family Medicine Units from Instituto Mexicano del Seguro Social (IMSS) in Mérida, Yucatán, México. Frequency of hypozincemia (Zn serum < 70 g/ml) and its relationship with the levels of Glycosylated Hemoglobin (HbA1c), cholesterol and triglycerides was analyzed.* **Results:** *70% of patients with DFU and 25% without DFU had hypozincemia (OR = 5.2, 95% CI 2.139-12.65, p = 0.0004). Patients with hypozincemia were older and the highest prevalence was between 50 and 60 years. The average area of the DFU showed no differences in patients with and without hypozincemia. Patients with DFU reported higher levels of HbA1c, cholesterol, triglycerides, BMI, and blood pressure compared to patients without DFU. Hypozincemia was associated with higher BMI values.* **Conclusion:** *The frequency of hypozincemia in diabetic patients with UPD is high and is behaving as a risk factor for presenting UPD, so its identification should be routine.*

Keywords: *Zinc. Diabetes mellitus. Wounds. Metabolism.*

Resumen

Objetivo: *Conocer la frecuencia de hipozinquemia en pacientes Mexicanos con úlceras de pie diabético (UPD) y su relacion con el perfil clínico y metabólico.* **Material y métodos:** *Estudio transversal, analítico, en pacientes con y sin úlceras de pie diabético, tratados en unidades de medicina familiar del Instituto Mexicano del Seguro Social (IMSS) en Mérida, Yucatán, México, que analizó la frecuencia de Hipozinquemia (Zn serico de < 70 μg/ml) y su relación con los niveles de Hemoglobina Glucosilada (HbA1c), colesterol y triglicéridos.* **Resultados:** *70% de los pacientes con UPD y 25% sin UPD tenían hipoziquemia (OR=5.2, IC95% 2.139-12.65, p=0.0004). La mayor prevalencia se encontró entre los 50 y 60 años. El área promedio de las UPD no mostró diferencias entre pacientes con y sin hipozinquemia. Los pacientes con UPD presentaron niveles más altos de HbA1c (p<0.001), colesterol (p<0.001), triglicéridos (p<0.001), IMC (p=0.01) y tensión arterial (p=0.009) en comparación con los pacientes sin UPD. Los pacientes con UPD e hipoziquemia tenían mayores valores de IMC.* **Conclusión:** *La frecuencia de hipozinquemia en pacientes diabéticos con UPD es alta y es se comporte como un factor de riesgo para presentar UPD, por lo que su identificación deberia ser rutinaria.*

Palabras clave: *Zinc. Diabetes mellitus. Úlceras. Metabolismo.*

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Introduction

Diabetes mellitus (DM) is a multifactorial disease in which prevalence, incidence, and trend worldwide[1], as well as locally, represent a huge public health problem[2,3]. DM tends to behave towards chronicity and the lack of metabolic control is the cause of other alterations, such as neurovascular dysfunctions, which favor the appearance and development of ulcerative skin lesions, feet being the most susceptible site[4] resulting in diabetic foot syndrome.

It is estimated that 15-30% of people with type 2 DM (T2DM) have had at least one diabetic foot ulcer (DFU) in their lifetime. Clinically, DFU could involve lesions from the epidermis to deep tissues, including fascia, tendons, muscles, and bones. Deeper and more extensive DFU have a worse prognosis, in some cases requiring amputations and even in extreme cases, death from sepsis and/or gangrene[5,6]. Therefore, early diagnosis and timely treatment of DFU, mainly in first-level health care units, is essential to reduce morbidity and mortality from this cause. Among the risk factors for amputation in patients with DFU are hyperglycemia, dyslipidemia, malnutrition, neuropathy, aggregate infections, high blood pressure, the time of evolution of DM, insulin use, and others[7]. Therefore, reducing these risk factors would mean improving DFU prognosis.

Zinc (Zn) is an essential bioelement for more than 300 biochemical reactions, including immunity, cell growth, tissue repair, and other physiological processes[8]. The involvement of Zn in the diabetic patient is important; it has been reported that serum Zn levels are usually decreased in diabetic patients[9], especially in those who are not controlled, and that Zn therapy improves insulin secretion and reduces glycemia levels[10]. Zn participates in improving the healing process: in injured tissues it could act as an antioxidant agent, reduces the formation and damage produced by free radicals[11], reduces the presence of certain bacteria in contaminated wounds[12], modifies the process of angiogenesis, the levels of expression of growth factors and other cellular mechanisms that promote the formation of new epithelial cells and the remodeling of connective tissue[13]. Therefore, Zn is indispensable in the processes of tissue repair.

This study aimed to determine the frequency of hypozincemia in Mexican diabetic patients with superficial foot ulcers, who attended an outpatient clinic at Instituto Mexicano del Seguro Social (IMSS), as well as its relationship with other risk factors.

Material and Methods

Design

Transversal and observational study in patients with T2DM and DFU, treated in four family medicine units at IMSS in Merida Yucatan, Mexico, between February 1st and September 30th, 2017. The main objective of this study was to know the levels of Zn in the population of diabetic patients with DFU, as well as its implication with some clinical, metabolic, and epidemiological characteristics.

Population

Patients aged 18 years or older, IMSS beneficiaries, who attended an outpatient clinic in one of the primary health care units, and whose reason for consultation was DFU, were included. Inclusion criteria comprised: non-infected ulcer, in stage I of Waggner classification (WUC),[14] wound size between 50 and 2000 mm^3. Excluded patients were those who had consumed zinc supplements and/or antibiotics during the month before consultation, as well as patients who reported intestinal absorption problems such as celiac disease, lactose intolerance, short bowel syndrome and other causes of malabsorption, which could produce biases in the interpretation of Zn levels not related to DFU.

Results of the present study follow the protocol authorized by the National Commission of Scientific Research of the Instituto Mexicano del Seguro Social, registration number R-2016-785-089. All ethical and legal norms were fulfilled. Patients who agreed to participate in the study signed an informed consent. The results included a total of 102 patients who met the selection criteria.

Anthropometry

Anthropometric evaluation was performed with the patient barefoot and with trousers/skirt and blouse/shirt, weight was measured employing a mechanical scale with a stadiometer Seca® model 700, calibrated according to manufacturer's standards, weight was measured in kilos and grams; for the size, the patient was measured standing up, in an upright position, with the view towards stadiometer of the scale, taking the

existing distance from the feet to the zenith of the head, in meters and centimeters. With height and weight, Body Mass Index (BMI) was determined, according to the following formula: weight (Kg)/Size2 (m); World Health Organization (WHO) criteria classifies patients according to their BMI as 18.5-24.9 = Normal; 25-29.9 = Overweight and 30 or more = Obesity.

Clinical and epidemiological data.

Vital signs were determined: heart and respiratory rate, temperature, and blood pressure, according to JNC8 criteria for each of these measurements.[15].Besides, they were asked about age, years of diabetes evolution, type of drugs they use and number of days from the onset of DFU to consultation.

Laboratory tests

Biochemical measurements of glycated hemoglobin (Hba1c), total cholesterol (CT), and serum triglycerides (TG), were performed at clinical analysis laboratory from Facultad de Medicina, Universidad Autónoma de Yucatán, México. All the anthropometric and biochemical measurements of the patients were made during the day, after a 12-hour fast, and they were only allowed to take their usual medications. Each patient had 9 ml of whole blood drawn from the ulnar vein of the arm, using a sterile 10 ml disposable syringe and a 20G x 38 mm hypodermic needle (Plastipak TM). Blood volume was divided into three 3-ml aliquots (two test tubes without anticoagulant and one test tube with commercial tripotassium EDTA added) which were used for the different determinations: the Nycocard HbA1c kit (Allere® USA) and the NycocardTM Reader II (Allere Technologies AS, USA) was used for measuring HbA1c. Cholesterol and triglycerides were measured using the PS-120 automated chemistry analyzer (Mindray®). According to the standards of the clinical analysis laboratory. Values considered as physiological were: for HbA1c ≤6.5%, for cholesterol ≤ 200 mg/dl and triglycerides ≤ 150 mg/dl.

Determination of serum zinc. Zn was measured in aliquots with one ml of serum from each patient with 8-hour fast. Determination was performed by atomic absorption spectrophotometry (SpectrAA-800), each sample was measured by triplicate and the average value was used. The results were expressed in g/dl and the values ≤ 70 g/dl of serum Zn were considered to be hypozincemia.[16]

Diabetic Foot Ulcers dimensions.

Lesion measurements were assessed after DFU washing and debridement, considering edges of healthy skin, photographs were taken captured by a Canon® model D70 camera, with a lens for macroscopic photography of 18-125 mm, taking care of the necessary conditions of illumination, angulation, calibration bar and focus, later these images were processed with the ImageJ software[17] to determine the area of the injuries, which were expressed in square millimeters.

Statistical analysis

Descriptive statistics with quantification by means and standard deviation were calculated for continuous variables. Prevalence and frequencies were expressed as percentages. Categorical variables were compared using chi-square, Odds Ratio (OR) with 95% confidence intervals (CI) and numerical variables with unpaired Student t test, after verification of compliance with statistical assumptions of normality according to the Shapiro-Wilks test. The statistical significance was with $p \leq 0.05$.

Results

Diabetic patients with DFU (n = 48), included 56% men and 44% women, the average age was 57.4±8.2 years (minimum 42 and maximum 80 years). Patients without DFU (n = 54), comprised 28% men and 72% women, aged 52.61±8.6 years (minimum 33 and maximum 72). Average time of evolution of T2DM in patients with DFU was 16.3±7.7 years (minimum 6 and maximum 40) and in patients without DFU it was 6.24 ± 4.89 (minimum 1 and maximum 24). Additionally, 91.1% (93/102) of the patients were managed with oral metformin and glibenclamide, 2.9% (3/102) with thiazolidinediones specifically pioglitazone, and only 5.8% (6/102) with insulin plus oral metformin scheme. No difference in treatment between groups with and without DFU was found

Serum Zinc

Serum Zn levels, in 102 patients reported an average of 81.6±29.5 g/dl: 68.6±4.8 g/dl for patients with DFU and 93.3±36.7 g/dl for patients without DFU. ($p < 0.001$). According to cut-off point of 70 g/dl; 70.83% of the patients with DFU had hypozincemia opposite to 25.9%

Table 1. Serum Zn in male ans female patients according age decade

	Male (n=41)		Females (n= 61)		TOTAL n= 102
	DFU	Non DFU	DFU	Non DFU	
41 a 50 years (n)	5	3	5	17	30
Zinc, µg/dl (mean±SD)	70.6±1.82	92.3±20.2	70.2±4.3	94.0±46.6	70.4±3.3
Hypozincemia (%)	4.8	0	3.2	11.4	10.78
51 a 60 years (n)	12	9	8	14	43
Zinc, µg/dl (mean±SD)	68.9±4.0	81.0±27.8	68.6±6.9	92.3±27.4	68.8±5.2
Hypozincemia (%)	21.9	9.7	9.8	1.6	20.58
>61 years (n)	10	2		9	29
Zinc, µg/dl (mean±SD)	68.0±3.2	164.3±1.3		88.2±33.5	88.2±33.5
hypozincemia (%)	19.5	0		3.2	15.68

of patients without DFU (chi2 = 12.48, OR 5.2, IC 95% 2.13-12.65, p = 0.0004). Classified by sex, DFU group reported 70.3% (19/27) men and 71.4% (15/21) women presenting hypozincemia; in the group without DFU, 13.3% of men (2/15) and 30.76% of women (12/39), had hypozincemia. No association was found between sex and the presence of hypozincemia (p = 0.79 with DFU and p = 0.30, without DFU). The amount of serum zinc in men with DFU averaged 68±83.4 g/dl and in women 68.2±6.2 g/dl. In patients without DFU, serum zinc was 119.73 ± 52.42 in men and 105.19 ± 62.37 in women, so, serum zinc was lower in the group of patients with DFU compared to patients without DFU (p < 0.001 in men and p = 0.009 in women).

In patients with DFU, the mean age of patients with hypozincemia was 59.3±7.6 years, while patients without hypozincemia were 52.9±08.2 years (p = 0.013). The chronicity of MD2 in patients with DFU and hypozincemia was 15.4±6.4 years and for patients without hypozincemia 16.6 ± 8.6 years (p = 0.385). In patients without DFU but with hypozincemia they reported 7.2±6.3 years of diabetes mellitus and patients without hypozincemia 5.8 ± 4.2 years (p = 0.92). Table 1 shows the percentages of hypozincemia in men and women by the decade of age.

Characteristics of Diabetic Foot Ulcers

Only patients with DFU were considered; area of ulcers in the whole group revealed an average of 430,4±442 mm3 in hypozincemia patients the area was 374±379.7 mm^3 (minimum of 51 and maximum of 1350 mm^2) and in patients without hypozincemia 567.6±558.3 mm^2 (minimum of 50 and maximum of 1843), p = 0.17. No difference was found in areas of ulcers between men and women, with and without hypozincemia (data not shown).

Time from lesion appearance to attention in health unit, was also assessed; the minimum time was 3 days and the maximum was 368. On average, patients with hypozincemia and wounds attended themselves after 124±50.4 days of evolution and patients without hypozincemia after 79.5±55.9 days (p = 0.513).

Metabolic control

To evaluate the metabolic profile of the participants, levels of HbA1c, total cholesterol, triglycerides, and BMI, were compared between patients with and without DFU, with and without hypozincemia, as clinical characteristics between patients with and without DFUs nad hypozincemia, the results are shown in Tables No.2 and 3.

Discussion

One of the main chronic complications of DM is DFU in countries where timely and appropriate management from the first level of care is efficient, the incidence seems to decrease[18] However, this behavior has not been observed in Mexico. The implication, in economic costs of medical care in patients with diabetes mellitus, is at least four times greater than in people without the disease[19], the costs of care for DFU, according to Mexican authors, increased proportionally to Wagner's classification; the highest costs were observed in hospitalized patients and were attributed to per diem costs and surgical treatments[20]. Importance of prevention and timely care at the first level of health care, when the patient could be managed as an outpatient basis, could be inferred from the above. In the present study, we

Table 2. Principal variables in patients with and without DFUs and with/ without hipozynchemia

	DFU (n=48)			Non DFU (n=54)			
	Hypo Zn	Nomo Zn	P*	Hypo Zn	Nomo Zn	P*	P**
Hba1c (%)	9.3±1.4	9.4±1.4	0.814	7.9±2.4	7.2±1.8	0.27	0.019
Cholesterol (mg/dl)	252±56	261±55	0.621	173±25	178±33	0.62	<0.001
Tryglicerides(mg/dl)	243±102	272±104	0.382	141±80	171±91	0.27	<0.001
BMI (kg/m2)	29.4±5.1	29.8±4.8	0.801	34.0±6.0	31.5±5.6	0.11	0.011
MBP (mm/Hg)	91.3±7.5	92±7.3	0.754	85.9±7.0	85.7±5.6	0.91	0.029

P* hypo zinc vs. normo zinc mean difference (independent intra group student t test).
P**, hypo zinc vs. hypo zinc in patients with and without DFUs (independent intergroup student t test) BMI: Body Mass Index; MBP: Median Blood Pressure.

Table 3. Clinical features comparing hypozincemia in patients with and without DFU

	Hipozinc and DFU	Hipozinc and Non DFU	H.R. (95%CI)	P*
HbA1c >6.5%, n/N (%)	32/34 (94.2)	8/14 (57.1)	0.24 (0.04-1.01)	0.003
cholesterol <300 n/N(%)	29/34 (85.2)	1/14 (7.1)	2.8 (0.5-21.4)	<0.001
Triglycerides >150n/N(%)	29/34 (85.2)	1/14 (7.1)	75.4 (7.9-71.3)	<0.007
Overweight	11/34 (32.3)	2/14 (14.2)	2.8 (80.5- 15.1)	0.178
Obesity n/N(%)	16/34 (47.0)	11/14 (78.5)	0.24 (0.05-1.02)	0.04
hypertension /N(%)	0/34 (0)	0/14 (0)		--

P* Chi^2 Test. HR: Hazzard Ratio.

found that DFUs occurred in greater percentage in men, although it was not statistically significant, probably due to T2DM prevalence worldwide, where it has been documented greater prevalence in men than in women[6,21]. Age ranges of Mexican patients with DFUs were very similar to those reported in other studies with diabetic patients[22]. It should be emphasized that the population studied were people entitled to IMSS, which has the greatest national coverage of Mexican population.

Mean time of evolution of DM is a risk factor to be considered in development of DFU, in our study we documented an average of 16.3±7.7 years. However, in other populations, the incidence has been less[23], which could mean less metabolic control and consequently more comorbidities and worse prognosis, as mentioned by Acar and Kacira; time with DM is a prognostic risk factor for amputation[24].

Zinc presence in physiological serum levels is important for cells and tissues to develop repair mechanisms and during healing process, particularly in wounds[25-27]. More than two-thirds of patients with DFUs had hypozincemia, and we considered this prevalence as very high and worrying, yet, worldwide hypozincemia in people with diabetes has been described as a common finding[22–24]. DFU represents a trauma able to produce a “stasis response”, which induces a series of neurochemical, inflammatory, and metabolic changes to promote a cellular microenvironment to resist the acute stage and maintain the necessary inputs to repair the injuries. Okada et al.[27] have shown that, in surgical injuries, Zn accumulates at sites near the wound, where cell division is required. Another change that occurs after acute inflammatory stage in response to stress is zinc redistribution. Serum zinc is redistributed to the liver, through gene expression favors zinc import into the hepatocyte and the decrease of exporters in the cell membrane, thus, with these changes hepatic zinc bioavailability increases to regulate gluconeogenesis, control reactive oxygen species, activate transcription factors and synthesis of acute-phase inflammatory protein[28]. Metallothioneins are proteins present in the stress or acute inflammatory phase, they sequester excess of Zn, preventing it from activating certain enzymes and

allowing a return to homeostasis[29]. This explains the presence of hypozincemia in patients with acute trauma. Nevertheless, the population studied presented wounds with a mean of three or four months of evolution, then, it was assumed that, by not achieving healing, the acute phase induced hypozincemia which could be prolonged and in chronic form, and, instead of favoring repair it could be delaying it. Thus, it becomes necessary to evaluate the molecular behavior of Zn in chronic processes, which leads us to explain related physiopathological mechanisms.

In the present study, we found that Zn levels decrease as the age of diabetic patients increases (with or without DFUs). Interestingly, despite hypozincemia prevalence in diabetic patients, in the Clinical Practice Guidelines and care protocols of Mexican diabetic patients, hypozincemia is not considered as a risk factor for comorbidities such as DFUs and neither is Zn supplementation recommended[26].

We have found that patients with DFUs, presented worse metabolic control than diabetics without DFUs. Serum glucose and lipid levels (cholesterol and triglycerides) were in higher ranges than recommended. These findings result from several factors, most of them related to consumption of oral euglycemic, however, treatment adherence was not evaluated as a fundamental pillar in glycemic control and a determining factor to control DM complications[30]. Very few patients have been managed with insulin and other drugs, although there are national reports of increased use of insulin for glycemic control[31]. On the other hand, the high prevalence of obesity and dyslipidemias, evidenced by higher levels of BMI, cholesterol, and serum triglycerides was higher in patients with DFUs. It is very likely that chronic response to increased stress in patients with DFUs, favors gluconeogenesis, utilization of liver glycogen, mobilization of free fatty acids from adipose tissue and decreased insulin secretion, which would lead directly to hyperglycemia and dyslipidemias, as ultimate factors that block healing and increase the risk of other comorbidities[32,33].

In the population studied, both BMI, lipid, and glucose levels were increased in patients with DFU together with a higher prevalence of hypokalemia. We assumed that metal deficiency was involved, as there is evidence that postulates Zn as a risk factor for developing metabolic syndrome[32].

In addition to the high rates of Zn deficiency in people with T2DM, there is an obesity “epidemic” in Mexico, which further complicates the outlook and prognosis for these patients[34]. However, some reports have shown that Zn supplementation improves glycemic and metabolic rates in diabetic patients[35] and that in those with DFUs it decreases wound size together to other therapeutic effects[26].

Conclusions

Identification of chronic hypozincemia in patients with DFUs should be done routinely at the first-level care so that timely Zn supplementation could be offered to improve their prognosis and quality of life.

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Conflict of Interest

The authors declare no conflicts of interest in this article

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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