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EDITORIAL

Mensaje de bienvenida

Gustavo E. Lugo-Zamudio

Dirección General, Hospital Juárez de México, Mexico City, Mexico

During the 176-year history of the Hospital Juárez de México, its essence has been and continues to be medical-surgical assistance. However, as the institution grew, educational activities were added, allowing for the training of excellent human resources, and it has also been recognized as a teaching hospital. Advances in science have also permeated, and today we have individuals within the organization conducting basic and clinical research, achieving results in various lines of study that can influence translational medicine.

Today, we embark on a project that will bring great benefits: having a means to present our academic and scientific ideas with methodological power will allow us to consolidate our institution, creating a platform that connects us in the dissemination of knowledge and links us with the development of science, contributing to the solution of the health challenges observed in our society and in the world.

May this first issue of the Clinical Innovations in Health Research-HJM journal mark the beginning of a new chapter for the community of Hospital Juárez de México, and for all those who are encouraged to contribute to its growth.

Juaristas forever!

Durante los 176 años de historia del Hospital Juárez de México, su esencia ha sido y es la asistencia médico-quirúrgica, pero en el crecimiento de la institución se agregaron actividades docentes que han permitido formar recursos humanos de excelencia, y ser además reconocido como hospital escuela. Los avances en ciencia también han permeado y hoy contamos con actores dentro de la organización que realizan investigación básica y clínica, alcanzando con varias líneas de estudio resultados que pueden influir en la medicina traslacional.

Hoy iniciamos con un proyecto que traerá grandes beneficios: contar con un medio para exponer nuestras ideas académicas y científicas con poder metodológico nos permitirá consolidar nuestra institución, creando una plataforma que nos enlace en la difusión del conocimiento y nos vincule con el desarrollo de la ciencia, contribuyendo en la solución de los retos en salud que hoy se observan en nuestra sociedad y en el mundo.

Que este primer número de la revista Clinical Innovations in Health Research-HJM marque el inicio de un nuevo capítulo para la comunidad del Hospital Juárez de México y de todos aquellos que se animen a contribuir en su crecimiento.

¡Juaristas por siempre!

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ORIGINAL ARTICLE

Factors associated with poor glycemic control in older adults with sarcopenia

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Abstract

Background: *Older adults have a high prevalence of type 2 diabetes mellitus (T2D) and sarcopenia. Aging-related changes such as loss of muscle mass and insulin resistance increase the development of T2D. Several factors have been associated with poor glycemic control in older adults.* **Objectives:** *The objectives of the study are to determine the factors associated with poor glycemic control in older adults with sarcopenia.* **Methods:** *This is a cross-sectional study in ambulatory older adults with T2D. European Working Group on Sarcopenia in Older People 2 criteria were used to define sarcopenia. The glycosylated hemoglobin (HbA1c) level is classified as poor glycemic control. Logistic regression analysis was performed with response variable: poor glycemic control, estimating the odds ratio, and 95% confidence intervals as a measure of effect size.* **Results:** *Sarcopenia was higher in subjects with poor glycemic control. The higher the HbA1c level, the greater the association with sarcopenia. In addition, poor glycemic control was associated with malnutrition, insulin resistance, the use of dipeptidyl-peptidase 4 inhibitors, sodium-glucose cotransporter type 2 inhibitors, and insulin.* **Conclusion:** *Poor glycemic control in older adults is associated with the presence of sarcopenia, low muscle mass, malnutrition, insulin resistance, and the use of some antidiabetics.*

Keywords: *Sarcopenia. Poor glycemic control. Muscle mass. Malnutrition. Type 2 diabetes.*

Introduction

The world's population is aging rapidly and at the same time, the prevalence of type 2 diabetes (T2D) is increasing, a situation considered a public health problem in our country. There is a 3% annual increase in the diagnosis of T2D, mainly between the fourth and seventh decade of life, reporting that more than 122 million older adults suffer from T2D, expecting an increase of more than double in the coming decades[1]. Older adults with T2D represent a great challenge, due to the heterogeneity of aging, the burden of morbidity, and geriatric conditions that increase the complexity of treatment[2].

The most relevant phenotypic change with aging is an increase in abdominal adiposity and a decrease in muscle mass, factors associated with impaired glucose metabolism regulation[3]. It has been estimated that muscle mass decreases by 30-40% at the age of 80 years; this muscle loss is also associated with glucose intolerance and an increased risk of T2D[4]. In turn, insulin resistance has been associated with a loss of muscle mass[5-7]. Elevated glycosylated hemoglobin

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(HbA1c) levels are inversely related to a low percentage of muscle mass[8,9], both in subjects with hyperglycemia but without a diagnosis of T2D and in those with T2D but without antidiabetic treatment[9]. Both low muscle mass and low muscle strength were determinants of poor glycemic control[10] and greater hyperglycemic fluctuation in hospitalized subjects[11]. A reduction of > 1% in HbA1c level improves muscle mass and gait speed[12].

The diagnosis of sarcopenia, which is defined by the loss of muscle mass and muscle strength related to the aging process, the overall prevalence of 10%[13], increases in subjects with T2D between 21% and 50%, depending on the years of disease evolution[14]. Therefore, people with T2D have an increased risk of sarcopenia (odds ratios [OR] 2.09; 95% confidence intervals [CI] 1.62-2.70) and sarcopenia is associated with T2D-related complications (OR 2.09; 95% CI 1.62-2.70)[15], especially when retinopathy, nephropathy, and peripheral neuropathy are present[16,17], maintaining a bidirectional relationship, between T2D and sarcopenia[18].

Older adults are more susceptible to poor glycemic control; social, clinical, and pharmacological factors are associated with higher HbA1c levels[19]. In older adults, comorbidity[19-24], diabetic complications[19,20,24], prolonged duration of T2D[19,21,22,24,25], low physical activity[21], complex treatments[19-21,23,24], poor adherence to treatment[22,23,26,27], and difficulty in making lifestyle changes[19,25,28,29] are predictive factors for increased therapeutic complexity and poor glycemic control. The following study was conducted to determine factors associated with poor glycemic control in older adults with sarcopenia.

Materials and methods

Study participants

A cross-sectional study was conducted in older adults with T2D, recruited on an outpatient basis, and evaluated in the period from July 2022 to July 2023. Inclusion criteria were as follows: (1) older adults' ≥ 60 years, (2) diagnosis of T2D as defined by the American Diabetes Association 2022[30]. Exclusion criteria were (1) the presence of any cognitive or physical limitation, (2) diagnosis warranting immediate emergency care or hospital admission, (3) terminal illness or advanced organ failure, (4) inconclusive diagnosis of T2D, (5) absence of antidiabetic treatment. Our study was approved by the Ethics and Research Committees of our institution with registration number DJSMEI-13149. All participants authorized and signed their written informed consent.

Clinical features

Demographic information was obtained by direct questioning of older adults. Social assistance was categorized according to where they lived in the past 90 days (living alone, with a spouse, with another family member, or in a retirement home). The number of teeth was quantified directly at the examination, categorized as edentulous (absence of teeth), < 20 teeth, > 20 teeth, or use of prosthesis (bilateral prosthesis). The Charlson index[31], with ≥ 3 diseases, was used to define comorbidity. The number of meals usually eaten was recorded, regardless of the quality and quantity of calories consumed, and categorized as: one meal/day, two meals/day, three meals/day, and four or more meals/day. The mini nutrition assessment questionnaire was used to define nutritional status, if ≤ 17 it was defined as malnutrition and ≥ 18 as adequate nutritional status[32].

The Fatigue, Resistance, Ambulation, Illness, and Loss of Weight (FRAIL) Scale was used, with a score ≥ 3 points diagnosed as frailty[33]. Polypharmacy was defined by the simultaneous use of ≥ 5 medications in the past month. Duration of T2D was assigned dichotomously: < 20 years and > 20 years. T2D-related complications were recorded: retinopathy, neuropathy, heart disease (including heart failure, myocardial infarction, angina pectoris, and atrial fibrillation); cerebrovascular disease (including transient cerebral ischemia and cerebrovascular event); peripheral angiopathy (including peripheral arterial disease and carotid stenosis); nephropathy (if glomerular filtration rate estimated by CKD-EPI was ≤ 60 mL/min/1.73 m^2 without inclusion of dialysis). Physical activity was assessed through the Duke Activity Status Index (DASI) questionnaire, calculating metabolic equivalents (METs) as follows: METs = total DASI score × 0.43 + 9.6/3.5; defining low physical activity when obtaining ≤ 5 MET[34].

Weight, height, waist, hip, and calf circumferences of the right leg were measured; body mass index was calculated using the formula: weight (kg)/height^2 (m). Biochemical variables were obtained from the clinical history of no more than 3 months. The triglyceride/glucose (TyG) index was calculated according to the following formula: Ln (triglyceride [mg/dL] × glucose [mg/dL]/2), a value ≥ 8.80 defined the presence of insulin resistance[35]. HbA1c levels were considered to establish glycemic control if HbA1c ≤ 7.5% and poor glycemic control if HbA1c ≥ 7.5%[36].

Definition of sarcopenia

The diagnosis of sarcopenia was made according to the European Working Group on Sarcopenia in Older People 2 criteria[13]. Muscle strength was obtained using a JAMAR® digital dynamometer, recording the highest value after three attempts with the dominant hand. Low muscle strength was considered in women if ≤ 16 kg and ≤ 27 kg for men. Appendicular skeletal muscle mass (ASM) was calculated using the formula ASM (kg) = 0.215 × calf circumference (cm) + 0.093 × hand grip strength (kg) + 0.061 × weight (kg) + 3.637 × sex + 0.112 × height (cm) - 16.449; where sex: male = 1; female = 0; considering low muscle mass in females if ≤ 15 kg and ≤ 20 kg for males[37]. Gait speed was timed over 4 linear meters and was used to assess physical performance. Each participant was instructed and evaluated on two occasions; the record of the best time was used to define low physical performance, with the cutoff point being ≤ 0.8 m/s.

Statistical analysis

The Kolmogorov–Smirnov test was performed for the distribution of the variables. Frequencies and percentages or means and standard deviations were represented. The Student's t-test and Chi-square test were used to compare numerical and categorical variables, respectively. Logistic regression models were used to analyze the association with the response variable: poor glycemic control. OR and 95% CI were estimated as a measure of effect size. OR estimates of poor glycemic control were adjusted for age, sex, and T2D-related variables. All statistical analyses were performed using IBM SPSS Statistics 29.0 software. Any $p < 0.05$ was considered significant.

Results

Characteristics of the participants

A total of 356 older adults who met the inclusion criteria were included. Fig. 1 shows the flow chart of the study participants. The general characteristics of the participants according to glycemic control are presented in Table 1.

Sarcopenia was present in 45.5% of the participants, women had a higher frequency of sarcopenia (59.9%) compared to men (40.1%). Poor glycemic control was present in 54.5% of the participants.

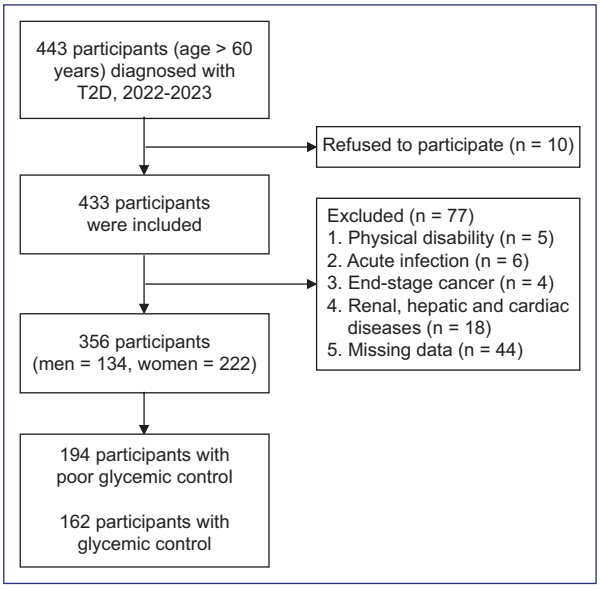

Figure 1. Flow chart in the selection of participants.

Older adults with poor glycemic control presented a higher frequency of edentulism ($p = 0.020$), malnutrition (< 0.001), frailty ($p = 0.002$), prolonged duration of T2D ($p = 0.009$), low physical activity ($p = 0.009$), sarcopenia ($p = 0.007$), and T2D-associated complications (< 0.001), with diabetic neuropathy being the most frequently related to poor glycemic control (38.3% vs. 59.3%, $p < 0.001$). Anthropometric measures were not associated with poor glycemic control. Only the means of muscle components, such as grip strength (18.3 kg vs. 20.0 kg, $p = 0.025$) and gait speed (0.70 m/s vs. 0.77 m/s, $p = 0.029$), were lower in subjects with poor glycemic control, with no differences in the amount of ASM. In participants with poor glycemic control, a higher frequency of use of DPP-4 inhibitors (74.2% vs. 59.3%, $p = 0.003$), SGLT2 inhibitors (43.8% vs. 20.4%, $p < 0.001$), and insulin (70.1% vs. 37.7%, $p < 0.001$) was observed.

Presence of sarcopenia according to glycemic control

In older adults with poor glycemic control, the frequency of sarcopenia was higher (52.1% vs. 37.7%, $p = 0.007$). HbA1c levels were shown to be associated with the presence of sarcopenia, HbA1c 6.5-7.5% (OR 2.29, 95% CI: 1.19-4.41, $p = 0.013$), HbA1c 7.5-8.5% (OR 3.73, 95% CI: 1.93-7.21, $p < 0.001$), and HbA1c ≥ 8.5% (OR 2.28, 95% CI: 1.23-4.23, $p = 0.009$). In the univariate model, sarcopenia (OR 1.79, 95% CI:

Table 1. Clinical characteristics of older adults according to glycemic control

Feature	Poor glycemic control (n = 194)	Glycemic control (n = 162)	p-value
Age (years)	75.4 (8.2)	74.5 (7.6)	0.311
Women (%)	123 (63.4)	99 (61.1)	0.657
Social assistance			
Lives alone (%)	25 (12.9)	18 (11.1)	0.315
Lives with spouse (%)	100 (51.5)	80 (49.4)	
Lives with another family member (%)	66 (34.0)	64 (39.5)	
Lives in retirement home (%)	3 (1.5)	0 (0)	
Number of teeth			0.020
Edentulism (%)	21 (10.8)	11 (6.8)	
< 20 pieces (%)	56 (28.9)	33 (20.4)	
> 20 pieces (%)	53 (27.3)	68 (42.0)	
Use of prosthesis (%)	64 (33.0)	50 (30.9)	
Comorbidity (Charlson ≥ 3)	145 (74.7)	116 (71.6)	0.505
Malnutrition (MNA ≤ 17)	134 (69.1)	76 (46.9)	< 0.001
Number of meals			0.077
One/day (%)	9 (4.6)	3 (1.9)	
Two/day (%)	67 (34.5)	41 (25.3)	
Three/day (%)	114 (58.8)	112 (69.1)	
Four or more/day (%)	4 (2.1)	6 (3.7)	
Fragility (Frail ≥ 3)	83 (42.8)	45 (27.8)	0.002
Polypharmacy (≥ 5 drugs)	146 (75.3)	116 (71.6)	0.436
Duration of T2D (years)	17.2 (9,6)	14.6 (9.4)	0.009
Physical activity (≤ 5 METs)	119 (61.3)	77 (47.5)	0.009
Sarcopenia (%)	101 (52.1)	61 (37.7)	0.007
T2D-related complications (%)	155 (79.9)	102 (63.0)	< 0.001
Retinopathy (%)	29 (14.9)	15 (9.3)	0.104
Neuropathy (%)	115 (59.3)	62 (38.3)	< 0.001
Heart disease (%)	42 (21.6)	24 (14.8)	0.098
Cerebrovascular (%)	27 (13.9)	25 (15.4)	0.687
Angiopathy (%)	41 (21.1)	25 (15.4)	0.168
Nephropathy (%)	28 (14.4)	31 (19.1)	0.235
Anthropometry			
BMI (kg/m^2)	27.1 (5.8)	27.4 (4.9)	0.600
Waist circumference (cm)	97.9 (13.0)	99.8 (13.7)	0.165
Hip circumference (cm)	104.0 (13.1)	106.6 (10.3)	0.044
Body Fat (%)	40.5 (9.2)	40.4 (8.0)	0.932
Muscle strength (kg)	18.3 (7.5)	20.0 (7.3)	0.025
Muscle mass (kg)	15.4 (3.7)	15.9 (3.9)	0.192
Gait speed (m/s)	0.70 (0.2)	0.77 (0.2)	0.029
Biochemical markers			
HbA1c (%)	9.2 (1.5)	6.5 (0.5)	< 0.001
Creatinine (mg/dL)	0.96 (0.5)	0.91 (0.5)	0.414
Albumin (g/dL)	3.7 (0.4)	3.8 (0.4)	0.041
Total cholesterol (mg/dL)	166.9 (45.8)	161.3 (40.1)	0.228
HDL cholesterol (mg/dL)	43.5 (11.2)	44.1 (11.4)	0.637
LDL cholesterol (mg/dL)	90.7 (34.1)	85.3 (33.3)	0.132
Triglycerides (mg/dL)	162.9 (68.4)	159.3 (74.4)	0.637
Uric acid (mg/dL)	5.8 (1.8)	5.9 (1.7)	0.382
TyG index	9.3 (0.5)	8.9 (0.5)	< 0.001
Antidiabetic medication			
Sulfonylureas (%)	7 (3.6)	5 (3.1)	0.786
Biguanides (%)	149 (76.8)	123 (75.9)	0.846
Thiazolidinediones (%)	2 (1.0)	2 (1.2)	0.856
DPP-4 inhibitors (%)	144 (74.2)	96 (59.3)	0.003
SGLT2 inhibitors (%)	85 (43.8)	33 (20.4)	< 0.001
GLP-1 analogs (%)	6 (3.1)	1 (0.6)	0.094
Insulin (%)	136 (70.1)	61 (37.7)	< 0.001

ASM: appendicular skeletal muscle mass; BMI: body mass index; GLP-1: glucagon-like peptide receptor type 1 agonists; HbA1c: glycosylated hemoglobin; iDPP4: dipeptidyl-peptidase 4 inhibitors; iSGLT2: sodium-glucose cotransporter type 2 inhibitors; MET's: metabolic equivalent; MNA: Mini-Nutritional Assessment; T2D: type 2 diabetes mellitus; TyG: glucose/triglyceride index. Results are expressed as frequency (%) or mean (standard deviation). P value (t-student or Chi-square).

Table 2. Risk factors for the presence of poor glycemic control

Feature	OR not adjusted		OR adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Comorbidity (Charlson > 3)	1.13 (1.01-1.27)	0.028	0.949 (0.81-1.10)	0.505
Muscle mass	1.73 (1.07-2.73)	0.016	1.74 (0.85-3.56)	0.128
Sarcopenia	1.79 (1.17-2.75)	0.007	0.95 (0.47-1.93)	0.899
Malnutrition (MNA ≤ 17)	2.52 (1.63-3.89)	< 0.001	2.16 (1.17-4.00)	0.013
Fragility	1.58 (1.22-2.05)	< 0.001	1.19 (0.79-1.79)	0.383
T2D-related complications	2.33 (1.45-3.75)	< 0.001	1.20 (0.58-2.49)	0.611
Physical activity (≤ 5 METs)	1.75 (1.14-2.67)	0.009	0.91 (0.47-1.76)	0.800
TyG index	3.75 (2.44-5.76)	< 0.001	5.16 (3.10-8.57)	< 0.001
Duration of T2D (> 20 years)	1.61 (1.03-2.51)	0.036	1.14 (0.66-1.97)	0.633
iDPP-4	1.98 (1.26-3.10)	0.003	1.88 (1.07-3.28)	0.026
iSGLT-2	3.04 (1.89-4.90)	< 0.001	2.53 (1.45-4.43)	0.001
Insulin	3.88 (2.49-6.04)	< 0.001	3.51 (2.01-6.12)	< 0.001
Diabetic neuropathy	2.34 (1.53-3.59)	< 0.001	1.11 (0.59-2.06)	0.743

iDPP4: dipeptidyl-peptidase 4 inhibitors; iSGLT2: sodium-glucose cotransporter type 2 inhibitors; MET's: metabolic equivalents; T2D: diabetes mellitus; TyG: glucose and triglyceride index. Results expressed as OR, odds ratio for prevalence; 95% CI, 95% confidence interval. OR adjusted through logistic regression.

1.17-2.75, p = 0.007) and low muscle mass (OR 1.73, 95% CI: 1.10-2.73, p = 0.016) were associated with the presence of poor glycemic control.

Association of the risk of poor glycemic control

Table 2 shows the associations by logistic regression analysis for poor glycemic control. In the univariate model, factors such as comorbidity, sarcopenia, low muscle mass, frailty, T2D-related complications, low physical activity, prolonged duration of T2D, and the presence of diabetic neuropathy stand out. In the adjusted model, poor glycemic control was only associated with the presence of malnutrition (OR 2.16), insulin resistance (OR 5.16), and the use of antidiabetic drugs such as dipeptidyl-peptidase 4 inhibitors (OR 1.88), sodium-glucose cotransporter type 2 inhibitors (OR 2.53), and insulin (OR 3.51).

Discussion

Our study showed that more than half of the participants presented poor glycemic control, being more noticeable in older adults in whom sarcopenia was diagnosed. A high frequency of sarcopenia was observed in this group of subjects with T2D, especially in women. In addition to these observations, the group with poor glycemic control presented a significantly higher frequency of conditions such as poor oral health, malnutrition, frailty, longer duration of T2D, low physical activity, and T2D-related complications, with diabetic neuropathy being the most frequent associated with poor glycemic control.

Previous studies have reported worryingly high rates of poor glycemic control, ranging from 45% to 93%[19,38,39], and multiple factors associated with the development of poor glycemic control have been identified and even classified into categories that relate to personal, morbidity, treatment, and behavioral situations[19]. This study agrees with previous observations, where the prolonged duration of T2D[19,21-24,39], diabetic complications[16,19,20,24,40], and low physical activity[16,21] are implicated in poor glycemic control in older adults.

Other factors that were not evaluated in our study, and that also maintain a relevant mention, are those related to access to the health sector and private treatment[38,41], poor access to measuring HbA1c levels[38], low educational level[19,38,40], and poor family support[19]. Even in cohort studies, the factors that predict the risk of presenting a hyperglycemic crisis are low income, depression, higher HbA1c levels, neuropathy, and

nephropathy, being treated with SGLT2 inhibitors and insulin[40].

We observed that almost half of the participants had the diagnosis of sarcopenia, being more evident as HbA1c levels increased. Only the calculated muscle mass of the participants maintained an association with poor glycemic control. In previous work, it was determined that states of hyperglycemia (pre-diabetes) and high HbA1c levels are associated with greater loss of muscle mass, lower muscle strength, and physical performance compared to the non-diabetic population[15,17]. Once diagnosed with T2D and having diabetic complications, subjects were at increased risk of sarcopenia[15]. Individually, components of sarcopenia are associated with poor glycemic control, such as grip strength[42,43], muscle mass[9-11], and gait speed[16,21].

The factors identified in our study that was associated with poor glycemic control in older adults were malnutrition, the presence of insulin resistance with higher mean levels of the TyG index, the use of antidiabetic drugs of specific groups such as DPP-4 inhibitors, SGLT-2, and the administration of insulin. Conventionally, dietary adherence and maintaining a good nutritional status are recommendations initially implemented for the treatment of T2D with the aim of improving glucose levels, patients with low dietary adherence, and poor physical activity are associated with a state of malnutrition and poor glycemic control[16]. Conversely, it is observed that subjects with sarcopenia and T2D are at increased risk of being malnourished[44]. The development of insulin resistance accelerates the loss of muscle mass[5-7], but it is also a predictor of poorer glycemic control and a higher risk of developing complications from younger age groups[45].

Therapeutic objectives in the elderly tend to be more permissible to decrease the risk of hypoglycemia[36], it is reasonable to observe that better glycemic control is positively associated with the combined use of oral antidiabetics and insulin[20], other studies show that not taking biguanide[46], exclusive use of insulin[19,21,23,24], polypharmacy of antidiabetics[24], and complexity of treatment[19], are the factors related to pharmacological treatment that is associated with poor glycemic control. Our study showed that subjects with poor glycemic control had a higher frequency of use of DPP-4 inhibitors, SGLT2 inhibitors, and insulin, and these types of drugs were significantly associated with poor glucose control.

Although these findings can be explorative, even in our country, the obtaining of this type of information is poor. We should seek to improve preventive intervention strategies in primary care in younger age groups and optimize treatments with the aim of breaking therapeutic inertia and reducing the progression in the development of T2D and its complications, as well as limiting as much as possible the deterioration of muscle mass and its functional consequences in the aging of this type of patients.

Our study has some limitations: the external validity of the findings of our analysis may not be representative of the population due to the small number of participants, from a single public institution and in reference to a limited group of patients in one specialty. In accordance with the type of study, glycemic control was only determined in a single measurement; to analyze the data and verify changes over time in HbA1c levels it will be necessary to consider a longitudinal study; to consider aspects such as the time to maintain glycemic control, adherence to treatment, pharmacological combinations, and their doses. To complement the state of malnutrition, it may be necessary to describe the type of diet, caloric quantity, average daily protein intake, and the use or not of nutritional supplements. The same applies to the evaluation of physical activity, which was determined by estimating the METs performed for activities of daily living; however, the intensity, frequency, and duration of each activity were not evaluated. These aspects may come to be considered in future studies to improve the quality of clinical findings.

Conclusion

Older adults represent a group with a high frequency of poor glycemic control; this tendency is related to the presence of sarcopenia, which increases with higher HbA1c levels. Conditions such as sarcopenia, low muscle mass, malnutrition, insulin resistance, and the use of certain antidiabetic drugs were determinants in the development of poor glycemic control.

These findings indicate the need to implement strategies focused on improving nutritional status and muscular aspects, in addition to reconsidering pharmacological pre-prescription behavior in the elderly to achieve better treatment goals.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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 have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The growing epidemic of diabetes mellitus. Curr Vasc Pharmacol. 2020;18:104-9.
2. Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. Nat Rev Endocrinol. 2021;17:534-48.
3. Koster A, Visser M, Simonsick EM, Yu B, Allison DB, Newman AB, et al. Association between fitness and changes in body composition and muscle strength. J Am Geriatr Soc. 2010;58:219-26.
4. Kohrt WM, Holloszy JO. Loss of skeletal muscle mass with aging: effect on glucose tolerance. J Gerontol A Biol Sci Med Sci. 1995;50 Spec No:68-72.
5. Lee CG, Boyko EJ, Strotmeyer ES, Lewis CE, Cawthon PM, Hoffman AR, et al. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. J Am Geriatr Soc. 2011;59:1217-24.
6. Alemán-Mateo H, López-Teros MT, Ramírez FA, Astiazarán-García H. Association between insulin resistance and low relative appendicular skeletal muscle mass: evidence from a cohort study in community-dwelling older men and women participants. J Gerontol A Biol Sci Med Sci. 2014;69:871-7.
7. López-Teros MT, Ramírez FA, Alemán-Mateo H. Hyperinsulinemia is associated with the loss of appendicular skeletal muscle mass at 4.6 year follow-up in older men and women. Clin Nutr. 2015;34:931-6.
8. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care. 2009;32:1993-7.
9. Kalyani RR, Tra Y, Egan JM, Ferrucci L, Brancati F. Hyperglycemia is associated with relatively lower lean body mass in older adults. J Nutr Health Aging. 2014;18:737-43.
10. Koo BK, Moon S, Moon MK. Muscle strength, an independent determinant of glycemic control in older adults with long-standing type 2 diabetes: a prospective cohort study. BMC Geriatr. 2021;21:684.
11. Shi X, Liu W, Zhang L, Xiao F, Huang P, Yan B, et al. Sex-specific associations between low muscle mass and glucose fluctuations in patients with type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2022; 13:913207.
12. Sugimoto K, Ikegami H, Takata Y, Katsuya T, Fukuda M, Akasaka H, et al. Glycemic control and insulin improve muscle mass and gait speed in type 2 diabetes: the MUSCLES-DM study. J Am Med Dir Assoc. 2021;22:834-8.e1.
13. Yuan S, Larsson SC. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. Metabolism. 2023;144:155533.
14. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. Nutrients. 2021;13:183.
15. Qiao YS, Chai YH, Gong HJ, Zhuldyz Z, Stehouwer CD, Zhou JB, et al. The association between diabetes mellitus and risk of sarcopenia: accumulated evidences from observational studies. Front Endocrinol (Lausanne). 2021;12:782391.
16. Massimino E, Izzo A, Castaldo C, Ferretti E, Rivellese AA, Della Pepa G. Risk of sarcopenia and associated factors in older adults with type 2 diabetes: an exploratory cross-sectional study. Healthcare (Basel). 2023;11:2081.
17. Sugimoto K, Tabara Y, Ikegami H, Takata Y, Kamide K, Ikezoe T, et al. Hyperglycemia in non-obese patients with type 2 diabetes is associated with low muscle mass: the multicenter study for clarifying evidence for sarcopenia in patients with diabetes mellitus. J Diabetes Investig. 2019;10:1471-9.
18. Chen S, Yan S, Aiheti N, Kuribanjiang K, Yao X, Wang Q, et al. A bi-directional Mendelian randomization study of sarcopenia-related traits and type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023;14:1109800.
19. Bin Rakhis SA Sr., AlDuwayhis NM, Aleid N, AlBarrak AN, Aloraini AA. Glycemic control for type 2 diabetes mellitus patients: a systematic review. Cureus. 2022;14:e26180.
20. Oliveira RE, Franco LJ. Glycemic control in elderly people with type 2 diabetes mellitus attending primary health care units. Prim Care Diabetes. 2021;15:733-6.
21. Espinosa MM, Almeida VR, Nascimento VF. Poor glycemic control and associated factors in diabetic people attending a reference outpatient clinic in Mato Grosso, Brazil. Invest Educ Enferm. 2021;39:e10.
22. Alqudah S, Jarab AS, Alefishat EA, Mayyas F, Khdour M, Pinto S. Factors associated with poor hemoglobin A1c control in patients with type 2 diabetes. Curr Diabetes Rev. 2019;15:164-70.
23. Xiang Y, Ren B, Chen Y, Jiang M, Wang N, Niu R, et al. Predictors of glycemic control among patients with type 2 diabetes in Western China: a multi-center cross sectional study. Biol Pharm Bull. 2021;44:620-6.
24. Wang J, Li J, Wen C, Liu Y, Ma H. Predictors of poor glycemic control among type 2 diabetes mellitus patients treated with antidiabetic medications: a cross-sectional study in China. Medicine. 2021;100:e27677.
25. Milo RB, Connelly CD. Predictors of glycemic management among patients with type 2 diabetes. J Clin Nurs. 2019;28:1737-44.
26. Al-Qerem W, Jarab AS, Badinjki M, Hammad A, Ling J, Alasmari F. Factors associated with glycemic control among patients with type 2 diabetes: a cross-sectional study. Eur Rev Med Pharmacol Sci. 2022;26:2415-21.
27. Yahaya JJ, Doya IF, Morgan ED, Ngaiza AI, Bintabara D. Poor glycemic control and associated factors among patients with type 2 diabetes mellitus: a cross-sectional study. Sci Rep. 2023;13:9673.
28. Zhu HT, Yu M, Hu H, He QF, Pan J, Hu RY. Factors associated with glycemic control in community-dwelling elderly individuals with type 2 diabetes mellitus in Zhejiang, China: a cross-sectional study. BMC Endocr Disord. 2019;19:57.
29. Yoshioka M, Noma Y, Kawashima Y, Fukui M, Nakae H, Yanagisawa S, et al. Factors associated with diabetes control: results of a 2-year cohort study of outpatients with type 2 diabetes. J Med Invest. 2023;70:28-33.
30. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. Diabetes Care. 2022;45:S17-38.
31. Khan SA, Shields S, Abusamaan MS, Mathioudakis N. Association between dysglycemia and the Charlson comorbidity index among hospitalized patients with diabetes. J Diabetes Complications. 2022;36:108305.
32. Dent E, Wright OR, Woo J, Hoogendijk EO. Malnutrition in older adults. Lancet. 2023;401:951-66.
33. Somagutta MR, Uday U, Bathula NR, Pendyala S, Mahadevaiah A, Jain MS, et al. Diagnosing frailty in primary care practice. Cureus. 2022;14:e23329.
34. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989;64:651-4.
35. Park HM, Lee HS, Lee YJ, Lee JH. The triglyceride-glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance. Diabetes Res Clin Pract. 2021;180:109042.
36. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 13. Older adults: standards of care in diabetes-2023. Diabetes Care. 2023;46:S216-29.
37. Ramírez E, Enríquez-Reyna MC, Garza-Sepúlveda G, Tijerina-Sáenz A, Ramos-Peña E, Gómez de la Garza M. Puntos de corte y validación de una ecuación antropométrica para estimar la masa muscular, en el estudio de la sarcopenia en población mexicana. Salud Publica Mex. 2015;57:485-6.
38. Gomes MB, Tang F, Chen H, Cid-Ruzafa J, Fenici P, Khunti K, et al. Socioeconomic factors associated with glycemic measurement and poor HbA1c control in people with type 2 diabetes: the global DISCOVER study. Front Endocrinol (Lausanne). 2022;13:831676.
39. Taderegew MM, Emeria MS, Zegeye B. Association of glycemic control and anthropometric measurement among type 2 diabetes mellitus: a cross-sectional study. Diabetol Int. 2021;12:356-63.

40. McCoy RG, Galindo RJ, Swarna KS, Van Houten HK, O'Connor PJ, Umpierrez GE, et al. Sociodemographic, clinical, and treatment-related factors associated with hyperglycemic crises among adults with type 1 or type 2 diabetes in the US from 2014 to 2020. JAMA Netw Open. 2021;4:e2123471.
41. Wijayaratna S, Lee A, Park HY, Jo E, Wu F, Bagg W, et al. Socioeconomic status and risk factors for complications in young people with type 1 or type 2 diabetes: a cross-sectional study. BMJ Open Diabetes Res Care. 2021;9:e002485.
42. Bawadi H, Alkhatib D, Abu-Hijleh H, Alalwani J, Majed L, Shi Z. Muscle strength and glycaemic control among patients with type 2 diabetes. Nutrients. 2020;12:771.
43. Choe H, Sung H, Kim GH, Lee O, Moon HY, Kim YS. Associations between grip strength and glycemic control in type 2 diabetes mellitus: an analysis of data from the 2014-2019 Korea National Health and Nutrition Examination Survey. Epidemiol Health. 2021;43:e2021080.
44. Velázquez-Alva MC, Irigoyen-Camacho ME, Zepeda-Zepeda MA, Lazarevich I, Arrieta-Cruz I, D'Hyver C. Sarcopenia, nutritional status and type 2 diabetes mellitus: A cross-sectional study in a group of Mexican women residing in a nursing home. Nutr Diet. 2020; 77:515-22.
45. Babic N, Valjevac A, Zaciragic A, Avdagic N, Zukic S, Hasic S. The triglyceride/HDL ratio and triglyceride glucose index as predictors of glycemic control in patients with diabetes mellitus type 2. Med Arch. 2019;73:163-8.
46. Suprapti B, Izzah Z, Anjani AG, Andarsari MR, Nilamsari WP, Nugroho CW. Prevalence of medication adherence and glycemic control among patients with type 2 diabetes and influencing factors: a cross-sectional study. Glob Epidemiol. 2023; 5:100113.

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ORIGINAL ARTICLE

Commensal strains of *E. coli* involved in infections in patients at the Hospital Juarez de Mexico

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Abstract

Background: *Escherichia coli is a microorganism that causes community and health care-associated infections. Infection rates for this microorganism have increased in several countries. Another problem that adds to E. coli infections is the presence of isolates antibiotic resistance mechanisms.* **Objectives:** *Work aims to describe the characteristics of E. coli isolates involved in infections in patients of the Hospital Júarez de México.* **Methods:** *A population of 34 patients (January to September 2021) from Hospital Juarez de Mexico was included in the study. Antimicrobial susceptibility testing and β-lactamase phenotypic detection of E. coli isolates from confirmed infections were performed. Resistance phenotypes were confirmed by polymerase chain reaction. The clonal association of the isolates was performed by analysis of the intergenic regions obtained, and finally, the phylogenetic association was performed by the Clermont algorithm.* **Results:** *E. coli isolates were mainly involved in urinary tract infections, extended-spectrum β-lactamase, carbapenemases, and class 1 integrons were detected. The strains were grouped particularly into commensal phylogroups, and clonality analysis revealed genetic diversity.* **Conclusion:** *Characterization analyses of E. coli isolates causing extraintestinal infections revealed a great genetic diversity, these isolates were mainly grouped in commensal strains, were B-lactamase producers, and presented Class 1 integrons.*

Keywords: *ESKAPE. Escherichia coli. Carbapenemases.*

Introduction

At present, the group of *Enterobacterales* has gained relevance in hospitals, since they are micro-organisms closely related to health care-associated infections (HAIs)[1,2]. In particular, *Escherichia coli* is a micro-organism that causes bloodstream and urinary tract infections (UTI)[3]. Infection rates for this microorganism have increased in several countries[3-5]. Another problem that adds to the increase of *E. coli* infections is the presence of isolates involved in these nosocomial and community infections with antibiotic resistance mechanisms, it is important to highlight that, in 2017, the World Health Organization[6] issued a report where it states that the group of *Enterobacterales* where *E. coli* is part of this, is categorized as a critical priority due to its resistance to antibiotics[4,7,8]. In recent years, an increase in the frequency of *E. coli* isolates with the production of β-lactamase has been reported, these antimicrobial resistance mechanisms limit therapeutic options and are related to increased mortality rates[9,10]. The acronym ESKAPE encompasses pathogenic micro-organisms such as *Enterococcus faecium*, *Staphylococcus aureus*,

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Klebsiella pneumoniae, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and species of the genus *Enterobacter* spp. This group of bacteria has over time been reported to be the most frequent HAIs[11]. However, bacterial epidemiology is changing from hospital to hospital, and it has been suggested that the acronym ESKAPE could be modified based on the most frequent micro-organisms in each particular hospital[12]. In various regions around the world, there are reports of *E. coli* as a common cause of HAIs and also of community-acquired infections, so it could be considered within the ESKAPE group[5,13-15]. Studies in various hospitals around the world have shown that micro-organisms such as *A. baumannii* and *P. aeruginosa* are the most frequent; however, *E. coli* has also been detected as one of the main micro-organisms related to infections derived from hospital care[15-20], in the last report of the hospital epidemiological surveillance network of Mexico indicated that *E. coli* was the most frequent micro-organism related to infections associated with health care. This work aims to describe the characteristics of *E. coli* isolates involved in infections in patients of the Hospital Júarez de México.

Materials and methods

Study population of patients with confirmed E. coli infection

A population consisting of 34 patients at the Hospital Juárez de México during the period from January to September 2021 was included in the study. These patients met the inclusion criteria for confirmed *E. coli* infection. The isolates were transferred to the research laboratory for analysis. In addition, demographic data were obtained from medical records to describe the patient population.

Isolation and identification of E. coli strains from patients of Hospital Juárez de México

Bacteriological isolates and samples obtained from UTI (urine), ventilator-associated pneumonia (sputum), and surgical infection (pus) were handled in a level 2 biosafety cabinet in accordance with laboratory biosafety standards. The operator wore a protective gown and mouth cover. Sputum and pus samples were mass-seeded using sterile swabs in MacConkey gelose and blood gelose (Becton Dickinson and Co., Franklin Lakes, NJ, USA). Urine samples were cultured using the culture media described above, a 10 μL calibrated loop was used, conventional urine culture procedure was followed, all gelose plates were incubated aerobically at 37°C for 24-48 h. Subsequently, bacterial isolates were purified on Luria Bertani gelose and cryopreserved in trypticase soy broth (TSA) supplemented with 50% glycerol. Isolates were stored at -70°C for future experiments. For identification, axenic cultures were sent to the Faculty of Chemistry of the Universidad Autónoma de México to be identified by mass spectrometry using Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight.

DNA extraction

For molecular biology assays, total DNA was isolated and purified from the strains using the DNeasy Blood and Tissue Kit (QIAGEN, Venlo, the Netherlands). Briefly from an overnight culture 200 μL were taken, bacterial lysis was performed according to the procedure and reagents provided by the DNA extraction kit, the lysis consisted of 200 μL of AL buffer and 20 μL of proteinase K, the tubes were incubated for 1 h at 56°C, washes were performed with AW1 and AW2 buffers; finally, the DNA was eluted in 200 μL of AE buffer. DNA integrity was visualized on 0.8% horizontal agarose gels.

Genetic confirmation of E. coli isolates by amplification and analysis of the ribosomal 16S rRNA gene

Amplification reactions were performed on a T100 thermal cycler (Bio-Rad, Germany) that polymerase chain reactions (PCR) of the *16S rRNA* gene were performed with the universal primers 27F and 1492R using the conditions recommended by DeSantis et al. (2007) (Table 1). The amplicons were analyzed on 1.5% horizontal agarose gels using 1 × Tris-Borate-EDTA (TBE) buffer. PCR products were purified and sequenced by de Instituto de Biología de la Universidad Autonóma de México (UNAM) using a DNA Analyzer 3730 × L (Applied Biosystems, Forrest City, CA, USA). Nucleotide sequences were compared with the nucleotide sequence database (GenBank) using the Blast algorithm (http://blast.ncbi.nlm.nih.gov), using parameters of coverage (> 80%) and identity (> 90%).

Determination of the antibiotic susceptibility profile in E. coli isolates

The determination of antibiotic susceptibility was performed based on Clinical and Laboratory Standard

Table 1. Oligonucleotide sequences used in this work

Primer	Molecular targer	5x-3x	Base pair	References
27F	16S rRNA	AGAGTTTGATCMTGGCTCAG	1495	21
1492R		TACGGYTACCTTGTTACGACTT		
MultiIMP_for	blaIMP	TTGACACTCCATTTACDG	139	22
MultiIMP_rev		GATYGAGAATTAAGCCACYCT		
MultiVIM_for	blaVIM	GATGGTGTTTGGTCGCATA	390	
MultiVIM_rev		CGAATGCGCAGCACCAG		
NDM-Fm	blaNDM	GGTTTGGCGAT CTGGTTTTC	621	23
NDM-Rm		CGG AATGGCTCATCACGATC		
IntI1-F	5 ′-Segment conserved “Integrase intI1”.	GTTCGGTCAAGGTTCTG	923	24
IntI1-R		GCCAACTTTCAGCACATG		
QacEΔ1-F	3 ′-Segment conserved “quacΔE1/sul11”.	ATCGCAATAGTTGGCGAAGT	800	
sul1-B		GCAAGGCGGAAACCCGCGCC		
in-F	Region variable	GGCATCCAAGCAGCAAGC	variable	
in-B		AAGCAGACTTGACCTGAT		
chua-F	Hemin uptake system	TGCCGCCAGTACCAAAGACA	279	
chua-R		GACGAACCAACGGTTCAGGAT		25
yjaA-F	Unknown	TGAAGTGTCAGGAGACGCTG	211	
yjaA-R		ATGGAGAATGCGTTCCTCAAC		
TSPE4.C2-F	Anonymous DNA fragment	GAGTAATGTCGGGGCATTCA	152	
TSPE4.C2-R		CGCGCCAACAAAGTATTACG		
arpA-F	Ankyrin-like regulatory protein	AACGCTATTCGCCAGCTTGC	400	
arpA-R		TCTCCCCATACCGTACGCTA		
ERIC1R	Intergenic consensus	ATGTAAGCTCCTGGGGATTCA	Variable	26
ERIC2		AAGTAAGTGACTGGGGTGAGC		

Institute (CLSI) guidelines using the plate susceptibility test (CLSI 2022)[27]. Briefly, from to 24 h culture from nutrient gelose, one loop was taken and adjusted in saline on the 0.5 scale of the McFarland nephelometer, massively streaked using sterile swabs on Mueller–Hinton gelose plates. The following uni disk antibiotics (BD, Brea, CA) were used in the determination, AN (30 μg): amikacin, AMC (20/10 μg): amoxicillin with clavulanic acid, FEP (30 μg): cefepime, CRO (30 μg): ceftriaxone, ETP (10 μg): ertapenem, GM (10 μg): gentamicin, IPM (10 μg): imipenem, MEM (10 μg): meropenem, FOX (30 μg): cefoxitin, SAM (10/10 μg): ampicillin-sulbactam, TZP (100/10 μg): piperacillin-tazobactam, TMP-STX (1.25/23.75 μg): trimethoprim-sulfamethoxazole (TMP-SMX), CIP (5 μg): ciprofloxacin. *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, and *S. aureus* ATCC 25923 were used as controls. Results were inferred as susceptible, intermediate or resistant by measuring the diameter of the inhibition zone. The frequency of antibiotic resistance was calculated and represented in percentages (%).

Detection of extended-spectrum β-lactamase (ESBL)

Phenotypic detection of ESBL was performed by the combined disk method using uni disks (BD, Brea, CA) of cefotaxime (30 μg) and ceftazidime (30 μg) alone or in combination with clavulanic acid (30/10 μg) based on

CLSI 2022. Briefly, from 24 h of culture from nutrient gelose, a loop was taken and adjusted in saline solution on the 0.5 scale of the McFarland nephelometer, massively spread with sterile swabs on Mueller–Hinton gelose plates; then, the Sensi-Discs previously described for this test were placed on the plates.

Detection of carbapenemases by the modified carbapenem inhibition method (mMIC)

E. coli isolates exhibiting resistance or intermediate carbapenems were subjected to the mMIC established by CLSI 2022. Briefly, two 1-μL loopfuls of *E. coli* colonies from an overnight blood gelose plate were resuspended in 2 mL of trypticase soy broth. Subsequently, a 10-μg meropenem disk (MEM) (BD, Brea, CA, USA) was plated on each suspension and incubated at 37°C for 4 h. In addition, a Mueller–Hinton (MH) gel plate was mass inoculated with a 0.5 McFarland nephelometer-adjusted suspension of *E. coli* ATCC 25922. Finally, MEM disks were removed from the bacterial suspension and deposited on the MH plate with the *E. coli* ATCC 25922 strain. The MH plates were incubated at 37°C for 18-24 h and the inhibition zones were measured as in the routine disk diffusion method. *K. pneumoniae* bla_{NDM-1} was used as a positive control[28].

Genetic detection of carbapenemases in isolates of E. coli

To know the genetic background of carbapenem resistance of *E. coli* isolates, RT-PCR assays were performed to detect the genes for metallo β-lactamases and serine β-lactamases, using the CRE ELITe kit MGB® (Turin, Italy) according to the manufacturer's manual. Isolates with positive PCR in first step were subjected to second PCR assays to detect specific carbapenemase genes (bla_{NMD}, bla_{VIM}, and bla_{IMP}) (Table 1).

Detection of class 1 integrons and their gene cassettes

E. coli strains were screened for the presence of class 1 integrons. Integrase 5' (intI1)-variable (qacEΔ1-sul1)3' were amplified with the primer pair, as shown in Table 1. The identity of the resistance cassettes resistance cassettes was analyzed by sequencing performed at the Instituto de Biologia, UNAM, using a 3730Xl DNA analyzer (Applied Biosystems, Foster City, California, USA) with in-F or in-B primers (Table 1). Nucleotide sequences were compared with the online sequence database (GenBank) using the BlastX algorithm (http://blast.ncbi.nlm.nih.gov). *Aeromonas salmonicida* 718 with plasmid pRAS1 (IncU, Class 1 integron [intI1-dfrA-16qacEΔ1/sul1]) was used as a positive control.

Phylotyping of E. coli isolates

Clermont et al. proposed an analysis based on the presence and/or absence of the *chuA*, *yjaA*, *arpA,* and *TspE4.C2* genes proposing six phylogenetic groups in *E. coli* strains. The multiplex PCR conditions were denaturation for 4 min at 94°C, followed by up to 30 cycles of denaturation for 5 s at 94°C, annealing for 20 s at 59°C, and extension for 1 min at 72°C, with a final extension of 5 min at 72°C of 5 min at 72°C. PCR products were developed on agarose agarose gels and documented under ultraviolet light and ethidium bromide. The primers used for this purpose and the length of the PCR products are shown in Table 1.

Molecular typing of E. coli isolates by enterobacterial repetitive intergenic consensus (ERIC)-PCR

Strains were subjected to molecular typing by ERIC-PCR using primers ERIC1R and ERIC235 (Table 1). The total reaction volume was 50 μL and consisted of molecular biological grade water, 1× PCR buffer 1×, 20 nM MgCl2, 25 mM deoxyribonucleotide phosphate, 100 pM of each primer, 3 units of Taq DNA polymerase (Thermo Scientific, Foster City, CA, USA), and 300 ng of template genomic DNA. Cycling conditions were as follows: pre-denaturation at 95°C for 7 s, denaturation at 90°C for 30 s, annealing at 58°C for 1 min, and extension at 65°C for 8 min, with a final extension at 68°C for 16 min at the end for 30 cycles. Gene profiles were run in 1 × TBE buffer, pH 8.3, and separated by horizontal electrophoresis on 1.5% agarose gels, visualized, photographed under UV illumination, and analyzed by intra-gel pattern matching using ImageLab 5.2.1. To confirm the reproducibility of the ERIC-PCR assays, three replicates were performed.

Results

Isolation of E. coli strains from patients with confirmed infection from Hospital Juárez de México

From January to September 2020, 34 *E. coli* isolates were recovered, mainly from UTI associated with 67.6%

(n = 23), followed by 20.5% (n = 7) of ventilator-associated pneumonia and 17.6 (n = 4) of surgical infections (Fig. 1).

Female sex patients were the most frequently associated with *E. coli* infections, with 67.6% (n = 23), compared to male sex, with 32.3% (n = 11). The services with the highest rate of infections by this microorganism were as follows: internal medicine (17.6%), gynecology (11.7%) and urology (17.6%), other services such as oncology, rheumatology, and general surgery showed frequencies of 8.8%, as shown in Fig. 2.

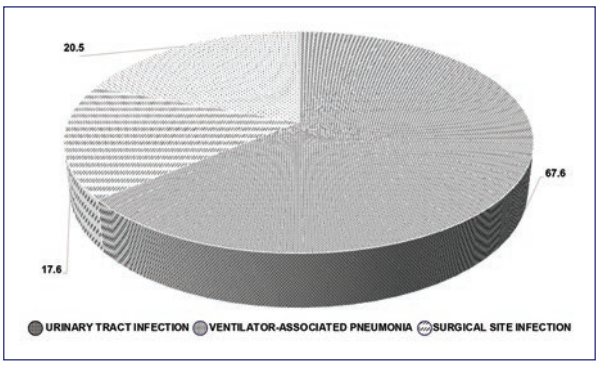

Figure 1. Distribution of *Escherichia coli* isolates by type of infection in Hospital Juárez de México patients. Urinary tract infection was the most frequent infection.

Resistance profile of E. coli strains isolated from patients with confirmed infection

The lowest antimicrobial activity against the isolates was observed mainly for sulfonamides, fluoroquinolones, and cephalosporins. The resistance and sensitivity profiles of all strains are shown in Fig. 3.

Phenotypic detection of carbapenemases and ESBL

Phenotypic detection of carbapenemase production was detected in (11.7%, n = 4) of the isolates, in (64. 7%, n = 22) the presence of ESBL was detected (Table 2).

Molecular screening for carbapenemases

Genes codifying for carbapenemases belonging to the bla_{NDM} (n = 3) and bla_{OXA-48} (n = 1) families were detected in four *E. coli* isolates with carbapenem resistance. The results of antimicrobial resistance genotype are shown in Table 2.

Detection of class 1 integrons and their gene cassettes

Integrase 1, *qacEΔ1-sul1,* and variable region genes were detected in 50% of the isolates (n = 17). The size of the variable region amplicons ranged from 500 bp to 1000 bp. The criteria for defining the identity of the amplicons obtained were the percentage match (> 75%), match length (> 100 bp), and similarity. From the BLAST alignment, seven class 1 integron arrays were identified, as shown in Table 3. The *aadA5-dfrA17* array was the one mostly found in 20.5% (n = 7) of the strains.

Cassettes are shown shaded in gray, arrows indicate transcript orientation. The letters A - G indicate the arrays found.

Phylogenetic assignment

The most prevalent phylogenetic groups were D (15/44%) and A (15/44%). Phylogroup F was observed with a frequency of 9% (n = 3) and the unknown group 3% (n = 1). The phylogenetic distribution of commensal groups (A, F, and the unknown group) and virulent strains (group D) was 66% and 44%, respectively (Table 3).

Clonal relationship in E. coli isolates

The diversity in the identification of intergenic regions allowed us to differentiate all isolates as unique strains. Fig. 4 shows the clonal distribution obtained by ERIC-PCR (Fig. 4).

Discussion

In this work, the studied isolates of *E. coli* came particularly from UTI, followed by surgical site infections and ventilator-associated pneumonias; in other works, it has been shown that this pathogen is prevalent in infections related to the genito-urinary tract associated with the community and health care; however, it is also involved in other types of infections, demonstrating that its virulent capabilities allow it to cause infectious processes in different anatomical sites[2,3,29,30]. It has been observed a direct relationship of UTI in the female sex by this microorganism; in this study, most of the patients where this bacterium was isolated were related to UTI in this sex, it has been reported that due to different factors, there is a marked predisposition toward the female sex particularly for genito-UTI caused by *E. coli*[31]. It has been reported that the vagina is an important

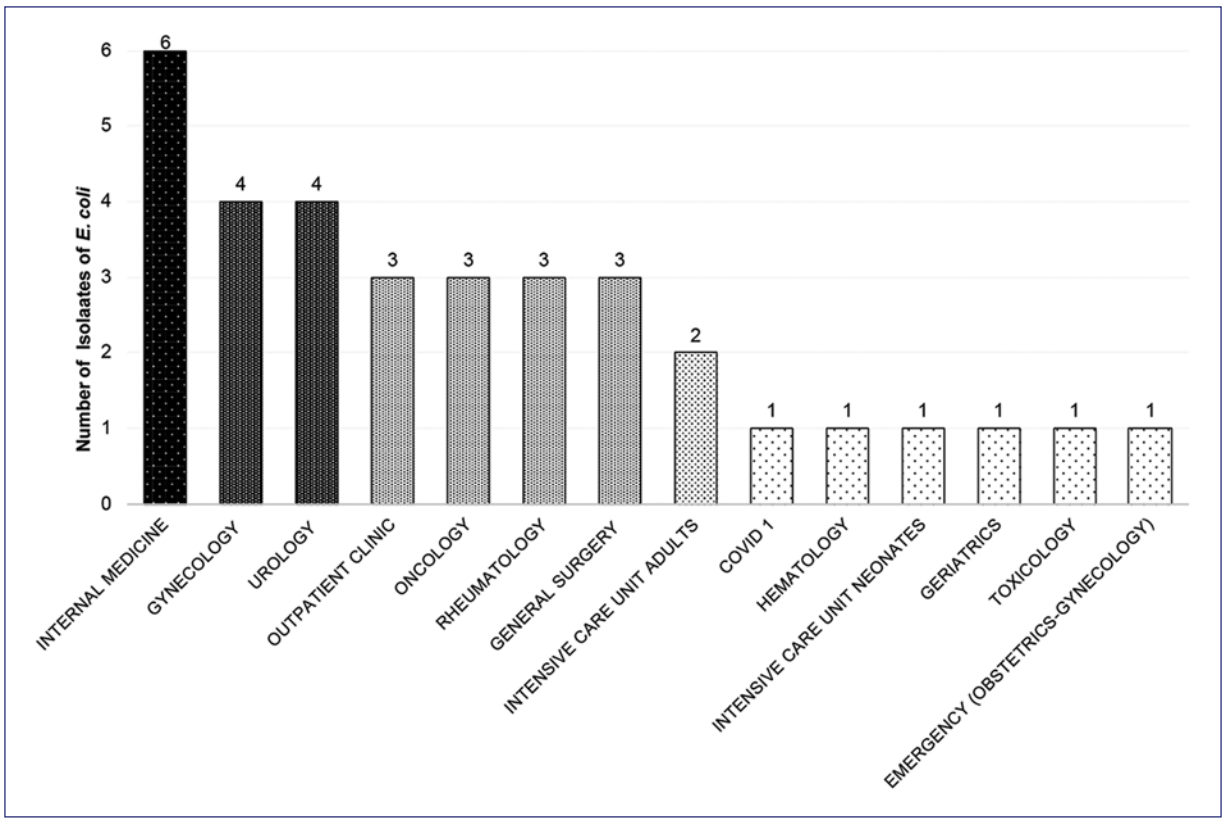

Figure 2. Distribution of *E. coli* isolates in the different services of Hospital Juárez de México. Internal medicine was the service with the highest frequency of *E. coli* infections. *E. coli*: *Escherichia coli.*

anatomical site in the pathogenesis of UTI caused by *E. coli* in women, the microbiota at this anatomical site in the female sex is a dynamic factor and closely related to this type of infections, changes in the characteristics of the vaginal microbiota may result in the loss of *Lactobacillus* spp., and this has been related to the risk of UTI[32]. Surgical site infections and ventilator-associated pneumonia were HAIs where *E. coli* was also involved in this study, other studies have reported this bacteria also related to this type of nosocomial infections[2,33]. *E. coli* is a microorganism that is part of the human microbiota, particularly in the gastrointestinal tract[34]. Different studies have shown that incorrect clinical practices by health personnel are related to the incidence of HAIs due to *E. coli*, due to cross-contamination caused by mishandling of patients so that the transmission dynamics of this microorganism within hospitals should be detected to implement measures that contribute to the reduction of the transmission of microorganisms causing HAIs[34,35]. Although in this work, there was no evidence of biofilm formation in the isolates analyzed, it has been shown that *E. coli* has the ability to form this microbial structure, there is even a direct relationship of biofilm formation with infections associated with medical devices, such as grafts, prosthetic joints, shunts, and urethral and intravascular catheters, so we speculate that the isolates of this work could have the genetic machinery necessary to produce this structure[36]. Future work will be aimed at demonstrating the formation of this structure in these isolates. B-lactams, fluoroquinolones, TMP-SMX, and Nitrofurantoin are the antibiotics recommended for antibiotic therapy in *E. coli* infections[37]; in this work, resistance was observed particularly to TMP-SMX, ciprofloxacin, and 3rd/4th generation cephalosporins (FEP, CRO), in a SENTRY type epidemiological surveillance study in which isolates collected from 1997 to 2016 were analyzed, increased resistance was observed particularly to 3rd- and 4th-generation cephalosporins as well as fluoroquinolones[38]. TMP-SMX is one of the first-line empirical therapies for the treatment of acute uncomplicated cystitis, resistance rates to this antibiotic have been reported to be > 20% for *E. coli*, the isolates analyzed in this work showed resistance mainly to this antibiotic so that empirical therapy with TMP-STX should be reconsidered[39]. Phenotypic tests to evidence ESBL production

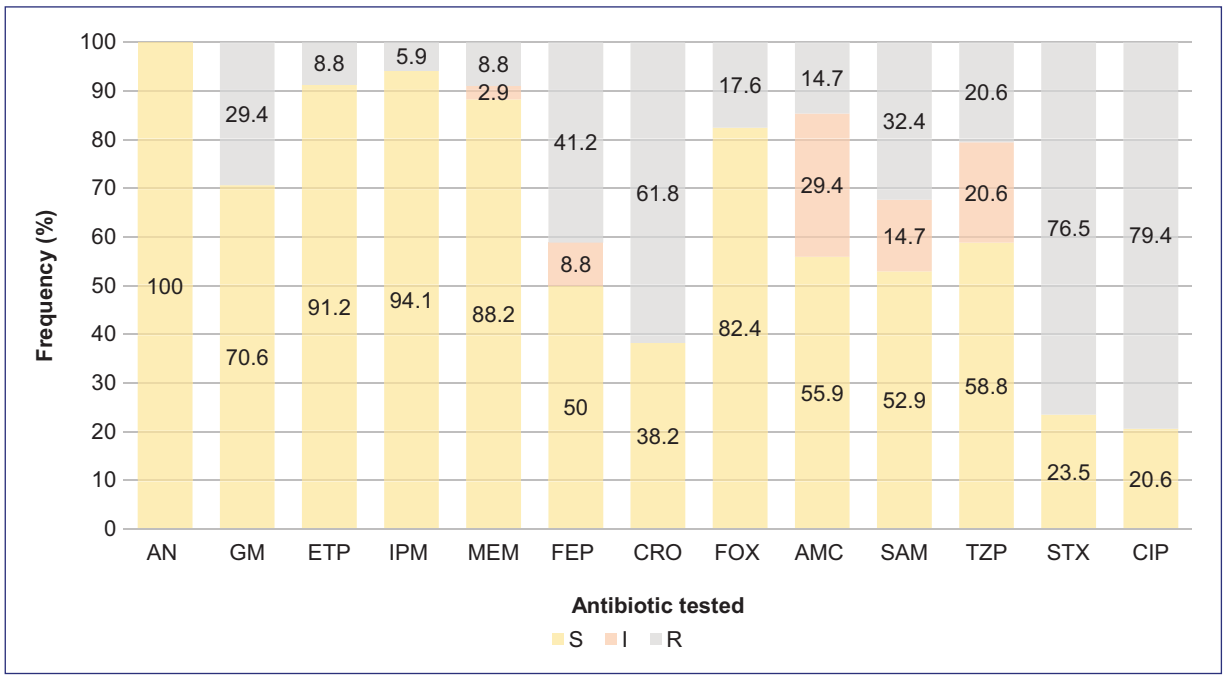

Figure 3. Resistance profile of *Escherichia coli* strains. A higher percentage of resistance is observed in STX and CIP, with greater susceptibility in AN. AN: amikacin, AMC: amoxicillin with clavulanic acid, FEP: cefepime, CRO: ceftriaxone, ETP: ertapenem, GM: gentamicin, IPM: imipenem, MEM: meropenem, FOX: cefoxitin, SAM: ampicillin-sulbactam, TZP: tazobactam piperacillin, TMP-STX: trimethoprim-sulfamethoxazole, CIP: ciprofloxacin, S: susceptible, I: intermediate, R: resistant.

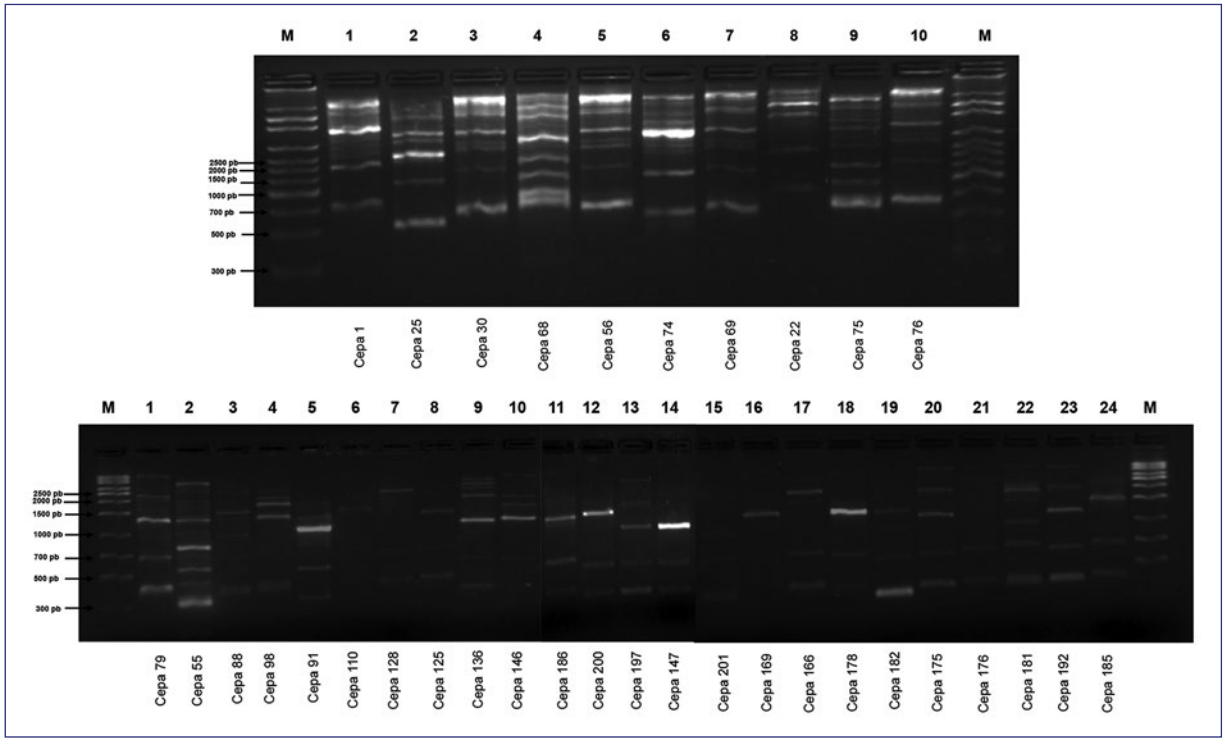

Figure 4. Electrophoretic patterns generated by the enterobacterial repetitive intergenic consensus-polymerase chain reactions of *Escherichia coli* strains isolated from confirmed infections. A high genetic diversity is observed in the isolates. Lanes: M: molecular size marker (Axygen 1Kb).

Table 2. Characteristics of *Escherichia coli* isolates

ID	mCIM*	Genotypic detection of carbapenemase[a]	Phenotypic determination of ESBL	Phylogenetic group	Infection type
1	–	NT**	+	A	UTI[b]
22	+	+ (bla_{NDM})	+	D	VAP[c]
25	–	NT	+	D	UTI
30	–	NT	+	D	UTI
68	–	NT	+	D	UTI
56	–	NT	–	D	UTI
74	+	+ (bla_{OXA-48})	+	D	UTI
69	–	NA	–	D	SI[d]
75	–	NA	+	D	UTI
76	–	NA	+	D	UTI
79	+	+ (bla_{NDM})	+	A	UTI
55	–	NT	+	A	VAP
88	–	NT	–	D	VAP
98	–	NT	–	A	UTI
91	–	NT	+	A	UTI
110	–	NT	+	A	VAP
128	–	NT	+	Unknown	UTI
125	–	NT	+	D	UTI
136	–	NT	–	D	UTI
146	–	NT	–	F	UTI
201	–	NT	+	A	SI
169	–	NT	–	F	UTI
166	–	NT	+	A	SI
178	–	NT	+	F	UTI
182	–	NT	–	A	UTI
175	–	NT	+	A	UTI
176	+	+ (bla_{NDM})	+	A	VAP
181	–	NT	+	D	VAP
192	–	NT	+	D	UTI
185	–	NT	–	A	SI
186	–	NT	–	D	SI
200	–	NT	–	A	UTI
197	–	NT	+	A	UTI
147	–	NT	–	A	UTI

*Modified carbapenem inactivation method.
**Not tested.
[a]Real-time PCR.
[b]Urinary tract infection.
[c]Ventilator-associated pneumonia.
[d]Surgical infection.
UTI: urinary tract infections; VAP: ventilator-associated pneumonia.

Table 3. Schematic map of class 1 integrons identified in *Escherichia coli* strains

Array	5´CS	3´CS	Variable Region (bp)	Strains ID	Resistance phenotype
A			910	125, 25	Trimethoprim and sulfamethoxazole
B			536	201	Trimethoprim and sulfamethoxazole
C			924	166, 30	Trimethoprim and sulfamethoxazole
D			592	186	Trimethoprim and sulfamethoxazole
E			915	146	Trimethoprim and sulfamethoxazole
F			905	55, 91, 56	Aminoglycosides, Trimethoprim and sulfamethoxazole
G			910	197, 181, 176, 110, 88, 76, 79	Aminoglycosides , Trimethoprim and sulfamethoxazole

Cassettes are shown shaded in gray, arrows indicate transcript orientation. The letters A-G indicate the arrays found.

showed that 65% of *E. coli* isolates were producers of this resistance mechanism, this type of enzyme is directly related to resistance to cephalosporins, in addition to being the most frequent resistance mechanism in this bacteria[38,40,41], the strains analyzed showed resistance to the antibiotics recommended in antibiotherapy, which limits treatment options and forces health personnel to escalate therapy to antimicrobial therapy, carbapenems are one of the last treatment options against serious infections caused by Gram-negative bacteria[42], although carbapenems in this work had low percentages of resistance, four isolates were detected with coding genes for carbapenemases; in other work, these resistance mechanisms have also been reported in isolates of *E. coli*[43]. The presence of carbapenemase-producing *E. coli* strains is a warning sign, because these resistance mechanisms have been shown to be associated with high mortality rates[44]. The most clinically important β-lactamase (carbapenemases and ESBL) have been reported particularly in plasmids and integrons[45,46], these genetic elements are related to the acquisition and/or dissemination of antibiotic resistance mechanisms[46]. In this work, the presence of class 1 integrons was detected in 50% of the isolates where the resistance related to these genetic elements was particularly to TMP-SMX, class 1 integrons are the most frequently identified in bacteria present in the nosocomial environment[47]. The importance of integrons in bacteria of medical interest present in the hospital environment lies in the fact that these genetic elements can carry out resistance gene replacement based on the needs of each microorganism, providing an advantage in terms of adaptability and resistance to antibiotics[48]. The problem of increasing antimicrobial resistance marks the importance of conducting epidemiological surveillance, implementing methodologies for timely detection and the implementation of containment measures to prevent these isolates from spreading, causing HAIs, and transferring and/or acquiring antibiotic resistance mechanisms. The phylogenetic analysis using Clermont's algorithm showed that the *E. coli* isolates belonged mostly to phylogroups D and A, pathogenic and commensal phylogroups, respectively; other work has reported results similar to our study[49] (Belmont-Monroy et al., 2022). Phylogroups B2, D, B1, and A have been related to extraintestinal infections[25], the phylotypification proposed by Clermont allowed differentiation between pathogenic and commensal isolates; however, over time, it has been demonstrated that isolates categorized in commensal phylogroups are also involved in infections. In this work, isolates belonging to commensal phylogroups were involved in the three types of infections observed in this work. Other studies have also demonstrated the role of commensal phylogroups as causative agents of infections, which have been characterized and the presence of virulence

factors and antibiotic resistance mechanisms have been demonstrated[25,50]. The analysis of intergenic regions by ERIC-PCR showed that infections caused by *E. coli* isolates were not related to each other, the high genetic diversity highlights the importance of continuing to study this microorganism since it is one of the most clinically important bacterial pathogens in the world. Its ubiquitous presence in the human intestinal tract, its ability to cause diverse infections, the presence of isolates belonging to commensal phylogroups with resistance mechanisms, and evolutionary capacity have made the control of *E. coli* infections an important public health priority.

Conclusion

Characterization analyses of *E. coli* isolates causing extra-intestinal infections revealed a great genetic diversity; these isolates were mainly grouped in commensal strains, were B-lactamase producers, and presented Class 1 integrons.

Funding

None.

Conflicts of interest

None.

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 no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Machado E, Costa P, Carvalho A, On Behalf of the Sarel Investigators. Occurrence of healthcare-associated infections (HAIs) by *Escherichia coli* and *Klebsiella* spp. producing extended-spectrum β-lactamases (ESBL) and/or carbapenemases in Portuguese long-term care facilities. Pathogens. 2022;11:1019.
2. Loyola-Cruz MÁ, Gonzalez-Avila LU, Martínez-Trejo A, Saldaña-Padilla A, Hernández-Cortez C, Bello-López JM, et al. ESKAPE and beyond: the burden of coinfections in the COVID-19 pandemic. Pathogens. 2023;12:743.
3. Ludden C, Coll F, Gouliouris T, Restif O, Blane B, Blackwell GA, et al. Defining nosocomial transmission of *Escherichia coli* and antimicrobial resistance genes: a genomic surveillance study. Lancet Microbe. 2021;2:e472-80.
4. MacKinnon MC, Sargeant JM, Pearl DL, Reid-Smith RJ, Carson CA, Parmley EJ, et al. Evaluation of the health and healthcare system burden due to antimicrobial-resistant *Escherichia coli* infections in humans: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2020;9:200.
5. Boletín Epidemiológico RHOVE 2022. (s.f.). Available from: https://www.gob.mx/salud/documentos/boletin-epidemiologico-rhove-2022 [Last accessed on 2023 Dec 09].
6. World Health Organization. WHO Publishes List of Bacteria for Which New Antibiotics are Urgently Needed; 2017 Available from: https://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en [Last accessed on 2023 Dec 05].
7. Aquino-Andrade A, Merida-Vieyra J, Arias de la Garza E, Arzate-Barbosa P, De Colsa Ranero A. Carbapenemase-producing *Enterobacteriaceae* in Mexico: report of seven non-clonal cases in a pediatric hospital. BMC Microbiol. 2018;18:38.
8. Poirel L, Madec JY, Lupo A, Schink AK, Kieffer N, Nordmann P, et al. Antimicrobial resistance in *Escherichia coli*. Microbiol Spectr. 2018;6.
9. Zhou R, Fang X, Zhang J, Zheng X, Shangguan S, Chen S, et al. Impact of carbapenem resistance on mortality in patients infected with *Enterobacteriaceae*: a systematic review and meta-analysis. BMJ Open. 2021;11:e054971.
10. Linkevicius M, Bonnin RA, Alm E, Svartström O, Apfalter P, Hartl R, et al. Rapid cross-border emergence of NDM-5-producing *Escherichia coli* in the European Union/European Economic Area, 2012 to June 2022. Euro Surveill. 2023;28:2300209.
11. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008;197:1079-81.
12. Peterson LR. Bad bugs, no drugs: no ESCAPE revisited. Clin Infect Dis. 2009;49:992-3.
13. Akinkugbe O, Cooke FJ, Pathan N. Healthcare-associated bacterial infections in the paediatric ICU. JAC Antimicrob Resist. 2020;2:dlaa066.
14. Gong L, Tang N, Chen D, Sun K, Lan R, Zhang W, et al. A nosocomial respiratory infection outbreak of carbapenem-resistant *Escherichia coli* ST131 with multiple transmissible blaKPC-2 carrying plasmids. Front Microbiol. 2020;11:2068.
15. Loyola-Cruz MÁ, Durán-Manuel EM, Cruz-Cruz C, Márquez-Valdelamar LM, Bravata-Alcántara JC, Cortés-Ortíz IA, et al. ESKAPE bacteria characterization reveals the presence of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* outbreaks in COVID-19/VAP patients. Am J Infect Control. 2023;51:729-37.
16. Ramírez-Castillo FY, Moreno-Flores AC, Avelar-González FJ, Márquez-Díaz F, Harel J, Guerrero-Barrera AL. An evaluation of multidrug-resistant *Escherichia coli* isolates in urinary tract infections from Aguascalientes, Mexico: cross-sectional study. Ann Clin Microbiol Antimicrob. 2018;17:34.
17. Alcántar-Curiel MD, Rosales-Reyes R, Jarillo-Quijada MD, Gayosso-Vázquez C, Fernández-Vázquez JL, Toledano-Tableros JE, et al. Carbapenem-resistant *Acinetobacter baumannii* in three tertiary care hospitals in Mexico: virulence profiles, innate immune response and clonal dissemination. Front Microbiol. 2019;10:2116.
18. Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother. 2019;63:e00355-19.
19. Sosa-Hernández O, Matías-Téllez B, Estrada-Hernández A, Cureño-Díaz MA, Bello-López JM. Incidence and costs of ventilator-associated pneumonia in the adult intensive care unit of a tertiary referral hospital in Mexico. Am J Infect Control. 2019;47:e21-5.
20. Cornejo-Juárez P, Cevallos MA, Castro-Jaimes S, Castillo-Ramírez S, Velázquez-Acosta C, Martínez-Oliva D, et al. High mortality in an outbreak of multidrug resistant *Acinetobacter baumannii* infection introduced to an oncological hospital by a patient transferred from a general hospital. PLoS One. 2020;15:e0234684.
21. DeSantis TZ, Brodie EL, Moberg JP, Zubieta IX, Piceno YM, Andersen GL. High-density universal 16S rRNA microarray analysis reveals broader diversity than typical clone library when sampling the environment. Microb Ecol. 2007;53:371-83.
22. Dallenne C, Da Costa A, Decré D, Favier C, Arlet G. Development of a set of multiplex PCR assays for the detection of genes encoding important beta-lactamases in *Enterobacteriaceae*. J Antimicrob Chemother. 2010;65:490-5.
23. Nordmann P, Poirel L, Carrër A, Toleman MA, Walsh TR. How to detect NDM-1 producers. J Clin Microbiol. 2011;49:718-21.

24. Cruz-Cruz C, Durán-Manuel EM, Delgado-Balbuena L, Bravata-Alcántara JC, Margarita Márquez-Valdelamar L, et al. Genotyping of *Escherichia coli* causing vaginal infection in dysplastic patients with similar genetic backgrounds between commensal and virulent strains. Jundishapur J Microbiol. 2021;14:e117488.
25. Clermont O, Christenson JK, Denamur E, Gordon DM. The clermont *Escherichia coli* phylo-typing method revisited: improvement of specificity and detection of new phylo-groups. Environ Microbiol Rep. 2013;5:58-65.
26. Versalovic J, Koeuth T, Lupski JR. Distribution of repetitive DNA sequences in eubacteria and application to fingerprinting of bacterial genomes. Nucleic Acids Res. 1991;19:6823-31.
27. Clinical and Laboratory Standard Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 31th ed. CLSI Supplement M100: Clinical and Laboratory Standard Institute; 2022.
28. Cortés-Ortíz IA, Juárez-Gómez JC, Cu-Quijano C, Flores-Paz R, Durán-Manuel EM, Cruz-Cruz C, et al. *Klebsiella pneumoniae* blaNDM-1 carrying a class 1 integron causing a hospital outbreak in a Mexican attention center. J Infect Dev Ctries. 2021;15:657-64.
29. Hamasuna R, Betsunoh H, Sueyoshi T, Yakushiji K, Tsukino H, Nagano M, et al. Bacteria of preoperative urinary tract infections contaminate the surgical fields and develop surgical site infections in urological operations. Int J Urol. 2004;11:941-7.
30. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2011-2014. Infect Control Hosp Epidemiol. 2016;37:1288-301.
31. Mohsin R, Siddiqui KM. Recurrent urinary tract infections in females. J Pak Med Assoc. 2010;60:55-9.
32. Stapleton AE. The vaginal microbiota and urinary tract infection. Microbiol Spectr. 2016;4(6): 10.1128/microbiolspec.UTI-0025-2016.
33. Montes CV, Vilar-Compte D, Velazquez C, Golzarri MF, Cornejo-Juarez P, Larson EL. Risk factors for extended spectrum β-lactamase-producing *Escherichia coli* versus susceptible *E. coli* in surgical site infections among cancer patients in Mexico. Surg Infect (Larchmt). 2014;15:627-34.
34. Martinson JNV, Walk ST. *Escherichia coli* residency in the gut of healthy human adults. EcoSal Plus. 2020;9(1):10.1128/ecosalplus.ESP-0003-2020.
35. Puig-Asensio M, Diekema DJ, Boyken L, Clore GS, Salinas JL, Perencevich EN. Contamination of health-care workers' hands with *Escherichia coli* and *Klebsiella* species after routine patient care: a prospective observational study. Clin Microbiol Infect. 2020;26:760-6.
36. Sharma G, Sharma S, Sharma P, Chandola D, Dang S, Gupta S, et al. *Escherichia coli* biofilm: development and therapeutic strategies. J Appl Microbiol. 2016;121:309-19.
37. Mueller M, Tainter CR. *Escherichia coli* infection. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
38. Castanheira M, Deshpande LM, Mendes RE, Canton R, Sader HS, Jones RN. Variations in the occurrence of resistance phenotypes and carbapenemase genes among *Enterobacteriaceae* isolates in 20 years of the SENTRY antimicrobial surveillance program. Open Forum Infect Dis. 2019;6:S23-33.
39. Wesolek JL, Wu JY, Smalley CM, Wang L, Campbell MJ. Risk factors for trimethoprim and sulfamethoxazole-resistant *Escherichia coli* in ED patients with urinary tract infections. Am J Emerg Med. 2022;56:178-82.
40. Uc-Cachón AH, Gracida-Osorno C, Luna-Chi IG, Jiménez-Guillermo JG, Molina-Salinas GM. High prevalence of antimicrobial resistance among gram-negative isolated bacilli in intensive care units at a tertiary-care hospital in Yucatán Mexico. Medicina (Kaunas). 2019;55:588.
41. Zurita J, Sevillano G, Miño AP, Haro N, Larrea-Álvarez M, Alcocer I, et al. Dominance of ST131, B2, blaCTX-M-15, and papA-papC-kpsMII-uitA among ESBL *Escherichia coli* isolated from bloodstream infections in Quito, Ecuador: a 10-year surveillance study (2009-2019). J Appl Microbiol. 2023;134:lxad269.
42. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis. 2022;75:187-212.
43. Rojas-Larios F, Martínez-Guerra BA, López-Jácome LE, Bolado-Martínez E, Vázquez-Larios MDR, Velázquez-Acosta MDC, et al. Active surveillance of antimicrobial resistance and carbapenemase-encoding genes according to sites of Care and age groups in Mexico: results from the INVIFAR network. Pathogens. 2023;12:1144.
44. Chen WK, Yang Y, Tan BH. Increased mortality among carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* carriers who developed clinical isolates of another genotype. Open Forum Infect Dis. 2019;6:ofz006.
45. Zhao WH, Hu ZQ. Acquired metallo-β-lactamases and their genetic association with class 1 integrons and ISCR elements in Gram-negative bacteria. Future Microbiol. 2015;10:873-87.
46. Wang Q, Wei S, Silva AF, Madsen JS. Cooperative antibiotic resistance facilitates horizontal gene transfer. ISME J. 2023;17:846-54.
47. Zhou W, Zhang E, Zhou J, He Z, Zhou Y, Han J, Qu D. Characterization and comparative genomics analysis of IncFII multi-resistance plasmids carrying blaCTX-M and Type1 integrons from *Escherichia coli*. Front Microbiol. 2021;12:753979.
48. Pérez-Valdespino A, Lazarini-Martínez A, Rivera-González AX, García-Hernández N, Curiel-Quesada E. Dynamics of a class 1 integron located on plasmid or chromosome in two *Aeromonas* spp. Strains. Front Microbiol. 2016;7:1556.
49. Belmont-Monroy L, Ribas-Aparicio RM, González-Villalobos E, Pérez-Ramos JA, Aparicio-Ozores G, Eslava-Campos CA, et al. Molecular typification of *Escherichia coli* from community-acquired urinary tract infections in Mexico. Int J Antimicrob Agents. 2022;60:106667.
50. Valat C, Drapeau A, Beurlet S, Bachy V, Boulouis HJ, Pin R, et al. Pathogenic *Escherichia coli* in dogs reveals the predominance of ST372 and the human-associated ST73 extra-intestinal lineages. Front Microbiol. 2020;11:580.

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ORIGINAL ARTICLE

A protocol on NINE measures for pressure ulcer prevention by nursing staff: a cohort study design

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Abstract

Background: *Pressure ulcers (PUs) are common skin lesions in hospitals caused by prolonged pressure on the skin and underlying tissues. Inpatients, especially in intensive care, are more susceptible. PUs affect patient autonomy and increase the risk of infection and sepsis, prolong hospital stays, and generate significant additional costs to the health-care system.* **Methods:** *We designed a prospective, observational, longitudinal study of a standardized protocol of NINE measures to prevent PUs in critically ill patients. These NINE measures incorporated four components to prevent PUs: (1) standardized PUs risk assessment, (2) comprehensive skin assessment, (3) planning and implementation of nursing care to carry out prevention, and (4) recording in the nursing professional's care plan of the measures performed on the patient.* **Results:** *These four components enhance best practices focused on PUs prevention on an individualized basis, allow for assessment, and care planning, communication with health-care professionals through records, identification of patients at risk for PUs development, and implementation and attention to any abnormalities before a skin lesion is formed.* **Conclusion:** *This benefits a wide range of at-risk patients, regardless of disease or specific clinical situation, to reduce the incidence and severity of these injuries.*

Keywords: *Pressure ulcer prevention. Nursing. Standardization of the protocol. Prone position. Cohort study design.*

Introduction

In most health-care settings, pressure ulcers (PUs) are a common concern. They are defined as a localized injury to the skin and/or underlying tissue over a bony prominence due to pressure or in combination with shear. PUs pose a significant problem for hospitalized patients. The most common predisposing factors for the development of PUs in the hospital include age, immobility, sensory loss, and impaired level of consciousness. In addition, patients admitted to intensive care units (ICU) are more susceptible to PUs due to invasive care measures such as central vascular lines and mechanical ventilation[1].

Pressure injury is associated with reduced patient autonomy, increased risk of infection and sepsis, the performance of additional surgical procedures on the patient, extended periods of hospital stay, and the imposition of further costs on the patient, the patient's family, and the health-care system. Patients with pressure injuries may experience certain complications such as depression, pain, topical infection, osteomyelitis, sepsis, and even death[2].

In addition to causing harm to patients, PUs imposes a significant financial burden on medical care. Costs vary from 1.4% to 4% of health-care costs. The prevalence rate in different countries worldwide varies from 6% to 18.5% in acute care settings. A systematic review

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of European studies showed rates of PUs ranging from 4.6% to 27.2% depending on the country, while a systematic review with meta-analysis of African studies showed a point frequency ranging from 3.4% to 18.6%. Large studies from different countries have found the following prevalences: in the United States and Canada, 9.2%; in Australia, 8.7%; in Italy, 17%; and in Portugal, 5.76%[3].

The issue of pressure injury prevention is a major concern in health-care today. Many physicians believe that developing pressure injuries is not the sole responsibility of nursing but of the entire health-care system. Optimizing overall care and increasing attention to prevention can save patients from unnecessary harm, requiring multidisciplinary collaborations, a good organizational culture, and operational practices that promote safety[4].

A literature review on PU prevention found that the International Clinical Practice Guideline (2019) remains the most comprehensive evidence-based guideline on preventing and treating injuries and PUs. The guideline chapters that comprise the section on Interventions for the Prevention and Treatment of Pressure Injuries focus on five areas of care (nutrition, early repositioning and mobilization, heel pressure injuries, support surfaces, and related pressure injury devices) that are important in both the prevention and treatment of pressure injuries. The recommendations in this section address assessment, device selection, strategies for pressure redistribution, and skin protection[5].

Due to the complexity of preventing pressure injuries, it was necessary to incorporate best practices in nursing care related to PUs. For this reason, a standardized protocol was designed with NINE measures to identify the possible development of PUs and prevent damage to determine the association of the NINE measures in preventing PUs with dermal injuries, friction injuries, and PU injuries in critically ill patients.

Methods

Study design

This prospective, observational, longitudinal study follows two cohorts of patients admitted to the ICU.

Selection criteria

Inclusion criteria: (1) critically ill patients with invasive mechanical ventilation and (2) patients who did not present PUs at admission. Exclusion: (1) patients who remained < 72 h on mechanical ventilation, (2) patients who, at admission to the ICU, during the assessment of UPs, the presence of pressure lesions were detected in any of its stages I, II, III, or IV, and. (3) patients who died.

Description of the NINE measures to prevent PUs

The prevention of PUs can be largely prevented if standardized protocols are established, so health professionals can intervene at any time to prevent damage.

Nursing practice is the most important part of preventing PUs. Nurses are responsible for identifying the risk of PUs, setting goals, planning and delivering interventions, as well as providing patient and family education, and keeping records of PU prevention interventions.

Each measure to prevent PUss is described in detail below (Fig. 1).

Measure 1. Risk assessment

The nurse assesses the level of risk for developing PUs using the Braden scale. Risk assessment is a key aspect of prevention, and risk assessment scales are used for this purpose. For this protocol, the Braden scale is a research-based instrument based on a conceptual scheme that rates six risk factors: sensory/perception, moisture, activity, mobility, nutrition, and friction/shearing. The Braden scale is used for patients aged 8-100. Substantial research supports its validity and reliability (Braden Scale: Cronbach's alpha between 0.48 and 0.75)[6].

Lower subscale numbers indicate higher risk, which should be addressed in the patient's PPI prevention care plan, regardless of the overall scale score. In the Braden scale, the scores for each of the six factors are summed to give an overall score ranging from 6 (highest risk) to 18 (at risk). An overall score of 19-23 indicates that the patient is not at risk[7].

Measure 2. Use of alternating pressure devices

The nurse will place an alternating pressure mattress or pressure pad. A special surface system for pressure management could be alternating air mattresses with optical pressure sensors. This system automatically regulates the airflow of the mattress by adapting the duration of inflation and deflation according to the pressure observed on the skin. Such a system appears more efficient and safer than standard alternating air surfaces because alternating air mattresses follow a

Figure 1. A protocol of the NINE measures for pressure ulcer prevention by nursing staff.

repetitive and cyclical inflation-deflating cycle, where it does not consider whether one body region suffers more pressure than others. This method is intended to achieve a pressure below 32 mmHg throughout the body[8].

Measure 3. Skincare

The nurse performs skin care by applying pure petrolatum to the entire body once per shift and at every diaper change in wet areas. Petrolatum is the most occlusive and physiological agent that reduces transepidermal water loss by 99%, allowing sufficient water vapor to leave the skin to initiate barrier repair. The purpose of emollients and their mechanism of action allow rehydration of the skin by two main mechanisms: occlusion, preventing water leakage, and hydration by attracting water located in the deeper zones of the epidermis and dermis[9].

When patients are admitted to acute care settings and are considered at high risk for developing PUs, skin assessments are performed to identify early signs of damage. This includes a thorough visual examination of the body parts at risk to identify the presence of erythema on the skin surface, followed by a manual test for non-palpating erythema, called a skin tolerance test[10].

Measure 4. Changes of position

Perform position changes every 2-3 h with a positioner clock placed at the head of the patient's bed. Regular position changes with a frequency determined according to risk assessment, as well as repositioning of medical devices are efficient in decreasing pressure areas and avoiding skin and soft-tissue rupture. Body repositioning should be performed at least every 2 h in patients who have been subjected to cycles of 12 h or more in this prone position[11].

Measure 5. Use of support surfaces

The nurse uses pads to eliminate pressure, align and distribute weight, and maintain balance (4 pads of 20 × 30 cm and 1 large pad made of cotton cloth and/or flannel cloth, 100% filled with millet or flaxseed, preferably with a cover for washing, the size will depend on the size of the patient). There are several devices available on the market to support prone positioning. They are made of various materials designed to redistribute pressure and reduce shear stress and deformation. Devices

include those designed specifically for the head and torso and cushions that can be molded to fit the body[12].

Measure 6. Place surgical drapes

The nurse places a third (surgical) sheet to mobilize the patient. A sliding sheet is the best way to avoid friction. Someone should be moved or pulled up in the bed correctly to avoid injuring the patient's shoulders and skin. If you do not have one, you can make a pull sheet from a bed sheet that is folded in half[13].

Measure 7. Placement of preventive dressings (hydrocellular)

The nurse places 8-9 hydrocellular dressings on bony prominences such as face: forehead, malar, chin, labial commissures, auricular pavilion, thorax, pectoral upper limbs for men, mammary glands for women, abdomen and genital region for men and lower limbs (knees, distal middle thirds of lower limbs, dorsum of both feet and toes). Hydrocellular dressings protect the skin from microorganisms without being occlusive, thus avoiding wound maceration. They swell when collecting exudates, acquiring a cushion consistency, which avoids compressing the wound surface. They maintain the humidity of the medium while preventing maceration, which allows effective skin protection[14].

Measure 8. Health education

The nurse counsels the patient and family on implementing preventive measures. Educating people about the risks of PUs and how to prevent them is considered an important part of preventive care, either by providing people with written information or by having them participate in various education programs. Learning for patients and their families within the patient and family education practice of nurses is an important part of person and family-centered care. Patients and their families must master health management or health promotion strategies to optimize their health outcomes. Nurses often provide support, but how nurses facilitate individual patient and family learning using cognitive learning principles seems invisible in the nursing literature[15].

Measure 9. Nursing professional records

The nurse records in the comprehensive plan the result of the evaluation and the preventive measures for PU prevention performed on the patient. The nursing clinical record format is an ethical-legal document that constitutes the written evidence of the care given to the patient, and at the same time, it is a means of communication and coordination that facilitates the work between the members of the health team; therefore, its correct completion allows guaranteeing the continuity of care and patient safety[16].

Standardization of the protocol

To facilitate the implementation of the NINE measures protocol, the Wound and Stoma Clinic staff began with the training program for the nursing staff of the morning, afternoon, and night shifts of the ICU. The first part of the program included a presentation of the protocol highlighting the objectives of the NINE measures for PU prevention, how to implement it with patients and the records to be made in the Nursing Care Plan.

The training consists of a 2-h course/workshop that presents topics on risk assessment for developing PUs through the Braden scale as a standardized tool. A detailed evaluation of the skin identifies skin without lesions or the beginning of the lesion to intervene preventively and correct the lesion before healing.

In the workshop part, the detailed demonstration is planned with the help of a mannequin. The placement of preventive dressings with 8-9 hydrocellular dressings on bony prominences is shown. Placement on patients in a prone position is specified. On the face: forehead, malar, chin, labial commissures, and auricular pavilion. In the thorax and upper limbs: pectorals for men and mammary glands in women. Abdomen and genital region for men. Finally, in lower limbs: knees, distal middle thirds of lower limbs, dorsum of both feet and toes. Furthermore, the placement is specified in patients in dorsal decubitus position: occipital area, thorax, and upper limbs (scapulae, elbows, hips: sacral region, coccyx), and lower limbs (heels and toes).

The support surfaces, the clinical sheet, and the alternating pressure mattresses were placed. At the end, each participant was evaluated on the knowledge acquired with the evaluation of the procedure.

Emphasis is placed on patient and family education on these measures with the help of the caregiver and the patient himself. Finally, the interventions of the NINE measures carried out with the patient in the comprehensive nursing plan are recorded.

Data collection

The Wound and Stoma Clinic nursing staff collected clinical information using an instrument designed for

this study. The variables included demography (age and sex), comorbidities (cardiac, respiratory, endocrine, and renal), admission diagnosis, and the severity status of the patient.

To evaluate the NINE measures to prevent PUs, the four components of the protocol were assessed at patient admission: (1) standardized assessment of PU risk using the Braden scale, (2) comprehensive skin assessment, (3) planning and implementation of nursing care with preventive interventions, and (4) recording in the nursing professional's care plan of the measures performed on the patient, including the education provided to the patient and family.

Subsequently, PUs were reassessed at 24, 48, and 72 h to detect compliance with all protocol measures and whether the onset time of dermal, friction, and PUs lesions was detected.

The two cohort groups (those exposed to the protocol's NINE measures and those not exposed to the protocol's NINE measures) are followed prospectively over time to track the development of dermal, friction, and PUs lesions (outcome variables).

Statistical analysis

Frequencies (percentages) will be used for qualitative variables, and mean (standard deviation) will be used for quantitative variables. Demographic, clinical characteristics, and comorbidities will be compared between the groups presenting and not presenting PUs using the Chi-square test with or without continuity correction. Each of the NINE measures of PU presentation will be evaluated using the relative risk (RR, as a measure of effect size) and 95% confidence interval. We will also calculate the effect size of the NINE measures of the protocol.

Ethical aspects

This protocol was registered with the Hospital's Research and Research Ethics Committees (Registration Number HJM 011/22-1). The informed consent had to be signed by the patient's responsible family member. Data confidentiality was guaranteed according to the Law of personal identification data and sensitive personal data.

Discussion

The prevention of PUs is mainly based on the observation and risk assessment that the nursing professional performs on each patient to reduce the risk factors that favor the appearance of ulcers, representing a significant challenge in the health-care setting. In most cases, appropriate preventive interventions are required, especially in patients facing pressure exerted by body weight, frictional rubbing of the skin and shear forces or sliding of the skin between underlying bony structures and external surfaces, mobility problems, and advanced age.

In this context, a protocol of the NINE measures for the prevention of PUs has been developed, designed to comprehensively address the various factors contributing to the development of these skin lesions.

Similar findings were indicated in a previous study; the results of the study suggest that, in general, prevention practices according to international guidelines were carried out quite frequently, and comprehensive skin assessments are crucial for assessing pressure injuries. Risk assessments allow for proper prevention and care planning and should use a structured and repeatable approach. Interventions to prevent pressure injuries should be initiated for patients at elevated risk. Pressure injury prevention focuses on assessing and optimizing nutritional status, repositioning the patient, and providing adequate support surfaces. Of these prevention practices, repositioning was the most used practice[17].

A systematic review included 14 studies, including randomized controlled trials, quasi-experimental, case series, and cross-sectional studies. The review identified four broad categories of interventions that are the most effective in preventing pressure injuries: (a) pressure injury prevention packages, (b) repositioning and use of surface support, (c) prevention of medical device-related pressure injuries, and (d) access to expertise. All included studies reported a reduction in pressure injuries after interventions; however, the strength of evidence was rated moderate-to-very low[18].

According to reviews and intervention studies suggesting using a care bundle for PUs, the National PUs Advisory Panel and others endorsed evidence-based practices to prevent PUs. The bundle includes ulcer risk assessment, skin assessment, skin care, nutrition management, activity management, moisture/incontinence management, and the management of support surfaces for critically ill patients[19].

Our study of the NINE measures to prevent PUs is an evidence-based set of measures. Each measure describes interventions to address the patient comprehensively. This unification of criteria and guidelines was a strategy for the nursing professional to have a guide to orient his or her interventions. The standardized PUs

prevention protocol details the steps necessary to comply with the best practice guidelines.

The NINE measures incorporated four components to prevent PUs: (1) standardized assessment of the risk of PUs with the Braden scale, (2) skin lubrication to carry out the comprehensive skin assessment, (3) planning and implementation of nursing care to carry out prevention, and (4) recording in the nurse's care plan of the measures applied to the patient. In addition, the patient and family education given to the patient during their hospital stay.

We can comment that it complies with international guidelines. As a new proposal, measure number 8, which refers to patient and family education, and measure number 9, which refers to the recording in the comprehensive plan of the interventions performed by the nursing professional on the patient, are included as interventions that are contemplated within the care of patient attention, to improve clinical practice and collect data that will be of interest to health personnel.

Conclusion

Implementing these NINE measures provides a comprehensive and effective framework for preventing PUs. This protocol can be used in patients in ICU but also in patients with spinal cord injuries (especially those with limited mobility or who are bedridden) or with neurological diseases that affect mobility (such as cerebral palsy, stroke, or multiple sclerosis). Patient-centered care, personalization of interventions, and continuing education are key pillars to ensure the success of this protocol in clinical settings.

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Conflicts of interest

The authors declare no conflicts of interest.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Ghorbani Vajargah P, Mollaei A, Falakdami A, Takasi P, Moosazadeh Z, Esmaeili S, et al. A systematic review of nurses' practice and related factors toward pressure ulcer prevention. Int Wound J. 2023;20: 2386-401.
2. Borojeny LA, Albatineh AN, Dehkordi AH, Gheshlagh RG. The incidence of pressure ulcers and its associations in different wards of the hospital: a systematic review and meta-analysis. Int J Prev Med. 2020;11:171.
3. Ahtiala MH, Kivimäki R, Laitio R, Soppi ET. The association between pressure ulcer/injury development and short-term mortality in critically ill patients: a retrospective cohort study. Wound Manag Prev. 2020; 66:14-21.
4. The Joint Commission. Estados Unidos Preventing Pressure Injuries (Updated March 2022) Initial Publication; 2016. Available from: https://www.jointcommission.org/-/media/tjc/newsletters/quick-safety-25-update-3-21-22.pdf
5. European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan PacificPressure Injury Alliance. In: Haesler E, editor. Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice-Guideline. The International Guideline. EPUAP/NPIAP/PPPIA; 2019.
6. Veiga TP, Rêgo AS, Montenegro WS, Ferreira PR, Rocha DS, Felipe IM, et al. Braden scale has low reliability in different patients under care in intensive care unit. Rev Assoc Med Bras (1992). 2022;68:1221-7.
7. Delmore BA, Ayello EA. Braden scales for pressure injury risk assessment. Adv Skin Wound Care. 2023;36:332-5.
8. Montserrat AJ. Avances en Úlceras Por Presión. Vol. 4. NPunto; 2021. p. 135-54. Available from: https://dialnet.unirioja.es/servlet/articulo?codigo=8221007
9. Gil-Castaño G, Cardona R. Emolientes: beneficios, elementos clave y aplicación clínica. Rev Alerg Méx. 2020;67:128-41.
10. Abiakam NS, Jayabal H, Filingeri D, Bader DL, Worsley PR. Spatial and temporal changes in biophysical skin parameters over a category I pressure ulcer. Int Wound J. 2023;20:3164-76.
11. Rojas LZ, Mora Rico LA, Acosta Barón JV, Cristancho Zambrano LY, Valencia Barón YD, Hernández Vargas JA. Plan de cuidados de enfermería para la prevención de UPP secundarias a la posición prono en pacientes COVID-19. Rev Cuidarte. 2021;12:e2234.
12. Virginia C. Pressure Injury Prevention PIP Tips for Prone Positioning. Available from: https://cdn.ymaws.com/npiap.com/resource/resmgr/press_releases/npiap_pip_tips_-_proning_202.pdf
13. Mannheim Jennifer K. Pulling a Patient up in Bed. Available from: https://medlineplus.gov/ency/patientinstructions/000429.htm [Last accessed on 2023 Oct 28].
14. Dekerle L, Depoortere C, Martinot-Duquennoy V. Prescripción de apósitos. EMC Cir Plást Reparadora Estét. 2022;30:1-13.
15. Thompson DL, May EJ, Leach M, Smith CP, Fereday J. The invisible nature of learning: patient education in nursing. Collegian. 2021;28: 341-5.
16. Soza Diaz C, Bazán Sánchez A, Diaz Manchay R. Percepción de las enfermeras sobre el uso de sus registros para garantizar la continuidad del cuidado. Rev Ene Enferm. 2020;14:14112.
17. Visconti AJ, Sola OI, Raghavan PV. Pressure injuries: prevention, evaluation, and management. Am Fam Physician. 2023;108:166.
18. Alshahrani B, Sim J, Middleton R. Nursing interventions for pressure injury prevention among critically ill patients: a systematic review. J Clin Nurs. 2021;30:2151-68.
19. Tilmazer T, Tuzer H. Pressure ulcer prevention care bundle: a cross-sectional, content validation study. Wound Manag Prev. 2019;65:33-9.

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NARRATIVE REVIEW

Risk factors, diagnostic criteria, and incidence of refeeding syndrome in the hospital setting: is there an elephant in the room?

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Abstract

Background: *Refeeding syndrome (RS) can be defined as a set of severe metabolic disorders that may occur in malnourished patients receiving refeeding through enteral or parenteral nutrition.* **Objectives:** *A narrative review of scientific literature on RS was primarily focused on its identification of risk factors, diagnostic, and incidence.* **Methods***: A search was carried out for articles through the PubMed database focused on meta-analyses, systematic reviews, case reports, and observational studies on RS.* **Results***: SR is a clinical challenge when initiating nutritional support in malnourished patients, with risks such as electrolyte imbalances, edema and neurological complications. This review presented the wide incidence ranging from 0 to 90%, the heterogeneity of the criteria for the diagnosis of RS, and its risk factors at the hospital setting.* **Conclusion***: RS is complex in hospital settings and is associated with aggressive initiation of feeding, increasing the risk of morbidity and mortality. It is necessary to conduct further research with the strongest methodological bases to validate the usefulness of the diagnostic criteria.*

Keywords: *Refeeding syndrome. Hypophosphatemia. Nutritional support. Enteral nutrition. Parenteral nutrition.*

Introduction

Refeeding syndrome (RS) is a serious and potentially fatal condition in patients associated with malnutrition or severe weight loss after a reintroduction of diet with high quantities of food consumption. RS is characterized by a generalized electrolyte imbalance and widespread redistribution of fluids as a compensatory alteration after the reintroduction of food intake-regardless of the feeding route: oral, enteral, or, parenteral nutrition in most cases.

This condition was once considered a "rare condition" that gained attention among physicians during World War II due to the clinical manifestations that developed after the reintroduction of oral feeding in prisoners and civilian victims who had undergone prolonged periods of starvation[1]. The study that laid the foundations of the physiology of RS is the "Minnesota Study" that subjected healthy volunteers to a caloric restriction during 6 months and observing after the refeeding period peripheral edema, sodium retention, and heart failure[2]. However, the oldest historical report dates to the 16th century, in which RS was used as a war tactic known as "Hyoro-zeme" or "food attack." Those who survived starvation faced death after immediate feeding on surrendering[3].

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RS occurs as a result of a prolonged deprivation of energy and nutrient intake, which still occurs in the hospital setting[1,4]. Nowadays, with the development of artificial routes of feeding (enteral, parenteral nutrition), there were noted similar complications in those severely malnourished patients who received an aggressive nutrition support, but fortunately could be prevented. Despite this not being a new clinical problem, but is a problem that in some cases, it is still unknown to health-care providers and is most likely to be delegated by nutritionists[5].

Establishing the incidence is a challenge especially when past years, there is still not a universal, validated, and precise definition of RS. Some definitions have primarily focused on the identification of risk factors or presence of severe hypophosphatemia (HP) - defined as serum phosphorus (P-) level that fell by > 0.16 mmol/L-< 0.65 mmol/L- because this last is the main feature of the RS[6,7]. However, the latest consensus of the American Society for Parenteral and Enteral Nutrition (ASPEN) considered not only the presence of HP, but the reduction of at least one or the combination of P-, potassium (K+), and magnesium (Mg2+) levels. As well as the clinical manifestation of thiamine (B1) deficiency, after the initiation of nutrient intake or food (within hours to days) in individuals who have been exposed to prolonged periods of undernourishment or starvation[8].

Establishing a comparative incidence of RS in the hospital setting has proven challenging due to the absence of a universal definition. A lack of prospective studies with robust methodologies, and ambiguity about how and by whom it should be identified contribute to the wide range of incidence values reported in the literature.

The analysis of the incidence according to the current diagnostic criteria for this condition is imperative in the clinical setting to identify the severity of the problem to evidence the elephant in the room. This narrative review aimed to show the variations in the incidence according to the diagnostic criteria used and, to describe the risk factors predisposing patients to RS in the hospital setting.

Methods

A PubMed search was conducted using the terms “refeeding syndrome,” “hypophosphatemia,” “hospital,” “risk factors,” and “incidence” to investigate the risk factors, diagnostic criteria, and incidence of RS in hospitalized adult patients. A search was conducted for articles focused on meta-analyses, systematic reviews, case reports, and observational studies on RS.

RS conceptualization

The concept of RS describes a lethal complication associated with the shift from catabolism to anabolism in patients who have developed malnutrition due to various clinical causes, occurring after the replenishment of nutrients. This is primarily associated with a prolonged period of fasting or starvation, which can result in a reduction of electrolyte levels in the blood, along with fluid disturbances[1]. It is primarily linked to a prolonged period of fasting or starvation, leading to reduced electrolyte levels in the blood and fluid imbalances. The pathophysiology remains unclear, but RS had been described after an adaptive phase occurring during prolonged fasting. This phase involves decreased insulin production and slight stimulation of glucagon/catecholamines. During refeeding, this adaptive phase shifts, leading to increased insulin levels, causing intracellular shifts of energy substrates, and potentially resulting in a severe drop in electrolytes. HP is often considered the hallmark of RS due to P- is necessary to produce cellular energy from glucose, contributing to the uptake of extra cellular P- by the intracellular need of cells (Fig. 1). But also, a low intracellular concentration of Mg2+, K+, and sodium (Na+) has also been well-documented due to the activity of the sodium-potassium-ATPase pump after refeeding[9].

Symptoms can vary depending on the imbalance of electrolyte dysregulation and can occur between 1 and 5 day after being refed or initiated nutrition support. However, despite this, there are no specific symptoms that definitively indicate RS exclusively; those are consequences of a depletion of serum levels of electrolytes, B1 and the Na+ retention. Additionally, edema represents another dangerous complication. The redistribution of fluids in the body can lead to an abnormal accumulation around vital organs such as the heart and lungs, hindering their functioning and increasing the risk of heart failure and breathing difficulties[9]. Nonetheless in severe cases, death is a possibility but also can be prevented. Described possible complications associated with the RS are described in table 1 and extensively addressed in ASPEN consensus[1,10].

The severity of the risks associated to RS depends on the severity and duration of malnutrition, alongside the pace at which nutrients are reintroduced[11]. Therefore, in clinical settings, a meticulous and gradual approach to reintroducing diet is necessary, closely monitoring electrolyte levels and organ function to prevent potentially fatal complications in hospitalized patients[12].

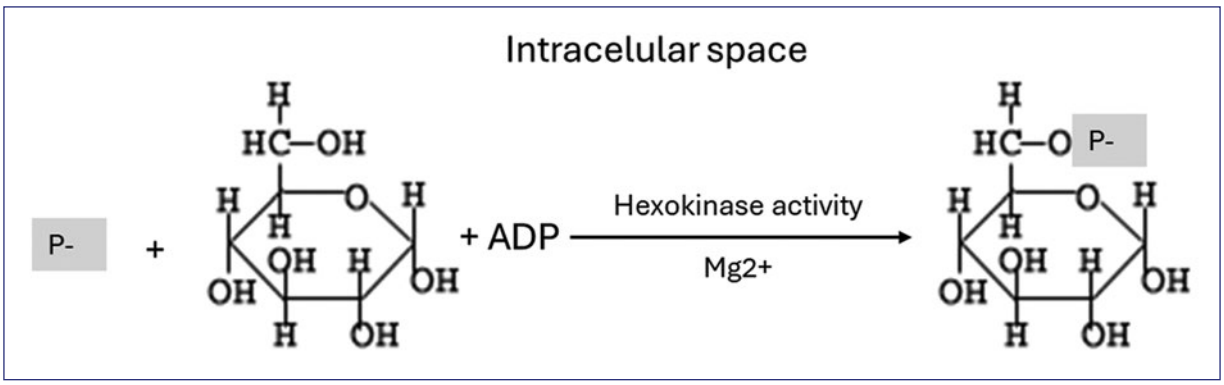

Figure 1. Intracellular uptake of phosphorus (P-) in the first step of glycolysis.

Potential risk factors for RS in the hospital setting

Clinical conditions predisposing patients to malnutrition, severe weight loss, inadequate energy intake, or low serum levels of P- or Mg2+ are described as risk factors for RS. Individuals at high risk described are prevalent and the vulnerable clinical conditions are anorexia nervosa, surgery, malnutrition, chronic alcoholism, chronic diarrhea or malabsorption, celiac disease, cancer, mental disorders, critically ill conditions, and renal failure/hemodialysis and old patients[9,10,13,14]. While these types of clinical conditions are associated with the development of the syndrome, it is important to note that relying on just one characteristic may be imprecise for patient risk classification.

The criteria established by the NICE society were the first published criteria related to nutrition support -and actualized at 2017- and has been widely used in literature[15,16]. However, based on the NICE criteria, the ASPEN consensus defined complementary criteria in 2020 and included the malnutrition as a characteristic for adult patients at risk for RS. Table 2 summarizes the criteria for both considerations. Validation of these criteria is necessary to ensure accuracy in identifying patients at risk of RS during nutritional assessment[10,16]. A retrospective study involving data from 3480 hospitalized patients in North America, considering ASPEN criteria, found that risk factors for RS included renal failure, elevated creatinine, and low platelet count, with a lower serum phosphorus level strongly associated with RS development[17].

Diagnosis for RS

Over the years, diagnosing RS has posed a challenge in clinical practice due to the absence of a standardized and universal definition and criteria[18]. Often, it goes undiagnosed until clinical signs and symptoms emerge. Severe low serum P- levels have been the primary characteristic used for diagnosis for years due to the lack of clarity in definition. In 2005, the ASPEN society introduced a classification for RS based solely on P-levels, grading severity as:

– Mild HP (asymptomatic), 2.3-2.7 mg/dL.
– Moderate HP (asymptomatic), 1.5-2.2 mg/dL
– Severe HP (symptomatic), 1.5 mg/dL.

In 2020, the ASPEN consensus introduced the latest update on the criteria for RS, considering its occurrence within 5 days of reinitiating or significantly increasing energy provision and noting a decrease in serum levels of P-, K+, or Mg2+. ASPEN maintained the RS grading based on electrolyte levels to align with published severity stratifications, outlined as follows:

– Mild, when: the reduction is between 10% and 20% of any P-, K+, Mg2+

Table 1. Clinical complications associated with refeeding syndrome[1,10]

Cardiovascular: Cardiovascular abnormalities or arrhythmia, cardiomyopathy, Cardiac arrest
Respiratory: Respiratory failure, diaphragmatic muscle weakness, failure to wean from mechanical ventilation
Muscular: Musculoskeletal o rhabdomyolysis, muscle pain and cramps, weakness
Neurologic: Confusion/delirium, Wernicke's encephalopathy, ataxia, tetany
Hematologic: Anemia, thrombocytopenia, decreased oxygen delivery to tissues

Fatal: coma, death.

Table 2. Risk-factor criteria for refeeding syndrome by NICE and ASPEN society[10,16]

Criterion	NICE criterio		ASPEN concensus criteria	
	High risk if patient has > 1 characteristic:	High risk if patient has > 2 characteristics:	Moderate risk: 2 risk criteria needed	Significant RISK: 1 risk criteria needed
BMI	< 16 kg/m^2	< 18.5 kg/m^2	16–18.5 kg/m^2	< 16 kg/m^2
Weight los	> 15% within the last 3-6 months	> 10% within the last 3-6 months	5% in 1 month	7.5% in 3 months or > 10% in 6 months
Caloric Intake	Little or no nutritional intake for more than 10 days	Little or no nutritional intake for more than 5 days	None or negligible oral intake for 5-6 days OR < 75% of EER, > 7 days during an acute illness or injury OR < 75% of EER, > 1 month	None or negligible oral intake for > 7 days OR < 50% of EER, > 5 days during an acute illness or injury < 50% of EER, > 1 month
Serum concentrations of electrolytes (P-, K+, Mg2+)	Low levels of potassium, phosphate or magnesium before feeding	–	Minimally low levels or normal current levels and recent low levels necessitating minimal or single-dose supplementation	Moderately/significantly low levels or minimally low or normal levels and recent low levels necessitating significant or multiple-dose supplementation
Historic abuse of drugs or alcohol	–	A history of alcohol abuse or drugs including insulin, chemotherapy, antiacids or diuretics	–	–
Loss of subcutaneous fat	–	–	Evidence of moderate loss	Evidence of severe loss
Loss of muscle mass	–	–	Evidence of mild or moderate loss	Evidence of severe loss
Comorbidities	–	–	Moderate disease	Severe disease

BMI: body mass index; EER: estimated energy requirement.

– Moderate, a reduction of 20% and 30% of any P-, K+, Mg2+
– Severe, a reduction > 30% of any P-, K+, Mg2+.

Despite the efforts for the correctly identification of RS, the evidence of RS reports has low evidence. Prospective studies that validate the criteria diagnostic developed in the past years are needed to get a major comprehension of RS. However, evidence pointing to aggressive nutritional support, such as enteral or parenteral nutrition, is the cause of the syndrome[19]. Historically, the primary nutrition support related with RS is parenteral nutrition and despite the years of knowledge it still has lethal consequences[20-23]. Regarding enteral feeding, a retrospective study developed by Adika et al., in 2022, used a large sample of hospitalized patients (n = 3480) needed nutritional support with enteral nutrition and used the ASPEN criteria for the identification of the RS. This study showed that pre-feeding P- levels (< 2.5 mg/dL) was strongly associated with mortality, 8% in non-RS cases versus 10% in the population with RS at 30-days, and not when ASPEN operationalization of RS was used, suggesting that ASPEN criteria should be refined[17].

Some reports showed that the diagnosis in clinical practice is based in P- levels not in the pre-feeding period but after clinical manifestations of RS occurred. Table 3 summarizes some case reports of hospitalized patients who presented with RF[24-28]. The HP was the criteria used to identify the RS, and the clinical manifestations were the alert to identify the RS through the electrolyte serum levels. All patients showed risk factors to developing the syndrome, showing there is still not a risk identification protocol and a lack of clarity about how to identify it and prevented it.

Furthermore, to the lack of recognition of RS is important to show that is a current clinical condition that

Table 3. Case reports with RFS diagnosis[24-28]

Authors	Sex and age	Population studied	Risk factors mentioned	Nutrition support	Electrolyte levels suggesting RS	Day of RS occurred	Clinical complications	Mortality	Diagnostic criteria
Adkins, 2009[25]	63-year-old white female	Lung cancer at chemotherapy treatment and dehydration secondary to vomiting	Vomiting, cachexia, fatigue, weight loss	Parenteral nutrition (energy not reported) non suspended, oral feeding at day 10.	Phosphate 1 mmol/l, Potassium 2.7 mmol/L, Magnesium 1.1 mg/dl	5	Chest congestion and oxygen support	Survived	Hypophosphatemia
Caplan JP, 2008[24]	61-year-old white man	Delirium, bipolar disorder, panic disorder, and cerebral aneurysm clipping, gait disturbance.	Weight loss of 80 pounds over the preceding 4 months	Improve oral inatke (energy intake not reported) after hospital admission	Phosphate 1.2 mg/dL, and Magnesium 1.0 meq/L	4	Dyspnea and wheezing, aspiration pneumonia,	Survived	Hypophosphatemia
Ouaz et al., 2021[27]	50-year-old male	Urothelial bladder tumor and a radical cystoprostatectomy	Weight loss with BMI of 13.26 kg/m, severe cachexia with poor general condition	Oral and parenteral nutriton (1500 kcal)	Sodium 117 mmol/l Potassium 2.7 mmol/L, Albumin 19 g/l, Urea, 16.36 mmol/L, Hemoglobin 8.4 g/dl, Phosphorus 0.68 mmol/L.	24 h	, mecanical ventilation, neurologycal failure, with multiple organ failure	Death reported 29 days after surgery	Hypophosphatemia
Hammami et al., 2018[26]	28-year-old Tunisian woman	Celiac disease	BMI of 14 kg/m^2, cachexia	Oral and parenteral nutrition (450 kcal/24 h)	Phosphate 0.3 mmol/L Calcium 1.54 mmol/L, Potassium 1.9 mmol/L, Gasometry: pH = 7.53, PCO2=19 mmhg, PO2=80 mmhg, HCO3- = 19 mmol/l).	2	Respiratory distress, and a state of cardiogenic shock, mecanical ventilation, with multiple organ failure	Death 2 days after multiple organ failure resulting from RS with celiac crisis	Hypophosphatemia
Lo Gullo et al., 2021[28]	79-year-old Caucasian woman	Acute pancreatitis and endoscopic cholangiopancreatography	BMI of 17.8 kg/m^2, and involuntary weight loss of > 10% had occurred in the previous 3 to 6 months, malnutrition	Enteral feeding (100 kcal/100 ml) < 1 day and stopped immediately. Npt started at 10 kcal/kg, with electrolyte supplementation and thiamine. Oral feeding at day 15	Phosphate 1.6 mmol/L, Potassium 2.4 mmol/L, Magnesium 1.3 mg/dL	< 1 day	Tachycardia, respiratory insufficiency (oxygen saturation of 85%), and severe hypotension	Survive	Hypophosphatemia

RS: refeeding syndrome; BMI: body mass index.

Table 4. Observational studies in hospitalized patients with incidence of RS reported[17,18,30-42]

Authors	Study type	Population	Participants	Mortality rate	Incidence (%)	Diagnostic criteria used
Dyson and Thompson, 2017[42]	Observational	Adult patients with parenteral nutrition support	192	8% at 30 days in patients with nutrition support	75	Nice guidelines (Risk factors)
Rasmussen et al., 2016[40]	Observational	Head and neck cancer patients	54	Not reported	< 20	Hypophosphatemia < 0.22 mmol/L
Kraaijenbrink et al., 2016[41]	Prospective cohort	Internal medicine ward	178	0%	54	Hypophosphatemia < 0.60 mmol/L.
Kameoka et al., 2016[39]	Observacional	Patients with anorexia nervosa	99	Not reported	21	Hypophosphatemia < 2.3 mg/dL
Fernández López, 2017[18]	Prospective cohort	Non-critical patients receiving enteral feeding.	181	Not reported	31.50	Not reported
Md Ralib and Mat Nor, 2018[38]	Prospective cohort	Adults ingested in an intensive care unit to initiate enteral feeding	109	RS: 25% versus Not RS 18.5%	42.60	Hypophosphatemia: plasma phosphate less than 0.65 mmol/L. Severe hypohosphatemia were not considered
Olthof et al., 2017[37]	Prospective cohort	Critically ill, invasive mechanically ventilated patients	337	RS: 33.9% versus Not RS: 31.5%	36.80	Refeeding syndrome was diagnosed by the occurrence of new-onset hypophosphatemia (< 0.65 mmol/l) within 72 hours of the start of nutritional support
Loncar et al., 2019[36]	Retrospective cohort	Hospitalized patients	73	None	41 (prevalence)	Nice guidelines (Risk factors)
Jeon et al., 2019[35]	Retrospective cohort	Patients with acute pancreatitis, malnourished patients	44	RS: 20.5% versus Not RS: 1.4%	20.50 (prevalence)	Nice guidelines (Risk factors)
Yoshida et al., 2020[34]	Cohort study	Adult patients who were admitted to the intensive care unit	542	7.2% for low risk, 16.3% for high risk, and 27.3% for very high risk	25.7 for low risk, 46.5 for high risk, and 2.0 for very high risk	Nice guidelines (Risk factors)
Wong et al., 2020[33]	Retrospective cohort	Adult patients with parenteral nutrition support	149	Nor reported	23-48 (prevalence)	> 0.16 mmol/L from baseline to phosphate < 0.65 mmol/L within 72 hours of PN administration, phosphate level drops by ≥ 0.15 mmol/L, to < 0.80 mmol/L in the first 7 days of PN administration, and serum phosphate level drops by > 30% from baseline in first 36 hours of PN administration
Rinninella et al., 2022[32]	Prospective cohort	Hospitalized patients	203		18.70	ASPEN concsnsus

(Continues)

Table 4. Observational studies in hospitalized patients with incidence of RS reported[17,18,30-42] *(continued)*

Authors	Study type	Population	Participants	Mortality rate	Incidence (%)	Diagnostic criteria used
Adika et al., 2022[17]	Prospective cohort	Hospitalized patients	3854	Mild RS: 28% versus 24%, Moderate RS: 19% versus 19%, Severe RS 20% versus 18%	Mild RS: 90, Moderate RS: 65, Severe RS 25	ASPEN consensus
Kells et al., 2023[31]	Cases and controls	Patients with anorexia nervosa and avoidant/ restrictive food intake disorder	307	Not reported	35 (prevalence)	Serum phosphorus < 2.9 mg/dL
Nguyen et al., 2023[30]	Prospective cohort	Hospitalized patients diagnosed with COVID-19	1207	Not reported	28.70	ASPEN consensus

RS: refeeding syndrome.

still happens despite the efforts to develop criteria for the identification of risk factors and diagnosis.

Incidence for RS in the hospital settings

The real incidence of RS remains unknown, literature reported a heterogeneous incidence ranging from 0% to 80%, according to the population studied and the criteria used[29]. A systematic review used in a large size of patients evidences the low quality of studies developed in the past years and reported the high incidence in patients with artificial nutrition whether enteral or parenteral nutrition. In the case of studies that not reported signs or symptoms related RS, those are based on the diagnosis of fluid and electrolyte shift, HP, and electrolyte imbalance, with no clarity about the method of diagnosis.

In the last decade, prospective and retrospective studies showed that HP is the key factor to determine the RS; however, other studies based on the risk factors criteria. Table 4 summarizes the representative observational studies that reported the incidence of RS in hospitalized patients[17,18,30-42]. These studies showed an incidence between were published between 2016 and 2023, and the incidence reported ranging from 2% to 90%, the most frequent incidence varied from 20% to 50%; however, it depended on the level of HP considered and the criteria selected. Even based on the new ASPEN criteria the form to present the incidence of RS is not specific. Mortality associated with RS from 0 up to 33.9% with the worse percentage in the critically ill patients.

The significant disparities reported in clinical practice reflected the urgently need for to fill the gap in the incidence, and clarity on its definition, identification, and the responsible parties. In some clinical scenarios, health-care professionals have never encountered a case of RS despite initiating nutritional supplementation at 100% of estimated requirements. Conversely, others perceive RS identification criteria as "excessively cautious," contributing to an underdiagnosis of RS within clinical settings[43]. Furthermore, there is a lack of comprehensive knowledge concerning nutrition care among clinical staff[5]. Some studies suggest that dieticians are solely responsible for nutrition care and individual follow-up, positioning RS as a simple nutrition problem rather than a concern involving the entire multidisciplinary team[44].

Conclusion

The incidence of RS is uncertain, wide-ranging from 0% to 90% and depends on the criteria used for the diagnosis Although the RS can be a fatal complication in a third of hospitalized patients with nutrition support, there is still not a universal and comprehensive definition. The RS is a big elephant in the room that can be identified and prevented with a routine evaluation of risk factors at hospital admission. The responsibility for identification lies with the multidisciplinary team. Further

prospective studies with a strong methodology are needed to validate the usefulness of current diagnostic criteria. This is a call for action to implement an RS risk screening in the hospital setting as routine care and to include this topic in the health-care professional curricula.

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References

1. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005;20:625-33.
2. Keys A, Brozek J, Henschel A. The Biology of Human Starvation. Mineapolis: University of Minesotta Press; 1950.
3. Kano Y, Aoyama S, Yamamoto R. Hyoro-zeme in the battle for Tottori castle: the first description of refeeding syndrome in Japan. Am J Med Sci. 2023;366:397-403.
4. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. Pharmacotherapy. 1995;15:713-26.
5. Ben-Tovim H, Theilla M. Role and knowledge of critical care nurses in the assessment and management of hypophosphataemia and refeeding syndrome. A descriptive exploratory study. Intensive Crit Care Nurs. 2021; 67:103097.
6. Machado JD, Suen VM, Chueire FB, Marchini JF, Marchini JS. Refeeding syndrome, an undiagnosed and forgotten potentially fatal condition. BMJ Case Rep. 2009;2009:bcr07.2008.0521.
7. Marik PE. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. Arch Surg. 1996;131:1043.
8. da Silva JS, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus recommendations for refeeding syndrome. Nutr Clin Pract. 2020;35:178-95.
9. Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z. Management of refeeding syndrome in medical inpatients. J Clin Med. 2019;8: 2202.
10. da Silva JS V, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus recommendations for refeeding syndrome. Nutr Clin Pract. 2020;35:178-95.
11. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3:943-52.
12. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013;3:e002173.
13. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62:687-94.
14. Pourhassan M, Cuvelier I, Gehrke I, Marburger C, Modreker MK, Volkert D, et al. Prevalence of risk factors for the refeeding syndrome in older hospitalized patients. J Nutr Health Aging. 2018;22:321-7.
15. National Institute for Health and Care Excellence (NICE). Nutrition support for adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. NICE Clinical Guidelines. Vol. 32. United Kingdom: National Institute for Health and Care Excellence; 2017.
16. National Collaborating Centre for Acute Care (UK), National Institute for Health and Clinical Excellence (NICE). Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. Guidance. Vol. 32. United Kingdom: National Institute for Health and Clinical Excellence; 2006.
17. Adika E, Jia R, Li J, Seres D, Freedberg DE. Evaluation of the ASPEN guidelines for refeeding syndrome among hospitalized patients receiving enteral nutrition: a retrospective cohort study. JPEN J Parenter Enteral Nutr. 2022;46:1859-66.
18. Fernández López MT. Incidencia de hipofosfatemia en pacientes ingresados no críticos con nutrición enteral. Nutr Hosp. 2017;34:761-6.
19. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr. 1981;34:393-9.
20. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012;27:34-40.
21. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition. 2010;26:156-67.
22. Crook MA. Refeeding syndrome: problems with definition and management. Nutrition. 2014;30:1448-55.
23. McCray S, Parrish CR. Refeeding the malnourished patient: lessons learned. Nutrition issues in gastroenterology. Pract Gastroenterol. 2016;155:56-66.
24. Caplan JP. Too much too soon? Refeeding syndrome as an iatrogenic cause of delirium. Psychosomatics. 2008;49:249-51.
25. Adkins SM. Recognizing and preventing refeeding syndrome. Dimens Crit Care Nurs. 2009;28:53-8.
26. Hammami S, Aref HL, Khalfa M, Kochtalli I, Hammami M. Refeeding syndrome in adults with celiac crisis: a case report. J Med Case Rep. 2018; 12:22.
27. Ouaz M, Zakhama W, Attia H, Sakly A, Bannour I, Masmoudi K, et al. Refeeding syndrome after radical cystoprostatectomy: a case report. Ann Med Surg. 2021;65:102349.
28. Lo Gullo A, Rifici C, Caliri S, Donato A, De Cola MC, Di Cara M, et al. Refeeding syndrome in a woman with pancreatitis: a case report. J Int Med Res. 2021;49:030006052098667.
29. Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: results of a systematic review. Nutrition. 2017;35:151-60.
30. Nguyen LT, Ta TV, Bui AT, Vo SN, Nguyen NL. Nutritional status, refeeding syndrome and some associated factors of patients at COVID-19 hospital in Vietnam. Nutrients. 2023;15:1760.
31. Kells MR, Roske C, Watters A, Puckett L, Wildes JE, Crow SJ, et al. Vitamin D and Hypophosphatemia in Patients with Anorexia Nervosa and Avoidant/Restrictive Food Intake Disorder: A Case Control Study. Durham: Research Square; 2023.
32. Rinninella E, D'Angelo M, Borriello R, Galasso T, Cintoni M, Raoul P, et al. Incidence and impact of refeeding syndrome in an internal medicine and gastroenterology ward of an Italian tertiary referral center: a prospective cohort study. Nutrients. 2022;14:1343.
33. Wong GJ, Pang JG, Li YY, Lew CC. Refeeding hypophosphatemia in patients receiving parenteral nutrition: prevalence, risk factors, and predicting its occurrence. Nutr Clin Pract. 2021;36:679-88.
34. Yoshida M, Izawa J, Wakatake H, Saito H, Kawabata C, Matsushima S, et al. Mortality associated with new risk classification of developing refeeding syndrome in critically ill patients: a cohort study. Clin Nutr. 2021; 40:1207-13.
35. Jeon TJ, Lee KJ, Woo HS, Kim EJ, Kim YS, Park JY, et al. Refeeding syndrome as a possible cause of very early mortality in acute pancreatitis. Gut Liver. 2019;13:576-81.
36. Loncar Y, Lefevre T, Nafteux L, Genser L, Manceau G, Lemoine L, et al. Preoperative nutrition forseverely malnourished patients in digestive surgery: a retrospective study. J Visc Surg. 2020;157:107-16.

37. Olthof LE, Koekkoek WA, van Setten C, Kars JC, van Blokland D, van Zanten AR. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: a retrospective study. Clin Nutr. 2018;37:1609-17.
38. Md Ralib A, Mat Nor MB. Refeeding hypophosphataemia after enteral nutrition in a Malaysian intensive care unit: risk factors and outcome. Asia Pac J Clin Nutr. 2018;27:329-35.
39. Kameoka N, Iga J, Tamaru M, Tominaga T, Kubo H, Watanabe S, et al. Risk factors for refeeding hypophosphatemia in Japanese inpatients with anorexia nervosa. Int J Eat Disord. 2016;49:402-6.
40. Rasmussen SO, Kristensen MB, Wessel I, Andersen JR. Incidence and risk factors of refeeding syndrome in head and neck cancer patients-an observational study. Nutr Cancer. 2016;68:1320-9.
41. Kraaijenbrink BV, Lambers WM, Mathus-Vliegen EM, Siegert CE. Incidence of refeeding syndrome in internal medicine patients. Netherlands J Med. 2016;74:116-21.
42. Dyson JK, Thompson N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7:e012663.
43. De Silva A, Smith T, Stroud M. Attitudes to NICE guidance on refeeding syndrome. BMJ. 2008;337:a680.
44. Janssen G, Pourhassan M, Lenzen-Großimlinghaus R, Jäger M, Schäfer R, Spamer C, et al. The refeeding syndrome revisited: you can only diagnose what you know. Eur J Clin Nutr. 2019;73:1458-63.