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July-December 2023, Vol. 3, No. 6

Contents

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Original research

Comparative nutritional, metabolic and body composition effect in patients of Roux-en-Y Gastric Bypass with Long or Short Pancreato-Biliary Limb

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ABSTRACT

Introduction: Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) is one of the most common techniques for the treatment of morbid obesity. However, evidence for the metabolic effects caused by the measures of intestinal limbs that are used in LRYGB is limited. The present study was conducted to assess the metabolic impact of using a long biliopancreatic limb (LBP-limb) versus a short biliopancreatic limb (SBP-limb) in patients with obesity undergoing LRYGB at six, nine and twelve months after the surgery to compare changes from baseline between the two procedures. **Methods:** Sixty-four patients with obesity participated in this study and underwent gastric bypass with either a 100-cm biliopancreatic limb (SBP-limb) and 150-cm alimentary limb (n = 31) or a 200-cm biliopancreatic limb (LBP-limb) and 50-cm alimentary limb (n = 33). Body weight, body fat (%), lean mass (%), total weight loss (%) and biochemical parameters glucose, glycosylated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, albumin and glycated hemoglobin were compared at the time of surgery and at six, nine and twelve months after surgery. **Results:** After surgery, the LBP-limb group had a greater total weight loss (P = 0.004) at twelve months after surgery, and a significant increase in HDL-C levels at six months (P = 0.001) compared with the SBP-limb group. However, no differences in the remission of comorbidities were found between the two groups. **Conclusions:** At the end of the first year after surgery the LBP-limb technique generated greater weight loss.

Key words: bariatric surgery; morbid obesity; long biliopancreatic limb; short biliopancreatic limb.

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RESUMEN

Introducción: El bypass gástrico laparoscópico en Y de Roux (BPGYR) es una de las técnicas empleadas en el tratamiento de la obesidad mórbida. Este estudio comparó el impacto metabólico del la técnica quirúrgica con asa biliopancreática larga (LBP-limb) versus un asa biliopancreática corta (SBP-limb) en pacientes sometidos a BPGYR a los seis, nueve y doce meses después de la cirugía comparando los cambios entre los dos procedimientos. **Métodos:** Sesenta y cuatro pacientes con obesidad sometidos a BPGYR en dos grupos, uno con asa biliopancreática de 100 cm (SBP-limb) y asa alimentaria de 150 cm (n = 31) y otro con una asa biliopancreática de 200 cm (LBP-limb) y asa alimentaria de 50 cm (n = 33). El peso corporal, grasa corporal (Fat Mass), masa libre de grasa (Lean Mass), peso total perdido y parámetros bioquímicos de glucosa, hemoglobina glucosilada (HbA1c), colesterol total, colesterol de baja densidad (c-LDL), colesterol de alta densidad (c-HDL), y albúmina fueron comparados a los seis, nueve y doce meses después de la cirugía. **Resultados:** Después de la cirugía se observó que en el grupo de LBP-limb existió una mayor pérdida de peso total (P = 0,004) a los doce meses después de la cirugía y un aumento significativo en los niveles de c-HDL a los seis meses (P = 0,001) en comparación con el grupo SBP-limb. Sin embargo, no se encontraron diferencias en la remisión de comorbilidades entre los dos grupos. **Conclusiones:** Al finalizar el primer año posoperatorio la técnica LBP-limb generó mayor pérdida de peso.

Palabras clave: cirugía bariátrica; obesidad mórbida; asa biliopancreática larga; asa biliopancreática corta.

INTRODUCTION

Obesity is a chronic disease that has tripled in prevalence since the 1970s and has been classified as a pandemic in recent years.[1] According to the World Health Organization (WHO), 650 million adults were estimated to have this disease in 2018, representing a prevalence of 13% worldwide. Obesity, especially morbid obesity with a body mass index (BMI) ≥ 40 kg/m^2, is one of the main pathologies that has been related to the incidence and prevalence of type 2 diabetes (DT2), with morbid obesity leading to a 23% greater risk of developing T2D.[2] Obesity has also been associated with an increased incidence of cardiovascular morbidity, arterial hypertension (AHT), insulin resistance and dyslipidemia.[2-5] A systematic review showed that morbid obesity is related to the development of heart disease, heart failure and cardiovascular mortality.[2-5] One of the strategies used to reduce this pathology and some of its complications is bariatric surgery. The use of this type of procedure has increased exponentially, and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) reported that 685,874 bariatric surgeries were performed worldwide in 2018.[6] Although laparoscopic Roux-en-Y Gastric Bypass (LRYGB) is the second most frequently performed surgery worldwide, and also in Mexico, LRYGB has become one of the most common surgeries and is the reference standard for the long-term treatment of obesity.[7] This surgical technique has yielded good results since its introduction in the 1960s, but due to the substantial variability of the technique as a result of the complexity of obesity, the long-term results remain controversial.[8-10] Bariatric surgery is performed as a treatment for morbid obesity with the primary objective to improve patients' health, achieve a healthy weight, and decrease or remit medical comorbidities causing weight and metabolic control. This procedure contributes to reducing the long-term comorbidities induced by the hormonal effects of weight loss.[9,11-14]

In recent years, weight regain has been observed in some patients who underwent LRYGB, and variations of the technique have been developed to prevent this situation. One of these variations involves lengthening of the alimentary limb (A-limb) and/or biliopancreatic limb (BP-limb).[15] Several studies have shown that short-length limbs, mainly BP-limbs, generate weight loss after bariatric surgery and facilitate the resolution of comorbidities.[11-15] However, such elongation has also been demonstrated to result in a high incidence of nutritional complications.[8,9,16] Currently, there are studies with inconclusive results regarding BP-limb lengths, thus the aim of this study was to assess the 12- month metabolic impact generated by the long BP-limb compared to the SBP-limb.

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MATERIALS AND METHODS

Participants

This study was carried out at the Surgery Clinic for Obesity and Metabolic Diseases of the Rubén Leñero Hospital in Mexico City, Mexico, from June 2018 to August 2019. Mexican patients aged 18 years to 65 years with a BMI of 40-49.[9] kg/m^2 were included. The exclusion criteria included a diagnosis of T2D for more than five years, secondary arterial hypertension (AHT) (renal malformation, unilateral renal agenesis), smoking and history of cancer and alcohol abuse. Additionally, participants were excluded if they left the city and/or abandoned the study or failed to attend their medical consultations/laboratory visits.

Design of the study

This study was a randomized and controlled clinical trial with the objective of comparing the nutritional, metabolic and body composition effect in patients of Roux-en-Y Gastric Bypass with Long or Short Pancreato-Biliary Limb.

The participants who met the inclusion criteria for bariatric surgery were instructed to follow a restrictive balanced dietary plan with a 55% carbohydrate, 20% protein and 25% fat distribution (1,500 kcal/day). After one month on the dietary plan and normalization of biochemical parameters and blood pressure, the patients were randomly selected using random allocation software (Microsoft Visual Basic 6) to assign their type of surgery by research. The evaluated techniques included LRYGB with a long BP-limb (LBP-limb) (50-cm A-limb + 200-cm LBP) and LRYGB with short BP-limb (SBP-limb) (150-cm A-limb + 100-cm SBP). One week before the date of surgery, the dietary plan was modified to a Mediterranean- type/anti-inflammatory hypocaloric (1,000 kcal/day) plan. The study consisted of five visits in total, including two pre-surgical (one month before surgery and the day before surgery) and post-surgical consultations at six, nine and twelve months. During the first consultation, the patients' medical and nutritional history was recorded, and during the postsurgical consultations, a twenty-four-hour dietary recall was carried out, and the type and duration of physical activity (aerobic or anaerobic) performed were recorded. Body composition evaluated via bioelectrical bioimpedance was also recorded. Biochemical parameters were measured prior to surgery at six, nine and twelve months after surgery.

The study was conducted in accordance with the Declaration of Helsinki. The ethics committees of the Dr. Rubén Leñero General Hospital (No. 2050101717) and Universidad Anáhuac México, North Campus (No. 201815) approved the study. A written informed consent was obtained from all participants in the first visit. The full protocol is available in Universidad Anáhuac México, North Campus.

Diet

The diet of the participants was modified before and after surgery. They consumed a restrictive balanced diet with a macronutrient distribution of 45-55% carbohydrates, 15-25% protein and 25-30% fat. After surgery, only the amount of protein was adjusted according to the intensity and type of exercise performed.

Compliance with the diet was evaluated by a twenty- four-hour dietary recall repeated three times to account for the time elapsed between visits, and the amount of protein ingested throughout the day was the main element quantified, where > 1.5 g of protein per kg of the ideal weight/day was indicative of compliance with the protein goal, and whereas a lower protein intake was indicative of noncompliance with the protein goal.[31]

INTERVENTION: SURGICAL TECHNIQUES OF LAPAROSCOPIC ROUX-EN-Y GASTRIC BYPASS USING A SHORT BILIOPANCREATIC LIMB OR A LONG BILIOPANCREATIC LIMB

Long alimentary limb Gastric Bypass

The pouch was created using the standard technique, omentum was divided and small bowel was counted 100 cm from the ligament of Treitz; we created gastro-jejunostomy with a linear stapler using a 32 Fr Bougie as a guide. A 150 cm alimentary limb was measured and jejuno-jejunostomy was created, we used a linear stapler to transect the bowel transforming the omega into a roux-en-y gastric bypass. The mesenteric and Petersen's defect were closed using non-absorbable suture.

Long biliopancreatic limb Gastric Bypass

After creating a pouch using standard technique and omentum was divided, small bowel was measured to 200cm from the ligament of Treitz, we created a gastro- jejunostomy using a 32 Fr Bougie as a guide. A 50 cm alimentary limb was counted and jejuno-jejunostomy was created. A linear stapled was used to transect bowel transforming to roux-en-y gastric bypass. The mesenteric and Petersen's defect were closed using non-absorbable suture.

Body composition measures

Height was recorded in duplicate according to the Lohman method.[17] Fat mass and lean mass percentages were obtained through a direct segmental multifrequency bioelectrical impedance analysis method using a total body position analyzer (InBody model 370, CO., LTD) one night before surgery following an eight-hour fast. The patient was barefoot, wore only light clothing and no metallic accessories and assumed an upright standing position (with each foot and hand on the corresponding electrodes) for the measurements.

Sampling and biochemical analysis

Blood samples were collected following a twelve-hour fast after each visit. The serum was obtained, and the blood was centrifuged at 1,500 x g for 10 minutes and stored at -70 °C until analysis. The biochemical parameters were determined using DxC600 equipment (Beckman Coulter).

Statistical Analysis

The sample size was calculated using the analytical formula for quantitative comparative studies, and a change of 40 mg in triglycerides at twelve months of follow-up as established in a previous study was used as a reference. A power of 80% was used, with a P value of 0.05. A total of thirty-one patients were required per group, and a loss to follow-up rate of 20% was considered; thus, thirty-six participants were included in each group. Baseline parameters were compared using Student's t-test for independent samples. One-way ANOVA adjusted for age, gender and baseline weight was performed to compare changes in body composition and the concentrations of biochemical parameters between the groups. $P < 0.05$ (one-tailed) indicated a significant difference. The data were analyzed by SPSS (version 20.00 SPSS Inc. Chicago, IL).

RESULTS

Baseline characteristics of the population

Sixty-four patients with morbid obesity scheduled for SBP-limb (n = 31) and LBP-limb (n = 33) gastric bypass surgery participated in the present study and they were followed for twelve months (Figure 1).

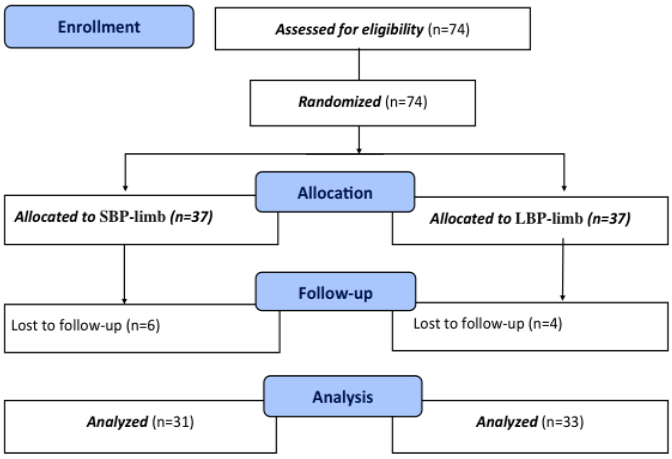

Figure 1. Flow chart of participant selection

The mean ages of the participants were 38 ± 9 years and 36 ± 7 years in the SBP-limb and LBP-limb groups, respectively. The percentage of women was 80% in the SBP-limb group and 75% in the LBP-limb group. The baseline fat mass percentage was 43.9 ± 1.70% in the SBP-limb group and 42.1 ± 2.10% in the LBP-limb group (Table I). No significant differences were found in baseline biochemical parameters or in the rates of comorbidities such as AHT, T2D and dyslipidemia between the participants in both groups (Table I).

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Table I. Baseline characteristics of the study population

	SBP-limb	LBP-limb	P value
Age (years)	38 ± 9	36 ± 7	*0.703*
Sex			
Female, n (%)	25 (81)	25 (76)	
Male, n (%)	6 (18)	8 (24)	
Body			
Weight (kg)	108 ± 18.8	110 ± 18.7	*0.473*
BMI (kg/m^2)	43.9 ± 1.70	42.1 ± 2.10	*0.924*
Fat mass (%)	49.3 ± 5.90	49.1 ± 5.01	*0.152*
Lean mass (%)	28.3 ± 2.50	28.8 ± 2.40	*0.164*
Biochemical			
Glucose	96.2 ± 13.1	97.1 ± 12.0	*0.875*
HbA1c (%)	6.01 ± 1.00	6.02 ± 1.01	*0.590*
Total cholesterol	176 ± 35.0	176 ± 37.1	*0.792*
HDL-C (mg/dL)	35.0 ± 6.01	35.0 ± 8.03	*0.404*
LDL-C (mg/dL)	118 ± 32.2	117 ± 35.1	*0.902*
Triglycerides	175 ± 78.0	139 ± 49.1	*0.107*
Comorbidities			
T2D, n (%)	11 (35)	11 (33)	*0.982*
HT, n (%)	10 (32)	9 (27)	*0.539*
Cholesterolemia	9 (29)	11 (33)	*0.850*
Triglyceridemia	13 (42)	12 (36)	*0.878*

The data are expressed as the means ± SD. The data were analyzed by an unpaired t-test. Body mass index (BMI); Total weight loss (TWL); Glycosylated hemoglobin (HbA1c); High-density cholesterol (HDL-C); Low-density cholesterol (LDL-C); Type 2 diabetes (T2D); Hypertension (HT). All results were considered statistically significant at $P < 0.05$.

Complications occurred in the SBP-limb group, with two patients exhibiting gastrojejunal anastomotic leakage. In the LBP-limb group, one patient had anastomotic leakage, and another patient developed cholelithiasis during the first three months after surgery. Regarding these 2 patients, the nasojejunal probe was placed because the 2 fistulas were presented in the gastrojejunal anastomosis. The probe was left until the fistula was resolved between 14 and 21 days and removed with results control endoscopy performed per month.

Percentage changes in biochemical parameters

Biochemical parameters allow us to evaluate the evolution and effectiveness of treatment. glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were determined at six, nine and twelve months after surgery. At the end of the follow-up, glucose concentrations were similar in both groups (Table II). Triglyceride, total cholesterol and LDL-C levels decreased, but they were not statistically significant (Table II). The HDL-C concentration showed a statistically significant difference between the groups at the end of the follow-up (Table II) ($P < 0.001$).

Table II. General anthropometric and biochemical characteristics of the participants based on surgical procedures

	SBP-limb				LBP-limb				P value
	0	6	9	12	0	6	9	12	
Body composition									
Weight (kg)	108 ± 18.8	80.2 ± 13.9	75 ± 12.6	72.6 ± 11.8	110 ± 18.7	79.6 ± 12.1	74.6 ± 11.3	72.5 ± 11.4	***0.004***
BMI (kg/m^2)	43.9 ± 1.7	30.3 ± 3.5	28.5 ± 3.00	27.5 ± 2.90	42.1 ± 2.1	29.8 ± 3.1	28.0 ± 3.01	28.0 ± 3.01	*0.128*
Fat mass (%)	49.3 ± 5.91	36.5 ± 6.40	32.2 ± 6.22	29.6 ± 7.23	49.1 ± 5.03	34.0 ± 7.61	31.0 ± 7.70	28.5 ± 7.60	*0.151*
Lean mass (%)	28.3 ± 2.50	34.6 ± 3.90	37.0 ± 3.70	38.6 ± 5.60	28.8 ± 2.41	35.9 ± 4.10	37.7 ± 4.21	38.6 ± 5.60	*0.388*
Biochemical parameters									
Glucose (mg/dL)	96.0 ± 13.1	85.0 ± 6.01	86.0 ± 6.01	86.0 ± 7.19	97.0 ± 12.0	83.0 ± 7.10	85.0 ± 6.02	85.1 ± 6.01	*0.772*
Total cholesterol (mg/dL)	176 ± 35.1	139 ± 23.1	143 ± 25.1	144 ± 23.1	176 ± 37.3	146 ± 24.4	147 ± 20.0	148 ± 23.6	*0.775*
HDL-C (mg/dL)	35 ± 6.00	34.0 ± 7.00	42.0 ± 8.00	45.0 ±11.0	35.0 ± 8.00	38.0 ± 8.00	44.0 ± 9.00	48.0 ±10.0	***0.001***
LDL-C (mg/dL)	118 ± 32.0	88.0 ± 19.0	84.0 ± 20.0	87.0 ± 24.0	117 ± 35.0	94.0 ± 25.0	85.0 ± 19.0	84.0 ± 23.0	*0.450*
Triglycerides (mg/dL)	175 ± 78.0	107 ± 26.0	94.0 ± 28.0	95.0 ± 27.0	139 ± 49.0	106 ± 28.0	97.0 ± 34.0	96.0 ± 35.0	*0.693*

The data are presented as the means ± SD. The statistical analysis was determined using one-way ANOVA. Body mass index (BMI); High-density cholesterol (HDL-C); Low-density cholesterol (LDL-C). All results were considered statistically significant at $P < 0.05$.

In SBP-limb group the biochemical parameters presented the greatest percentage changes in total cholesterol (-31.7 ± 6.54 mg/dL), LDL-C (-30.5 ± 5.69 mg/dL) and especially triglycerides (-79.3 ± 14.8 mg/dL) after the follow-up period (Table III). As a result, hypertriglyceridemia decreased by 73.5% and 83.4% (the SBP-limb and LBP-limb groups, respectively).

Table III. Changes in the anthropometric and biochemical parameters of the participants based on surgical procedures

	SBP-limb		LBP-limb	
	Before	**Changes (%)**	**Before**	**Changes (%)**
Body composition				
Weight (kg)	108 ± 18.8	-37.5 ± 2.02	110 ± 18.7	-37.8 ± 2.05
BMI (kg/m^2)	43.9 ± 1.7	-13.4 ± 0.70	42.1 ± 2.10	-14.0 ± 0.64
Fat mass (%)	49.3 ± 5.91	-19.7 ± 1.37	49.1 ± 5.01	-20.5 ± 1.16
Lean mass (%)	28.3 ± 2.50	10.2 ± 5.32	28.8 ± 2.40	9.92 ± 3.43
Biochemical parameters				
Glucose (mg/dL)	96.0 ± 13.1	-0.71 ± 0.12	97.1 ± 12.0	-0.74 ± 0.12
Total cholesterol (mg/dL)	176 ± 35.1	-31.7±6.54	176 ± 37.3	-27.6 ± 6.16
HDL-C (mg/dL)	35.0 ± 6.00	9.41 ± 1.83	35.0 ± 8.00	13.8 ± 1.95
LDL-C (mg/dL)	118 ± 32.0	-30.5 ± 5.69	117 ± 35.1	-33.2 ± 5.79
Triglycerides (mg/dL)	175 ± 78.0	-79.3 ± 14.8*	139 ± 49.0	-43.4 ± 9.04

The data are presented as the means ± SD. The statistical analysis was determined using one-way ANOVA. Body mass index (BMI); High-density cholesterol (HDL-C); Low-density cholesterol (LDL-C). All results were considered statistically significant at $P < 0.05$.

Changes in the body compositions of the participants

After the postsurgical follow-up, the body compositions of the patients were evaluated. Table II shows the changes in body weight, BMI and fat mass and lean mass percentages observed at six, nine and twelve months. At the end of the follow-up, body weight was significantly reduced in both the SBP-limb and LBP-limb groups (72.6 ± 11 and 72.5 ± 22.4, respective) ($P < 0.004$). The difference observed in body weight may be associated with fat loss because the fat mass percentage was lower in the LBP-limb group (28.5 ± 7.60) than in the SBP-limb group (29.6 ± 7.23). In addition, significant decreases in the percentage of total weight loss (TWL), BMI and fat mass were observed, and lean mass percentages were similar in both groups (Table III). This is important because the maintenance of lean mass during weight loss may improve metabolic profile and may delay weight regain in bariatric patients.[31]

Glycosylated hemoglobin and albumin levels of the participants

The SBP-limb group glycosylated hemoglobin (HbA1c) levels tended to decrease at the end of the follow-up without a significant p value (Fig. 2). No significant change in albumin was observed in either group (Fig. 2), only a tendency to increase this level was observed at six months after surgery in the LBP-limb group.

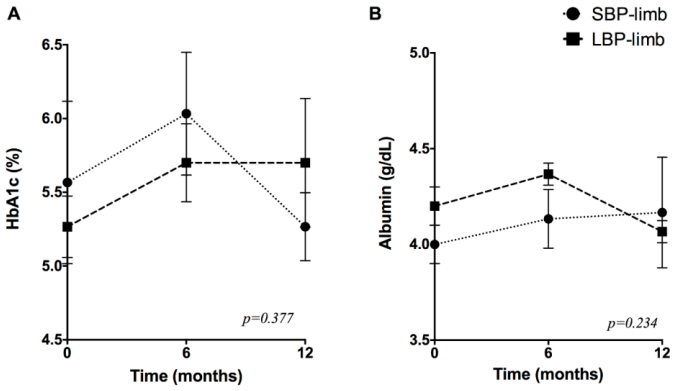

Figure 2. Glycosylated hemoglobin (HbA1c) and serum albumin levels of the patients at zero, six and twelve months after laparoscopic Roux-en-Y Gastric Bypass using a short biliopancreatic limb (SBP-limb) (n = 31) or a long biliopancreatic limb (LBP-limb) (n = 33).

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DISCUSSION

Bariatric surgery is one of the most frequently used techniques for weight loss treatment, and several factors are related to the risk of weight regain in patients who undergo this procedure. The present study was designed to compare the effects of two sizes of BP-limbs in bariatric surgery on body composition and biochemical parameters throughout a follow-up period of twelve months.

Several studies have shown that the use of an SBP-limb generates greater weight loss and improvements in the resolution of comorbidities after bariatric surgery.[18-22] Furthermore, evidence for the long-term effect of the LBP-limb technique is currently lacking in body composition. Our results demonstrate that the use of LBP-limbs is no less comparable to results obtained to the SBP-limbs. The improvement in body weight was due to a decrease in fat mass and was not associated with lean mass depletion, suggesting that the use of LBP-limbs may be a good predictor of long-term weight and fat-free mass maintenance without causing its catabolism.[21-24] It is important to emphasize this, because there are studies that show the significant loss of muscle and bone mass during the first year of surgery, so it is important to comment that with proper medical nutritional monitoring, in addition to proper monitoring and implementation of physical exercise in early stages of surgery, one can largely prevent the loss of muscle mass, so the surgical technique despite having deleterious effects on loss of fat-free mass, is not a determining factor.[8,21,23,24,30]

Our results are similar to those reported by Nergaard et al. 2010 and Zerrweck and col,[25,32] whose comparative study showed that patients with long BP-limbs had higher percentages of weight loss and greater BMI reductions as well as better control of comorbidities at one and two years of follow-up respectively ($P < 0.001$). Several mechanisms have been proposed through which the effects caused by lengthening the BP-limb can be explained, with tolerance and eating behavior being the most prominent. After bariatric surgery, the concentration of bile acids is increased in the terminal ileum, and the secretion of hormones such as insulin is stimulated due to increasing incretins in the distal intestine.[26, 27] Therefore, the metabolic effect may be due to stimulation of gastrointestinal hormones as shown by recent studies on metabolic surgery.[22, 25, 26,32] Weight loss and regulation may affect long-term metabolic control in patients with an LBP-limb. In this context, the present study shows that improvements in body composition were reflected in the biochemical parameters, which may suggest a better basal metabolic rate. A recent study evaluated the long-term effects of different lengths of BP-limbs over a ten-year follow-up period in patients with morbid obesity. In this study, greater long-term weight loss and maintenance were observed among patients with longer BP-limbs throughout the follow-up period. However, the length of the common canal is unknown in the study, and the metabolic effect may be due to a greater length of the BP-limb.[27]

Changes in body composition and normalization of biochemical parameters may be reflected in the presence of different comorbidities. In the present study, patients with an LBP-limb were not inferior in terms of outcomes in resolving comorbidities such as T2D compared to patients with an SBP-limb. Although these results may vary in the long term, greater long-term control of Type 2 diabetes has been observed after surgery with a long BP-limb.[8] Accordingly, we observed that after twelve months, the SBP-limb group showed a tendency toward decreased HbA1c levels, just the opposite of what was found in Zerrweck and cols study.[32]

In a CONSORT study conducted by Murad and Cohen in 2017,[22] in patients diagnosed with T2D and grade I obesity, implementation of the LBP-limb technique (a 200-cm BP-limb) found to decrease the severity of T2D (HbA1c < 6%) and dyslipidemia, and hypoalbuminemia was not observed in any patient (albumin < 3.5 mg/dL).[25] In the present study, albumin levels were normal (4-4.5 mg / dL) in patients with an LBP-limb, so no cases of malnutrition were found in contrast to the findings in Zerrweck and cols in 2021.[32] This outcome is important because the albumin concentration has been proposed as a prognostic marker in many pathological conditions and mainly malnutrition[28] because serum albumin has anti-inflammatory, antioxidant, anticoagulant and antiplatelet properties.[29]

CONCLUSION

The use of LBP-limbs in bariatric surgery significantly impacted weight loss over twelve months of follow-up as well as normalization of HDL-C levels. In addition, a tendency toward decreased glucose, HbA1c levels, fat and lean mass percentages were equal observed, while malnutrition associated with albumin levels was not observed. The implementation of the LBP-limb surgical technique is not inferior to the SBP-limb surgical technique, it is a safe and effective technique, and the fact that during the first year there is no significant loss of lean mass could be a promising indication that it is a technique with greater long-term effectiveness in maintaining both weight and comorbidities, given that the maintenance of muscle mass is essential for basal metabolism.

Limitations

The number of patients is low and the one-year follow-up is relatively short on the additional maintenance of weight loss and body composition, however it is the beginning to observe long-term results in a greater number of patients.

Conflict of interest

The authors have declared no conflict of interest.

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Review Article

Effect of treatment with probiotics in the reduction of altered levels of the lipid profile in humans and rats: a systematic review

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ABSTRACT

Introduction: Evidence suggests that the use of probiotics can prevent or help in the treatment of diseases such as obesity, acute infectious diarrhea, irritable bowel syndrome, liver problems, and the correction of hyperlipidemia, whether in total cholesterol, c-HDL, c-LDL or triglycerides. Probiotic strains have been studied so that with various mechanisms they can decrease lipid levels in children, adults and rats. **Objective:** To demonstrate the lipid-lowering effect of some probiotic strains tested in humans and rats, by compiling research that supports it. **Methods:** A search was carried out for articles with a year of publication between 2013 and 2023, experimental, observational and cohort studies published in English, full text available and analysis of the decrease in some lipid profile marker due to the use of probiotics. The MESH terms and the Boolean operators used for the search were "probiotics, lipid-lowering, children; Adults; rats and lipid profile". Data sources: the databases used were PubMed, Google Scholar, Elsevier, Clinical Key, and ScienceDirect. **Results:** From a total of 2150 articles, 30 were included. After the analysis of the selected articles, the results reveal that probiotics have a beneficial effect on the lipid profile by 25,01%. Total cholesterol level was reduced by 16,65%, c-LDL 32,02% and c-HDL was raised by 21,71%. **Conclusion:** Supplementation with specific strains of probiotics has a lipid-lowering effect, it especially reduces hypercholesterolemia through various mechanisms, but more studies are required to determine the dosage and treatment time.

Key words: probiotics; lipid-lowering; children; adults; rats and lipid profile.

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RESUMEN

Introducción: Las evidencias sugieren que el uso de probióticos puede prevenir o ayudar en el tratamiento de enfermedades como la obesidad, diarrea aguda infecciosa, síndrome de intestino irritable, problemas hepáticos y la corrección de la hiperlipidemia ya sea del colesterol total, HDL-C, LDL-C o triglicéridos. Se han estudiado cepas probióticas que con diversos mecanismos pueden disminuir los niveles lipídicos en niños, adultos y ratas. **Objetivo:** Evidenciar el efecto hipolipemiante de algunas cepas probióticas probadas en humanos y ratas, recopilando investigacionesqueloavalen. **Métodos:** Se realizó una búsqueda de artículos con año de publicación entre 2013 a 2023, estudios experimentales, observacionales y de cohortes publicados en inglés, texto completo disponible y análisis de la disminución de algún marcador del perfil de lípidos por el uso de probióticos. Los términos MESH y los operadores booleanos utilizados para la búsqueda fueron "probióticos, hipolipemiante, niños; adultos; ratas y perfil de lípidos". Fuentes de datos: las bases de datos utilizadas fueron PubMed, Google Scholar, Elsevier, Clinical Key y ScienceDirect. **Resultados:** De 2150 artículos, 30 fueron incluidos. Después del análisis de los artículos seleccionados, los resultados revelan que los probióticos tienen un efecto benéfico sobre el perfil de lípidos en un 25,01%. Se redujo 16,65% el nivel de colesterol total, 32,02% LDL-C y elevando el HDL-C un 21,71%. **Conclusión:** La suplementación con cepas específicas de probióticos tiene efecto hipolipemiante, en especial es reductor de la hipercolesterolemia a través de diversos mecanismos, pero se requieren más estudios para determinar la dosificación y el tiempo de tratamiento.

Palabras clave: probióticos; hipolipemiante; niños; adultos; ratas; perfil de lípidos.

INTRODUCTION

Dyslipidemias are alterations of lipid metabolism, they are associated with atherosclerotic process and ischemic processes. The cardiovascular risk to which each of them is predisposed is different, depending on the type of lipoprotein that is altered and its concentration, total cholesterol levels and serum triglycerides.[1] The National Health and Nutrition Survey (ENSANUT) 2020, in Mexico, states that the most common dyslipidemias in adults were hypercholesterolemia (26,1%), hypertriglyceridemia (49%) and low-density cholesterol (c-HDL) level (28,2%).[2] The objective of the treatments for alterations in the lipid profile is largely focused on reducing the levels of total cholesterol, low-density lipoproteins (c-LDL), elevated triglyceride values and increasing high-density lipoproteins (c-HDL) to prevent the stiffness of the arteries due to the generation of atherogenic plaque, cerebrovascular accidents that have poor prognoses, increasing morbidity and mortality.[3]

Cholesterol is part of all steroid hormones and vitamin D analogues, therefore, a deficiency of cholesterol in the circulation can result in an inability to distribute vitamins K and E to vital organs, causing severe consequences. In contrast, hypercholesterolemia, or cholesterol buildup, is caused by excess dietary cholesterol or a genetic abnormality and can result in cardiovascular disease and death.[4] Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid storage, steroid hormone production, and bile acid formation. Lipoproteins are categorized based on their density, and c-LDL, c-HDL, IDL, VLDL, and chylomicrons can be isolated by ultracentrifugation.[5] Triglycerides have a transcendental role in the energy reserve of our organism, the normal value of serum triglycerides should be less than 150 mg/dL, since above this figure alterations are observed in the increase of c-LDL, that are related to atherogenic risk.[6] The 2018 Guidelines of various associations such as the American Heart Association (AHA), American Diabetes Association (ADA), Expert Panel on Cholesterol Levels in Children for cholesterol management mentions acceptable ranges for total cholesterol (TC) concentrations > 200 mg/dl, c-LDL <130 mg/dl, c-HDL > 60 mg/dl and TG < 150 mg/dl in adults and in children TC > 170 mg/dl, c-LDL <110 mg/dl, c-HDL > 45 mg/dl, TG < 75 mg/ dl (0-9 years) and < 90 mg/ dl (10-19 years).[7]

Probiotics in the reduction of altered levels of the lipid profile

Probiotics are defined as those live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the host. They are considered safe for human consumption. The most researched and used probiotics in the clinical area include bacteria of the following genera: *Lactobacillus, Lactococcus, Leuconostoc, Pediococcus, Propionibacterium, Bifidobacterium, Bacillus, Streptococcus, Enterococcus, Escherichia coli* and yeasts of the genus *Saccharomyces*.[8] According to Lye *et al*. (2010), some bacterial strains or consortia have been shown to reduce cholesterol, lipoprotein, and triglyceride levels.[9] There are different

mechanisms proposed to explain the reduction in c-LDL, in relation to the intake of probiotics, which include:

1. Deconjugation of bile acids, by the production of enzymes such as bile salt hydrolase, which interfere with the ability of cholesterol to be incorporated into mixed micelles, thus reducing its absorption.

2. Interference of the bioavailability of cholesterol in the small intestine through the absorption of cholesterol in bacterial cell walls.

3. Production of short-chain fatty acids through colonic fermentation of indigestible carbohydrates, which can inhibit cholesterol synthesis and suppress the release of free fatty acids from adipose deposits, a substrate for triglyceride synthesis.[10]

The cholesterol-lowering ability of probiotics has been extensively reviewed through various clinical trials. Several mechanisms have been proposed, but one of the most accepted is the ability to deconjugate bile by the production of bile salt hydrolase (BSH). Deconjugated bile salts are less reabsorbed in the intestines compared to conjugated salts, resulting in greater fecal excretion because they are more hydrophobic. Cholesterol, being the precursor of bile salts, is used to produce new bile salts, resulting in a decrease in serum concentrations.[11]

To prove that probiotics do not cause harm to the consumer, *in vitro* tests are necessary, followed by preclinical tests in animal models such as rodents and finally in humans.[12] Rats are a type of mammals that are used in research due to their physical and genetic characteristics similar to humans, in addition, their size is small, they are accessible, they adapt to all habitats, among others.[13] Experimentation with rodents continues to be the most used in biomedical research, its purpose is to obtain the greater good through protocols and methodologies reviewed, approved and supervised by ethics committees to guarantee their well-being from birth.[14]

The objective of this review is to determine the effect that some probiotic strains have on the reduction in abnormal levels of total cholesterol, triglycerides and c-LDL, as well as the increase in serum c-HDL.

METHODS

Literature search

This review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[15]

Search strategy

The databases required to search for scientific articles were PubMed, Google Scholar, Elsevier, ClinicalKey, and Science-Direct. The MESH terms and the Boolean operators used for the search were “probiotics”, “lipid-lowering”, “children”, “adults”, “rats”, “lipid profile”, studies published in English and Spanish.

Eligibility criteria

All research articles with a year of publication between 2013 and 2023, experimental, observational, and cohort studies published in English and Spanish. The degree of efficacy of some probiotic strains on markers including the lipid profile (TC, c-HDL, c-LDL, and triglycerides) was determined. In addition, the inclusion of the use of probiotics in patients with dyslipidemia is proposed, since conventional treatment includes only drugs and eating plans to reach normal levels of lipid markers.

Study selection

Article records were individually recognized and identified by three investigators and, if necessary, decisions to include or not include a record were made by consent and agreement between them.

Quality assessment

One of the researchers performed the evaluation of the records using the Microsoft Excel data tool. Investigators had full access to all registration, evaluation, and data extraction spreadsheets.

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RESULTS

The schematic representation for the selection of the articles is found in Figure 1. A total of 2150 articles were found, then a debugging was carried out to eliminate some duplicates, leaving 1157, also some were excluded after reviewing the abstracts. In addition, an evaluation of the complete contents of the remaining 126 articles was carried out. Subsequently, 21 were excluded for not being released, 105 for not including the necessary terms and 75 for not expressing the results clearly. Finally, the articles included in the review are 30. Table 1 shows the summary of those selected.

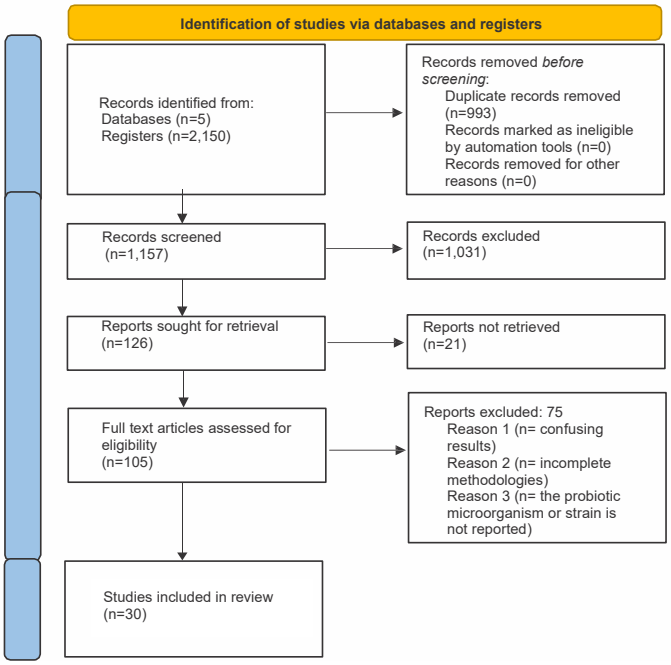

Figure 1. PRISMA flow chart. Represents the bibliographic search strategy for this systematic review.

Table 1. Summary of the results and main findings in the 30 studies included in this systematic review

	Author	Year	Country	Population	Study duration	Results
Articles on children						
1	Karyana I.P.G., *et al.*,[16]	2022	Indonesia	N=52 obese patients. Group 1: Treatment with probiotics (*Streptococcus thermophilus*, *Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum*) and group 2: placebo	8 weeks	Group 1: total cholesterol decreased by 22.6 mg/dL, c-LDL decreased by 16.9 mg/dL, TG decreased by 30.8 mg/dL, and c-HDL increased by 1.4 mg/dL.
2	Fortes PM, *et al.*,[17]	2020	Brazil	N=12 patients with nephrotic syndrome, 2 groups Grupo 1: *Lactobacillus plantarum*, cepa Lp-G18 2,5 x 10^9 CFU/ capsule Grupo 2: placebo	12 weeks	Group 1: average TC decrease of 41.5 mg/dL and TG decreased by 6.0 mg/dL. Group 2: TC increased (8.0 mg/dL), TG increased 49.5 mg/dL.

3	Guardamagna, *et al.*,[18]	2014	Italy	N=38 children with dyslipidemia (2 groups). Group 1 with placebo, group 2 treatment with probiotics (*B. animalis* subspecies *lactis* MB 2409, *B. bifidum* MB 109B, and *B. longum* subspecies longum BL04)	12 weeks	In the group treated with probiotics, they reduced TC by 3.4% and c-LDL by 3.8%.
Articles on adults						
4	AkbariRad M, *et al.*,[19]	2023	Iran	N=70 prediabetic patients. Group 1: Supplementation with Lactocare probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus termófilos* with fructooligosaccharide as a prebiotic) and group 2: Placebo.	12 weeks	Group 1: c-LDL and TG levels were reduced (2.61% and 11%, respectively) and the serum concentration of c-HDL increased by 8.68%
5	Wang S, *et al.*,[20]	2022	China	N= 365 patients (4 groups) Group 1: probiotics* + Berberine (BBR); group 2: probiotics* + placebo; group 3: BBR + placebo and group 4: placebo + placebo. **Bifidobacterium longum* CGMCC No. 2107; *Bifidobacterium breve*CGMCC No. 6402; *Lactococcus gasseri* CGMCC No. 10758; *Lactobacillus rhamnosus* CNCM I-4474; *Lactobacillus salivarius* CGMCC No. 6403; *Lactobacillus crispatus* CGMCC No. 6406; *Lactobacillus plantarum*; CGMCC No. 1258; *Lactobacillus fermentum* CGMCC No. 6407; and *Lactobacillus casei* CNCM I-4458.	12 weeks	Group 2: reduction TCp= 7.83%, pc-LDL = 21.4% Group 4: TCp reduction = 6.88%, pc-LDL= 17.28%
6	Guerrero-Bonmatty R, *et al.*,[21]	2021	Spain	N=39 patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactoplantibacillus plantarum* strains (CECT7527, CECT7528, and CECT7529) combined with yeast rice extracts.	12 weeks	The use of probiotics in combination with rice yeast extract reduced TC (31.4 mg/dL), in addition to a decrease in serum c-LDL (23.6 mg/dL).

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7	Trotter RE, *et al.*,[22]	2020	EE.UU.	N= 88 humans (4 groups). Group1: Placebo + maltodextrin; group 2: *Bifidobacterium lactis* cepa BL04; group 3: PreforPro bacteriophages; group 4: *Bacillus subtilis* strain DE111.	4 weeks	Group 3: reduction TC= 2.27%, c-LDL = 0.48%. Group 4: reduction TC= 4.64%, c-LDL = 7.96% and increase c-HDL= 0.5%.
8	Ruscica, M, *et al.*,[23]	2019	Italy	N=32 patients Group 1: Nutraceutical combination (probiotic *Bifidobacterium longum* BB536 and RYR extract), group 2: placebo.	12 weeks	Group 1: Reduced TC (16.7%) and c-LDL (25.7%)
9	Ahmadian, Fatemeh, *et al.*,[24]	2018	Iran	N=60 patients (2 groups). Group 1 with placebo, group 2 intervention with probiotics (*Lactobacillus plantarum*, *L.acidophilus*, L.fermentum, *L. gasseri*)	6 weeks	Increase in c-HDL levels (P = 0.002) in the probiotic group. In addition to the decrease in the atherogenic index (1.09)
10	Costabile, Adele, *et al.,* [25]	2017	United Kingdom	N=46 humans, 2 groups Group 1: placebo Group 2: intervention with *Lactobacillus plantarum* ECGC 13110402 ($2x10^9$ CFU)	12 weeks	Group 2: TC=36.7% reduction, c-HDL= increased 0.23 mmol/l, c-LDL = decreased 0.39 mmol/l (13.9%).
11	Fuentes, *et al.*,[26]	2016	Spain	N=60 patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactobacillus plantarum* (LpPRO)	12 weeks	In the group with probiotic intervention, there was a 24.4 mg/dL reduction in c-LDL, a decrease in total cholesterol (33.7 mg/dL), an increase in c-HDL (2.9 mg/dL), and a decrease in of serum TG levels (29.1 mg/dL)
12	Kullisaar Tiiu, *et al.*,[27]	2016	Estonia	N= 45 patients. Group 1: consume Reg'Activ Cholesterol capsules, group 2 receive a placebo. Who consumed RAC containing an antioxidant and antiatherogenic probiotic *Lactobacillus fermentum* ME-3 (LFME-3)	4 weeks	With the intervention of the probiotic, the levels of TC (12.3%), c-LDL (17.7%) and TG (4.37) were reduced, and c-HDL (4.37%) increased.
13	Rajkumar H, *et al.*,[28]	2014	India	N= 60 overweight adults (4 groups). Group 1 with placebo, group 2 treatment with probiotic VSL#3 (*Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium* breve, *Lactobacillus acidophilus*, *Lactobacillus paracasei, Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus plantarum, Streptococcus salivarius subsp. thermophilus*), group 3 supplemented with Omega 3, group 4 probiotic plus Omega 3.	6 weeks	In group 4 (probiotics plus Omega 3) c-HDL increased by 21.06%, c-LDL, triglycerides and TC decreased by 10.45%, 7.5%, 4.94%, respectively. Being this group where the lipid profile was improved the most.

14	Nabavi S, *et al.*,[29]	2014	Iran	N=72 patients diagnosed with nonalcoholic fatty liver disease (NAFLD) in 2 groups. Group 1: conventional yogurt and group 2: probiotic yogurt (*Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12)	8 weeks	In group 2 TC reduced 4.1% and c-LDL 6.92% compared to group 1.
15	Fuentes, *et al.*,[30]	2013	Spain	N=60 hypercholesterolaemic patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactobacillus plantarum* strains CECT 7527, CECT 7528 and CECT 7529	12 weeks	Treatment with the three strains of *L. plantarum* showed a reduction in TC levels (17.4%), and c-LDL (17.6%).
Articles on rats						
16	Zafar Hamza, *et al.*,[31]	2022	Pakistan	N=55 rats, 11 groups. Group 1: Diet 1. High-Fat Diet (HCFD), Group 2: High-Fat Diet and with Statin Treatment (SDHF), Group 3: Normal Diet, Groups 4-11: HCFD Diet plus probiotics such as: *Lacticaseibacillus rhamnosus* FM9, *Limosilactobacillus fermentum Y57*, etc.	30 days	Group 2: Decreased total cholesterol level (5%) and c-HDL improved 46%. Groups 4 to 11: Decrease in cholesterol, especially *L. rhamnosus* FM9 (9%), *L. fermentum* Y57 (8%) and *L. fermentum* FM6 (7%), decrease in c-LDL with strains Y57 (41%), FM9 (37%) and FM6 (31%).
17	Munir, *et al.*, [32]	2022	Pakistan	N=30 rats, 5 groups: Group 1: negative control, group 2: positive control, group 3: HFCD plus *L. brevis* MT950194, group 4: HFCD plus *L. brevis* MW365351, group 5: HFCD plus a mixture of the two investigated probiotics.	75 days	The reduction of TC in groups 3 and 4 was 54%, while in group 5 it was 60%, which indicates a better lipid-lowering action when the two strains are combined.
18	Fossi, *et al.*, [33]	2022	Cameroon	N= 18 rats, 3 groups: Group 1: feeding with HFCD plus pw4 (*L. plantarum*), group 2: negative control (oral gavage with deionized water), group 3: HFCD plus deionized water.	4 weeks	In group 1, the levels of TC (17.2%), TG (32.14%), and c-LDL (69.5%) were significantly reduced, the level of HDL-C (75.8%) increased, compared to group 3.
19	Abdelshafy, A. M., *et al.,* [34]	2022	Egypt	N=40 rats. Group 1 (control): Basal diet, group 2: Basal diet with non-fermented quinoa, Group 3: Diet with quinoa fermented by *L. plantarum,* Group 4: Diet with quinoa fermented by *L. delbrueckii subsp. bulgaricus*.	30 days	Group 3: reduction of TC (6.48%), c-LDL (43.64%) and TG (18.76%). Increase in c-HDL levels (25.08%). Group 4: reduction of TC (4.58%), c-LDL (39.46%) and TG (12.46%). Increase in HDL-C (19.35%).

https://doi.org/10.36105/psrua.2023v3n6.02

20	Asad F., *et al.,*[35]	2020	Pakistan	N=40 hypercholesterolemic rats. Group 1: Hypercholesterolemic diet (HC-CON), group 2: HC diet and supplemented with *Agaricus bisporus* mushrooms (HC-*A. bisporus*), group 3: mixture of probiotic (Protexin; Probiotics International Ltd., Somerset, UK) (HC-PB) and group 4: combination of AB and mixture of probiotics (HC-AB.PB).	6 weeks	Group 3: c-HDL levels increased (1.98%). The values of TC (19.41%), c-LDL (5.96%), and TG (34.10%) decreased. Group 4: c-HDL levels increased (7.62%). The values of TC (11.24%), c-LDL (13.92%), and TG (30.25%) decreased.
21	Wa Y, *et al.,* [36]	2019	China	N=40 rats. Group 1: control (C), group 2: high fat diet (HF) model, group 3: fermented milk diet with a single probiotic (*L. rhamnosus* LV108) (HFPB) and group 4: diet with a combination fermented milk with probiotic (*L. rhamnosus* LV108-fermented milk, *L. casei* grx12-fermented milk and *L. fermentum* grup grx08-fermented milk) (HFPBS).	4 weeks	Group 3: the lipid profile reduced the TC (27.83%), the c-LDL (57.14%), and the TG (21.53%), in addition, the value of c-HDL increased (4, 0%) Group 4: reduced TC (22.71%), decreased c-LDL (35.71%) and there was also a decrease in TG (16.92%). c-HDL levels increased (2.0%) compared to group 2.
22	Nocianitri, K.A., *et al.,*[37]	2017	Indonesia	N=24 rats. Group 1: High-fat diet (HF), group 2: HF and *L. rhamnosus* SKG34 (HF-SKG34), group 3: *L. rhamnosus* FBB42 (HF-FBB42) and HF and group 4: combination of the two probiotics (*L. rhamnosus* and *L. rhamnosus* SKG34 FBB42; HF-SKG34-FBB42).	4 weeks	Compared with group 1, group 2 (HF-SKG34) reduced the levels of TC (13.60%) and c-LDL (71.22%), in addition, there was an increase in c-HDL (15.29%). Group 3 (HF-FBB42) reduced the concentrations of TC (16.22%), c-LDL (66.01%), and GT (20.76%). The levels rose c-LDL (8.71%). Group 4: decrease in TC values (13.32%), c-LDL (72.18%), and TG (17%). The amount of HDL-C increased by 15.23%.
23	Chuan, Li, *et al.*,[38]	2014	China	N= 40 rats, 4 treatment groups: Group 1: normal diet. Group 2: HFCD fed, Group 3: HFCD + *Lactobacillus plantarum* NCU116L (10^8 CFU/ml), Group 4: HFCD + *Lactobacillus plantarum* NCU116H (10^9 CFU/ml).	5 weeks	The results suggest that *L. plantarum* NCU116 was able to modify lipid metabolism and reduce cholesterol level, in particular, in HFCD rats through regulation of gene expression of key factors related to LDL receptor and CYP7A1.

24	Park Do-Young, *et al.*,[39]	2013	Republic of Korea	N=27 rats, 3 groups. Group 1: High-Fat Diet (HDF) + placebo, group 2: Normal diet, group 3: HDF + probiotic (*Lactobacillus curvatus*HY7601 y*Lactobacillus plantarum*KY1032)	10 weeks	Group 3: Total cholesterol decreased (17%) compared to group 1.
25	Salaj, *et al.*,[40]	2013	Slovakia	N= 40 rats, 4 groups: Group 1: control, group 2: HFCD, group 3: HFCD plus *Lactobacillus plantarum* LS/07, group 4: HFCD plus supplementation with *Lactobacillus plantarum* Biocenol LP96	10 weeks	The administration of *Lactobacillus plantarum* LS/07 resulted in greater decreases in TC (20%) and c-LDL (24%), while TG and VLDL levels were reduced by 39% in the group with *Lactobacillus plantarum* Biocenol LP96
26	Mohania, Dheeraj, *et al.*,[41]	2013	India	N=21 Rats on a hypercholesterolemic diet. 3 groups. Group 1 with Dahi probiotic (*Lactobacillus plantarum* Lp9), group 2: Dahi probiotic in milk, group 3: buffalo milk)	120 days	Group 1: reduction in total cholesterol (35%) and triglycerides (72%), increase in c-HDL (116%), and decrease in LDL-VLDL (59%). Group 2 and 3: increased total cholesterol and triglycerides.
27	Yoo SR, *et al.*,[42]	2013	Republic of Korea	N=50 rats, 5 groups Group 1: (HFCD), Group 2: HFCD + *L. plantarum* (*PL*) KY1032 (PL, 10^{10}CFU/día). Group 3: HFCD + *L. curvatus* (*LC*) HY7601 (CU, 10^{10}CFU/día), Group 4: HFCD + (PL y CL), Group 5: Normal diet.	9 weeks	Group 2, 3 and 4: They reduced the accumulation of fat and total cholesterol in plasma. Group 4: Decreased enzymatic activities related to the oxidation of fatty acids and their gene expressions.
28	Kumar Manoj, *et al.*, [43]	2013	India	N=35 rats, divided into 5 treatment groups. Group 1: Normal Control Diet, Group 2: Hypercholesterolemic (HD) Diet, Group 3: HD Diet + *Lactobacillus rhamnosus* GG (LGG), Group 4: HD Diet + Aloe Vera Gel, and Group 5: HD Diet + LGG Probiotic + Aloe Vera Gel.	45 days	Group 3: decrease in total cholesterol (32%) and triglycerides (41%), group 4: reduction in total cholesterol (43%), and triglycerides (23%), and group 5: decrease in triglycerides (45%) and atherogenic index at 2.45. VLDL (45%) and c-LDL (30%).
29	Huang, Ying, *et al.*,[44]	2013	China	N= 40 rats, 3 treatment groups: Group 1: High cholesterol diet (HC), Group 2: HC diet + *Lactobacillus plantarum* Lp09 (HC-Lp09) and Group 3: HC diet + *Lactobacillus plantarum* Lp45 (HC-Lp45).	4 weeks	Group 2: reduced TC= 30.5%, TG= decrease 23.7%, c-LDL: 47.9% reduction Group 3: reduced TC =18.4%, TG= 12.3% reduction, c-LDL = 21.5% reduction

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30	Park Do-Young, *et al.*,[45]	2013	South Korea	N=36 rats. Group 1: Probiotic with low dose LP (*L. plantarum* and *L. curvatus* 10^9 CFU), Group 2: Probiotic with high dose HP *(L. plantarum* and *L. curvatus* – 10^{10} UFC) and Group 3: With placebo (High fructose diet: HF)	6 weeks	Treatment with high or low dose probiotics helped lower triglycerides by 46% compared to group 3.

TC, total cholesterol; TCp postprandial total cholesterol; TG, triglycerides; c-LDL; pc-LDL, postprandial low density cholesterol; c-HDL: high density cholesterol; N, sample; HFCD, High-Fat Diet; CFU, Colony Forming Units.

The selected bibliography indicates that the investigations of probiotic supplementation have beneficial effects in the reduction of hyperlipidemia, decreasing the level of total cholesterol by 16,65%, the decrease in the concentration of c-LDL by 32,02%. In addition, an increase of 21,71% of the c-HDL level was demonstrated in the study subjects, with respect to the concentrations of triglycerides, a 29,67% decrease is reported in some articles. The trials using probiotics were carried out from 3 to 12 weeks, concluding the minimum period of consumption in which probiotics manifest their benefits which is after 6 weeks. The probiotics that were used are *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lacticaseibacillus rhamnosus*, *Limosilactobacillus fermentum*, *Lactobacillus curvatus*, *Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus crispatus, Lactobacillus casei, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus, Streptococcus salivarius subsp. thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium infantis, Bacillus subtilis* and *Lactobacillus gasseri.*

Study characteristics

The date range of the articles was from 2013 to 2023. The investigations were carried out: two from Indonesia, one from Brazil, two from Italy, four from China, three from Spain, one from EE.UU., three from Iran, one from Egypt, one from the United Kingdom, one from Estonia, three from India, three from Pakistan, one from Cameroon, two from the Republic of Korea, one from Slovakia and one from South Korea.[16-45]

Population studied

The tested population consisted of fifteen human investigations, between women and men, (total N=1099, n=102 children and n=997 adults)16-30 and in fifteen investigations they included rats (total N=536).[31-45]

Instruments used to measure

The database software used in the articles selected for the systematic review were MINITAB for Windows 11.[21] and nine were registered in SPSS (Statistical Package for Social Sciences). Subsequently, the statistical tests for comparison between the groups in each particular s7tudy were: Tukey's test, Duncan's method, ANOVA, Friedman, MANCOVA, Chi-square, similarity analysis (ANOSIM), unpaired and unpaired Student's T test, U Mann-Whitney and Newman-Keuls multiple comparisons test. In addition, the Kolmogorov–Smirnov test was used for the distribution of data in one article, and the Bonferroni post-hoc test was used to determine the simultaneous confidence level for a set of intervals.[16-45]

Record appraisal

The objectives set out in the investigations were clear, they had study designs in accordance with the purposes they sought. Fifteen investigations involved humans,[16-30] and 15 rats.[31-45] The variables were considered and measured according to each investigation correctly, as well as the risk factors considered with respect to the stated objectives.[16-45] The effects of the probiotics in the reduction of the lipid profile were evaluated with conventional methods and in the period between 30 days and 12 weeks.[16-45] The following table 2 and 3 presents the summary of the variables of the selected articles.

TABLE 2. Record appraisal

	Authors	Aims/ Clear objectives	Study design appropriate for the stated aim(s)	Sample size justified	Target population defined	Sample appropriate to represent the target population	Selection process of participants likely to represent the target population	Measures undertaken to address non responders	Risk factors and outcome variable measure appropriately to the aims	Clear statistical significance defined
1	Karyana I.P.G., *et al.,* (2022)	YES	YES	YES	YES	NO	YES	NO	YES	YES
2	Fortes PM, *et al.,* (2020)	YES	YES	YES	YES	NO	YES	NO	YES	YES
3	Guardamagna, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
4	AkbariRad M, *et al.,* (2023)	YES	YES	YES	YES	NO	YES	NO	YES	YES
5	Wang S, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
6	Guerrero-Bonmatty R, *et al.*, (2021)	YES	YES	YES	YES	YES	YES	NO	YES	YES
7	Trotter RE, *et al.*, (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES
8	Ruscica, M, *et al.*, (2019)	YES	YES	YES	YES	YES	YES	NO	YES	YES
9	Ahmadian, Fatemeh, *et al.*,(2018)	YES	YES	YES	YES	YES	YES	NO	YES	YES
10	Costabile, Adele, *et al.*, (2017)	YES	YES	YES	YES	YES	YES	NO	YES	YES
11	Fuentes, *et al.*, (2016)	YES	YES	YES	YES	YES	YES	NO	YES	YES
12	Kullisaar Tiiu, *et al.*, (2016)	YES	YES	YES	YES	YES	YES	NO	YES	YES
13	Rajkumar H, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
14	Nabavi S, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
15	Fuentes, *et al.*, (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
16	Zafar Hamza, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
17	Munir, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
18	Fossi, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES

https://doi.org/10.36105/psrua.2023v3n6.02

19	Abdelshafy, A. M., *et al.,*(2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
20	Asad F., *et al.,* (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES
21	Wa Y, *et al.,* (2019)	YES	YES	YES	YES	YES	YES	NO	YES	YES
22	Nocianitri, K.A., *et al.,* (2017)	YES	YES	YES	YES	YES	YES	NO	YES	YES
23	Chuan, *et al*., (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
24	Park Do-Young, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
25	Salaj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
26	Mohania, Dheeraj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
27	Yoo SR, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
28	Kumar Manoj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
29	Huang, Ying, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
30	Park Do-Young, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES

TABLE 3. Continuation of record appraisal

	Methods described sufficiently to be repeated	**Basic data described**	**Response rate described**	**Ifappropriate, information about non responders described**	**Results internally consistent**	**Presence of results for the analyses described**	**Discussion and conclusions justified**	**Limitationsdiscussed**	**Fundingor conflict of interests that could affect results**	**Ethical approval or informed consent attained**
1	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
2	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
3	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
4	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES

5	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
6	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
7	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES
8	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
9	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
10	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
11	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
12	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
13	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
14	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
15	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
16	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
17	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES
18	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
19	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
20	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
21	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
22	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
23	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
24	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
25	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
26	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
27	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
28	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES

https://doi.org/10.36105/psrua.2023v3n6.02

29	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
30	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES

DISCUSSION

Various investigations indicate that the intestinal microbiota can intervene in multiple mechanisms such as, the production of specific substances peptides, vitamins, fatty acids, etc., help the intestinal barrier, influence the endocrine, nervous, immune systems and metabolism lipids, among other functions.[46,47] Cardiovascular diseases are increasing, and conventional treatments to treat them include drugs and diet, but there is currently evidence that some probiotic strains can improve the lipid profile and hypercholesterolemia. The use of probiotic supplements is a topic that has currently gained more interest in the general population, due to the search for new therapies and treatments for various pathologies.

Cholesterol reduction from probiotics happens through some mechanisms such as interference of cholesterol bioavailability in the small intestine, producing short-chain fatty acids through colonic fermentation of indigestible carbohydrates, and deconjugating bile salt hydrolase production. Bile acids, which is the best-known mechanism for performing the lipid-lowering effect.[10] Among the scientific community, multiple investigations have also been carried out to find out more benefits of probiotic bacteria to help in the problem of hyperlipidemia that can cause more severe problems such as, cardiovascular events, Hendijani F, *et al*. (2018), conducted a systematic review and meta-analysis of 641 randomized controlled trials where they conclude that for the control of dyslipidemia and hypertension in type 2 diabetic patients the use of probiotics reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP), TC, c-LDL, c-HDL and TG.[48] This same effect was evaluated in a meta-analysis of 14 randomized placebo-controlled trials in 702 participants demonstrating that probiotics in fermented milk generate a reduction of 3,10 mmHg (95% CI: 24,64; 21,56) in systolic BP and 1,09 mmHg (95% CI 22,11; 20,06) in diastolic BP in prehypertensive and hypertensive subjects.[49] Some research that talks about the benefits of probiotics in relation to the effect on lipid metabolism is the case of a meta-analysis of 32 controlled trials with 1971 patients that concludes that probiotic supplements can produce a reduction in total cholesterol. It is recognized that a longer consumption use in the form of capsules can increase the curative effect.[50]

In the present review, it was found that various probiotics such as *Lactobacillus plantarum, L. acidophilus, L. fermentum, L. gasseri, L. curvatus, L. rhamnosus*, among others can help reduce TC and c-LDL levels, in turn raise the level of c-HDL. This also, in accordance with what was mentioned by the research of Hu YM, et al., that probiotics are a biotherapeutic potential that improve lipid metabolism.[51] Or in the case of the findings of Sharma S, *et al.* (2016), it is concluded that the serum levels of total cholesterol and c-LDL are significantly reduced, which helps in the risk of cardiovascular diseases.[52]

This review found that the consumption of probiotic supplements helps reduce total cholesterol by 16.65% and c-LDL by 32.02%. In addition, they raise the concentration of c-HDL by 21,71%, and reduce the concentration of TG (29,67%), this agrees with Shimizu M, *et al*., (2015), in the meta-analysis of 11 randomized clinical trials in patients with normal hypercholesterolemia or mild, probiotic supplementation which demonstrate reduction in total cholesterol (TC) (mean difference -0,17 mmol/L, 95% CI -0,27 to -0,07 mmol/L) and c-LDL. (Mean difference -0,22 mmol/L, 95% CI -0,30 to -0,13 mmol/L).[53]

Strengths

This systematic review is so far the only one that focuses specifically on the percentage of modification exerted by probiotics on the lipid profile. In addition, it is a current investigation, which contemplates some variables such as the reduction of total cholesterol, c-LDL and the increase in c-HDL, which is important for cardiovascular health.

Limitations

We found some limitations in this research, some articles are not freely available, others do not mention the results

clearly or with the values expressed as a percentage, in the case of the effect of probiotics on the level of triglycerides, very few researchers mention the result. Different investigations were outside the searched time period.

CONCLUSIONS

Supplementation with specific strains of probiotics has a lipid-lowering effect, it especially reduces hypercholesterolemia through various mechanisms, but more studies are required to determine the dosage and treatment time. This review reveals that a larger number of experiments in humans and with supplementation over a longer time range are needed to verify the effects of probiotics specifically in relation to lipid profile.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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Review Article

Alteration in the clinical manifestations of monkeypox in the presence of HIV

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ABSTRACT

Introduction: The monkeypox virus is an orthopox virus belonging to the Poxiviridae family, being a zoonotic infection, with prevalence in the male population, on reproductive age, mainly in men who have sex with men. The virus enters through direct contact with infected skin, body fluids or respiratory droplets. The clinic begins with general prodromal symptoms, followed by a phase of skin lesions in different areas of the body. **Objective:** To compare the development of monkeypox infection in immunocompromised individuals with respect to a normal course of the disease. **Materials and methods:** Review of bibliographic data from 33 scientific articles, using databases such as PUBMED and Google Scholar, with the keywords "Monkeypox", "2022", "Clinical manifestations" that included complete characteristics of the virus and published within a 5 year range. **Results:** There is evidence that demonstrates the existence of a coinfection of monkeypox with HIV, increasing the possibility of being a case of opportunism, resulting in an atypical picture in the evolution of the disease. It begins with rash in the genital area with pain and pustules; 3 days later general symptoms of an infectious process are added, ending with diffuse pruritus accompanied by pustules on the back and extremities. **Conclusions:** A relationship was determined between seropositive male patients with atypical lesions of the disease, affecting the symptomatologic evolution and a correct diagnosis.

Key words: monkeypox; human immunodeficiency virus; men who have sex with men; clinical manifestations.

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RESUMEN

Introducción: El virus de la viruela símica es un ortopoxvirus perteneciente a la familia Poxiviridae, siendo una infección zoonótica, con prevalencia en la población masculina, en edad reproductiva, principalmente en hombres que tienen sexo con hombres. El virus ingresa a través del contacto directo con piel infectada, fluidos corporales o gotitas respiratorias. El cuadro clínico comienza con síntomas generales prodrómicos, seguidos de una fase de lesiones cutáneas en diferentes zonas del cuerpo. **Objetivo:** Comparar el desarrollo de la infección por viruela símica en individuos inmunocomprometidos respecto a un curso normal de la enfermedad. **Materiales y métodos:** Revisión de datos bibliográficos de 33 artículos científicos, usando bases de datos como PUBMED y Google Académico, con las palabras clave "Monkeypox", "2022", "Manifestaciones clínicas" que incluyeran características completas del virus y teniendo un rango de 5 años de antigüedad como límite. **Resultados:** Existe evidencia que demuestra la existencia de una coinfección del monkeypox junto con el VIH, aumentando la posibilidad de tratarse de un caso de oportunismo, dando como resultado un cuadro atípico en la evolución de la enfermedad. Éste comienza con una erupción en zona genital con dolor y pústulas, 3 días posteriores se agregan síntomas generales de un proceso infeccioso. Finaliza con prurito difuso acompañado de pústulas en dorso y extremidades. **Conclusiones:** Se determina una relación entre pacientes masculinos seropositivos, con lesiones atípicas de la enfermedad, afectando la evolución sintomatológica y un correcto diagnóstico.

Palabras clave: viruela símica; virus de la Inmunodeficiencia humana; hombres que tienen sexo con hombres; manifestaciones clínicas.

INTRODUCTION

Monkeypox virus (MPXV) is an emerging zoonotic poxvirus belonging to the Poxiviridae family, it belongs to a group of DNA viruses. The virus has an oval or brick shape, wrapped in a lipoprotein membrane.[1,2] In this outer membrane, it expresses surface proteins to adhere to, and penetrate host cells; it is a complex structure that serves as protection for the densely packed genetic material, which forms the nucleus and contains enzymes, transcription factors, and a double-stranded linear DNA genome. All this content is necessary for all poxviruses to be able to replicate inside the infected cells, in addition to using the machinery of the host.[3]

Epidemiology

The discovery of the virus can be traced back to 1958 in Denmark, in an animal facility that formed a non-fatal outbreak. 10 years after this event, the first report in humans was present in the Democratic Republic of the Congo in a 9-month-old child, with a history of not having been vaccinated against smallpox. Over the next 3 decades, cases of monkeypox were typecast in African countries; in 2003 numerous cases were reported in the United States of America, the first cases outside the African continent, and the infectious agent was traced to small exotic mammals imported from Ghana. Successively between 2018 and 2021 the United Kingdom and Israel reported several cases, having an exponential growth.[4-10] In 2022, cases were detected in 107 countries, but only in 7 of those countries most cases have usually occurred. This data from the OMS shows the importance and magnitude of the outbreak. By the year 2023 there are already 111 countries that have reported cases of monkeypox.

Transmission and pathogenesis

The most frequent mechanism of transmission of monkeypox is by direct contact, this can be by contact with infected materials, from animals to humans, the most frequently are rodents and primates mainly; the most common form of transmission is from human to human.[6] In the latter, transmission has been observed with greater incidence in those who had previous sexual exposure with an infected person, where most patients identify as men who have sex with men (MSM).[1,11-14]

There are two ways of acquiring the disease, one direct, typical of animals infected by bites or consumption of poorly processed foods; and the indirect by human-to-human contact, this being the most common.

The virus enters the body through contact with infected skin, body fluids, or respiratory droplets. Replication occurs rapidly at the inoculation site, which is commonly the airway epithelium, for further spread through regional lymph nodes.[15] The incubation period is usually 7 to 14 days. After the initial viremia, the virus spreads to different areas of the body, such as the face, continuing with a cephalocaudal pattern, this is how it can cause localized lesions in the initial stage of the disease.[16-17]

Manifestations

Monkeypox is different from the other orthopoxviruses in that it produces disseminated skin lesions in the infected host, with signs and symptoms lasting from 2 to 5 weeks. The initial stage begins with prodromal symptoms, including fever, chills, headache, myalgia, asthenia, and lethargy.[18-22]

The disease progresses and is characterized by developing in stages. The primary lesion appears on the third day, being of an enanthem character, which is located in the tongue and mouth; later, on the fifth day of the disease, macules, flat and without flanges, occur in the area of the face and extremities. Around the seventh day, papules develop, which progress to greasy lesions and vesicles, which will continue to form pustules. Finally, a healing period begins around the second week, indicating the terminal stage of the infection, which includes the formation of crusts and their respective desquamation, which may be accompanied by hyper or hypopigmentation. It should be emphasized that the degree of rashes and lesions depends on the viral load in the bloodstream during the viremia stage.

Complications related to monkeypox are encephalitis, pneumonia, bronchopneumonia, respiratory distress, keratitis, and scarring of the cornea that can end in permanent vision loss.[6,8,22-25]

Diagnosis

There are multiple laboratory options to make the timely diagnosis of monkeypox, among which are the enzyme immunoassay, viral cultures, electron microscopy, histological sample, immunohistochemistry, virus isolation tests; and before all existing tests the polymerase chain reaction assay is used as a reference test due to its high specificity and sensitivity. It is important to mention that the differential diagnosis is severe chickenpox with lesions on hand palms and foot soles, as well as the presence of lymphadenopathy in the submandibular, inguinal, and cervical areas.[3,16,26-29]

Treatment and prevention

The Food and Drug Administration (FDA) approved the vaccine JYNNEOS in 2019 as a prevention of monkeypox for adults 18 years and older, who are at high risk of infection. Despite the absence of an FDA-approved treatment, there are drugs that serve as supportive measures for the treatment of monkeypox, which are only available through clinical studies, these are TPOXX (tecovirimat) approved by the FDA in 2018, under the Animal Rule and Tembeza (brincidofovir) approved by the FDA in 2021. Both approvals are based on efficacy data from animal studies.[30]

Risk factors for the disease have been associated such as high-risk sexual activity such as men who have sex with other men, and carrying base immunodeficiency, among the most prominent is HIV positive.[3,18,28-29]

METHODS

A review of bibliographic data of scientific articles was carried out, with peer review; using database search engines such as PUBMED and Google Scholar, with the keywords: “Monkeypox”, “2022”, and “Clinical manifestations”. We chose 33 articles in English and Spanish, based on their relevance to the topic, as well as their originality and contribution to the targeted area of knowledge. The inclusion criteria for the selection of the articles were that they included the characteristics of the description of the virus, pathogenesis, clinical and diagnostic characteristics; including a 5-year age limit of publication and a specific focus on the features mentioned above.

The indexed articles are based on multicenter observational and prospective cohort studies of standardized data related to the life and sexual practices of patients confirmed with monkeypox.

RESULTS

From the literature reviewed, it was determined that 90% of the patients reported with monkeypox, were identified as men who have sex with sexually active men who have had unprotected sex. In addition to this, cases have been

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detected where there is a coinfection of the monkeypox virus and HIV, this being very characteristic in the reports presented since it could speak of a case of opportunism on the part of the MPX, as well as the development of the symptomatology could also be involved. There is evidence that demonstrates the onset of atypical symptoms with a genital rash accompanied by pustules with white liquid content and persistent pain in that area, 3 days later general non-specific symptoms typical of infection such as fever, fatigue, headaches, myalgias, and lymphadenopathy are added and 5 days after the presence of the first sign observed, diffuse pruritus begins with pustules on the back and extremities, corresponding to an atypical picture due to monkeypox infection (Figure 1; Table 1).

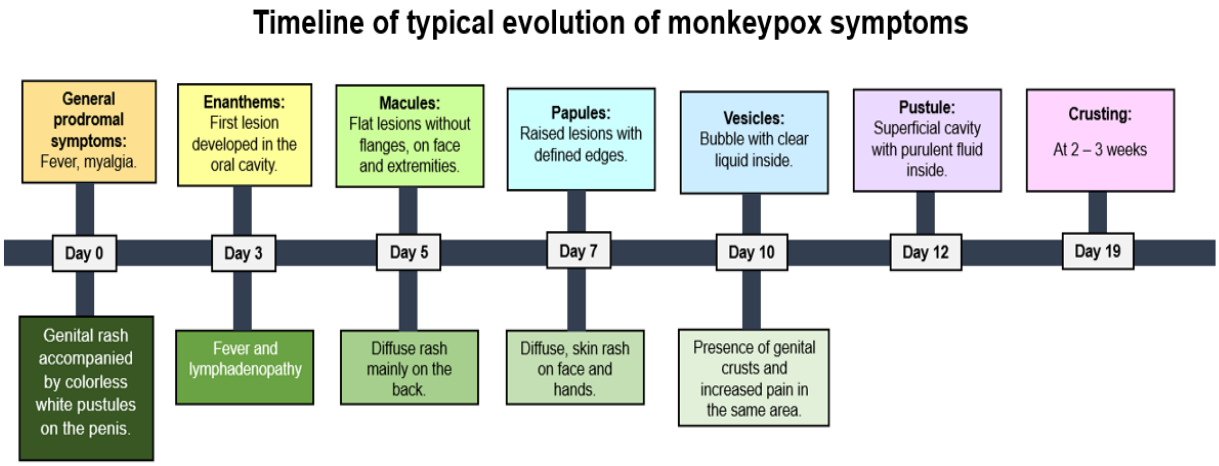

Figure 1. Comparative timeline of a typical and atypical evolution of monkeypox symptoms.

Table 1. Comparative table of manifestations between patients with monkeypox disease and HIV-positive patients with monkeypox disease without antiretroviral treatment

Typical evolution of monkeypox	Atypical evolution of monkeypox in HIV-positive patients without antiretroviral treatment
Symptoms	**Symptoms**
• General prodromal symptoms: Fever, myalgia, headache, backache, and lymphadenopathy. • First lesion are the enanthems developed in the oral cavity, especially on mucous membranes, common in patients with viral illnesses. • The second lesions are the macules, flat lesions discolored, without flanges, on face and extremities. Generally, do not include a change in the texture of the skin. • The third skin lesions are the papules, which are solid or cystic raised lesions with defined edges, less than 1 centimeter. • The vesicles are the fourth visible lesion, which are bubble with clear liquid inside. • At the end of the second week, superficial bulge with purulent fluid inside appear, which are the pustules. • Between the second and third week the crusting begins.	• Genital rash accompanied by colorless white pustules on the penis. • Fever, headache, myalgia, chills, and lymphadenopathy. • Diffuse rash mainly on the back. • Diffuse, skin rash on face and hands. • Presence of genital crusts and increased pain in the same area.

According to the joint United Nations Programme on HIV/AIDS (UNAIDS) data, approximately 15.2 million people with HIV do not receive treatment. This group is considered the highest risk for presenting an atypical evolution and worse prognosis of monkeypox.[31]

DISCUSSION

The emerging infection of monkeypox has a great impact on the health system since it implies a high risk to the community; given that it has been identified together with smallpox as the most frequent poxvirus infection; with a significant percentage of 1 to 10% as fatal cases. It is relevant that currently, the existing reports describe a predominance of the male sex in infected patients, in particular men who have sex with men. It was determined that there is a relationship between seropositive male patients with atypical lesions, concerning compromise in their immune status, which affects the correct development of the disease since in a typical monkeypox infection, the expected symptomatology begins with nonspecific constitutional symptoms, followed by first enanthems lesion in the oral cavity, which evolve into macules, followed by papules, vesicles, pustules and finally scarring with a period of desquamation, indicating that the individual is no longer contagious.

It is essential to study the disease in the many possible contexts because the severity is varied, it depends as well on the state of immunity of people because those with HIV have a compromised immune system, which could quickly evolve into septic shock, leading to the death of the individual. Medical specialists in urology must have the ability to make a correct diagnosis of the present disease and know how to differentiate it from any other sexually transmitted diseases.

CONCLUSIONS

Evidence suggests that unexpected course of the disease compared to the predicted clinical picture of a typical monkeypox infection occurs in HIV patients without antiretroviral treatment (ART). A poor prognosis was detected in patients who do not have a previous diagnosis of acquired immunodeficiency (AIDS) and therefore do not have an ART treatment. For this reason, the centers for disease control and prevention (CDC) recommends starting ART treatment immediately upon receiving the newly diagnosed coinfection of HIV and monkeypox, regardless of viral load.[32]

It was found that in patients who refused HIV antiretroviral therapy and infected with monkeypox resulted in higher number of hospital admissions, complications, and higher mortality.[33]

The relevance of this topic is the timely detection of monkeypox, with a correct intervention of public health, as well as an effective clinical correlation in immunosuppressed patients, mainly seropositive.

It is necessary to take control and prevention measures towards this disease, including sex education as a follow-up protocol. In addition to continuous immunization of the population for the reduction of new cases and/or symptoms in severe cases.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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Case Report

Gorham-Stout syndrome with cervical involvement treated with radiotherapy: a case report

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ABSTRACT

Gorham-Stout disease (GSD), vanishing bone or phantom bone disease, is an uncommon disease whose etiology is uncertain and its pathophysiology poorly understood. This syndrome is characterized by the spontaneous destruction of the bone matrix associated with massive osteolysis and proliferation of lymphatic vascular structures in the affected areas. In the present article we present a case of GSD in a 10-year-old male patient with osteolytic lesions affecting the skull base, including the occipital bone, the petrous portion of the temporalis and clivus, as well as the vertebral bodies from C1 to C5. This syndrome should be suspected when there is bone pain that does not subside with analgesic treatment. An initial study with an x-ray will help us infer the disease in search of a bone deformity. The treatment depends on the characteristics of the lesion, the best being surgery with radiotherapy.

Key words: Gorham-Stout Syndrome; bone resorption; vanishing bone massive; osteolysis.

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RESUMEN

La enfermedad de Gorham-Stout, o enfermedad del hueso evanescente, es una patología infrecuente cuya etiología es incierta y su fisiopatología poco conocida. Este síndrome se caracteriza por la destrucción espontánea de la matriz ósea asociada a osteólisis masiva y proliferación de estructuras vasculares linfáticas en las zonas afectadas. El presente artículo reporta un caso de enfermedad de Gorham-Stout en un paciente masculino de 10 años con lesiones osteolíticas que afectan la base del cráneo, incluyendo hueso occipital, la porción petrosa del temporal y clivus, así como los cuerpos vertebrales de C1 a C5. Este síndrome se sospecha cuando existe dolor óseo que no cede con tratamiento analgésico. Un estudio inicial con una radiografía nos ayudará a sospechar la enfermedad en busca de una deformidad ósea. El tratamiento depende de las características de la lesión, siendo la mejor, la cirugía con radioterapia.

Palabras clave: Síndrome Gorham-Stout; resorción ósea; osteólisis; hueso evanescente.

INTRODUCTION

GSD is a rare disease characterized by progressive spontaneous bone resorption with massive osteolysis and proliferation of vascular structures in the affected areas; its etiology remains unknown, there's no hereditary pattern identified.[1] This disease is often seen in young adults with no sex predilection. It was first described in 1838 and again in 1872 by Dr. Jackson. However, it was not until 1955 that Dr. Gorham and Stout defined it as a specific ontological syndrome. There are just a few cases reported worldwide.[2] The clinical presentation is related to the bone affected being scapula (26%), jaw (15%) the most affected, also skull and pelvic cursing with pain, local inflammation and progressive deformity.[3] The diagnosis is based on histological findings characterized by progressive osteolysis with associated angiomatosis of blood and lymphatic vessels,[4] the treatment remains in discussion with a combination of pharmacotherapy, radiotherapy and surgery due to an unknown cause.[5] Mortality increases when osteolysis affects the spine, ranging from 6% to 50%.[6]

CASE REPORT

A 10-year-old male was brought by his parents for medical evaluation for referring pain in the cervical region during the last two months. The pain initially had a moderate intensity (referred with a score of 7/10) and was exacerbated by cervical mobilization and limited range of motion. Days after, the pain increased in intensity, until reaching a score of 10/10. He was treated with non-steroidal anti-inflammatory drugs, without obtaining an effective response. The patient has no medical, personal or psycho-social history of importance.

During the medical examination only pain was found on cervical mobilization during flexion, extension and bilateral rotation movements, predominantly posterior.

A non-contrast computed tomography of the cervical spine and skull showed extensive lytic lesions in the form of osteoporotic patches involving part of the sphenoid bone, clivus, temporal and left occipital bones, and the cervical vertebral bodies from c1 to c5 (Figures 1-2). Paraclinical examinations, blood cytometry, blood chemistry and urinalysis showed no changes. Only alterations in serum electrolytes were observed (Table 1).

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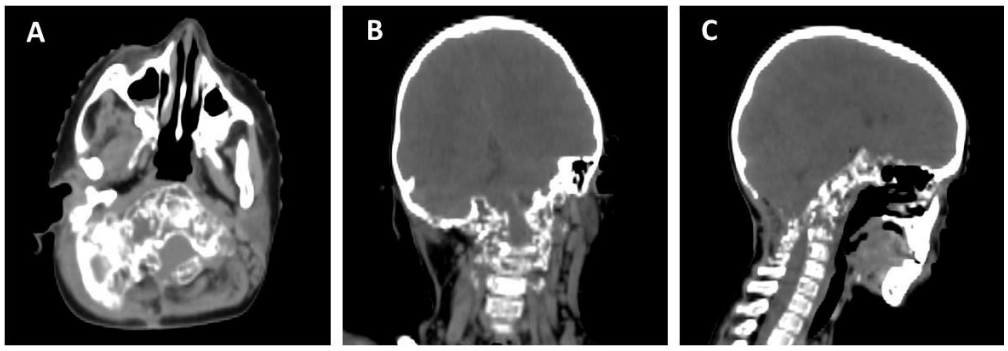

FIGURE 1. Computed tomography images taken before radiation therapy treatment. This figure shows three examples of computed tomography images obtained for radiation therapy planning. In axial view (**A**) we can observe a large osteolytic lesion over the petrous region of the temporal bone and the left occipital bone. The coronal view (**B**) shows osteolytic lesions of predominantly petrosal form bilateral with extrusion to the vertebral bodies of C1 and C2. The sagittal image (**C**) shows extensive osteolytic lesions in the clival region and the center of the occipital bone extending to the vertebral bodies and spinous apophysis of the first vertebrae.

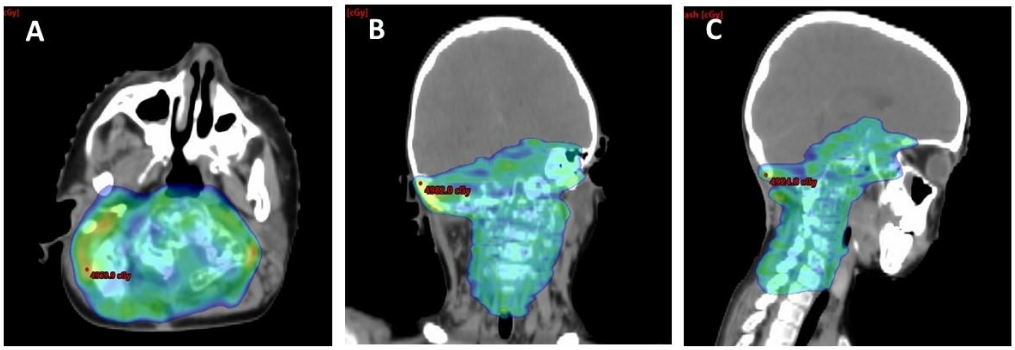

FIGURE 2. Radiation therapy planning. This figure shows three examples of CT scan axial (**A**), coronal (**B**) and sagittal images (**C**) used for radiation therapy treatment. The dose distribution is shown in wash color on the target volume in the three images.

TABLE 1. Serum electrolytes

Electrolyte	Test during clinical approach	Test after three months follow-up	Age-specific reference values
Sodium	138 mEq/L	141 mEq/L	135 – 147 mEq/L
Potasium	3.7 mEq/L	4.2 mEq/L	3.4 – 4.7 mEq/L
Chlorine	108 mEq/L	102 mEq/L	96 – 106 mEq/L
Calcium	11.3 mg/dL ↑	9.9 mg/dL	8.8 – 10.8 mg/dL
Magnesium	2.4 mg/dL	2.2 mg/dL	1-6 – 2.4 mg/dL
Phosphorus	5.3 mg/dL ↑	4.4 mg/dL	2.7 – 4.5 mg/dL
During the clinical approach, laboratory studies showed mild elevation of serum total calcium, serum calcium and phosphorus levels which decreased to normal values after medical treatment for three months.			

The pediatric neurosurgery department obtained a biopsy of the bone lesions taken from the vertebral body of C5 which were described by the pathology department as osteolytic lesions with angiomatous vascular proliferation of benign characteristics, without presenting cellular atypia or osteoblasts. In addition, a possible infectious disease was ruled out.

The neurological surgery department analyzed the case and decided not to perform surgical treatment due to the extension and deep location of the lesions. The patient was referred to our institution to be treated with radiotherapy (RT) and medical treatment with bisphosphonates.

RT was performed in Varian CLINAC iX equipment, with a total dose of 45 Gy in 25 fractions of 1.8 Gy per day, using a volumetric technique for beam modulation (VMAT) (Figure 2).

As for medical treatment, calcitriol capsules 0.25 mg every 24 hours and calcium carbonate pills 500 mg every 24 hours were administered.

During the medical follow-up 3 months after radiotherapy treatment, the pain on cervical mobilization decreased in intensity to 3/10. In addition the following labs were obtained: creatinine 0.31 mg/dL, alkaline phosphatase 114 U/L, total calcium 10.2 mg/dL, phosphorus 5 mg/dL and magnesium 2 mg/dL. The disease remained stable until the first year of follow-up (Table 1).

Subsequently, the patient was sent back to his home for clinical and radiological follow-up in the coming months, which are pending.

DISCUSSION

GSD, also known as Gorham's disease, phantom bone disease, vanishing bone disease, progressive osteolysis, acute bone absorption, primary lymphangioma, and massive idiopathic osteolysis, is a rare disease. This syndrome is characterized by spontaneous destruction of the bone matrix associated with massive osteolysis and proliferation of lymphatic vascular structures. GSD does not have a gender or race predilection and generally affects individuals under the age of 40. Currently, only about 400 cases have been reported, with an overall mortality rate of 13%. Mortality increases when osteolysis affects the spine, ranging from 6% to 50%.[6,7,8]

The pathophysiology of this disease is multifactorial, involving genetic factors such as somatic mosaic mutations. The associated genes include PTEN (phosphatase and tensin homolog) which appears to be one of the first genes affected in this disease and whose mutation leads to the formation of malignant and benign tumors, TREM2 (triggering receptor expressed on myeloid cells 2), and TNFRSF11A (TNF receptor superfamily member 11a) which causes familial expansive osteolysis expansive and expansive skeletal hyperphosphatasia. Mutations in the KRAS pathway, which promote bone angiogenesis through signaling cascades, have also been reported.[9,10,11]

The clinical presentation of GSD depends on the location affected by the osteolytic process and is characterized by pain (the main symptom), edema, weakness, and impairment of the affected limbs, pathological fractures, neurological alterations, paralysis, respiratory failure, and, in some cases, death.[12,13] Our patient presented cervical pain of two months of evolution that increased until cervical mobilization was difficult and range of motion decreased.

There are different diagnostic criteria for GSD, with the main criterion being an osteolytic radiographic pattern, absence of dystrophic calcifications, absence of visceral involvement, and the presence of hereditary, neoplastic, metabolic, infectious, or immunological etiology. Radiologically, this disease manifests itself as intramedullary and subcortical radiolucent areas resembling "osteoporosis patches." It is an irregular and slow process, with local progression of concentric contraction in the affected bones. Bone regeneration does not occur even if the progression of osteolysis subsides. This leads to bone deformity and loss of bone mass, increasing the risk of pathological fractures. Clinical laboratory tests are not effective in this syndrome as they are usually normal, apart from alkaline phosphatase, which may be elevated in some cases. The main differential diagnoses of this disease include osteomyelitis, rheumatoid arthritis, hereditary multicentric osteolysis, hyperparathyroidism, and eosinophilic granuloma.[14,15] Non-contrast computed tomography of the cervical spine and skull of our patient reported extensive lytic lesions in the form of osteoporotic plaques that involved part of the left sphenoid, clivus, temporal, and occipital bones, and the cervical vertebral bodies from c1 to c5. The pathology service described C5 osteolytic lesions with angiomatous vascular proliferation of benign characteristics, without presenting cellular atypia or osteoblasts.

Regarding the treatment of GSD, different therapies are included, classified as surgical, medical, and radiation treatment. Surgical treatment is the preferred option for

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patients at risk of developing pathological fractures and involves resection of the affected bone and joint reconstruction with prostheses. Pharmacology treatment offers various alternatives, including the use of bisphosphonates to provide protection to the affected bone. Scientific evidence also suggests the use of vitamin D analogs, calcium, interferon-alpha-2b, androgens, and adrenal extracts to protect against osteolysis.[9] Radiation therapy is indicated for patients with long-standing, functionally debilitating instability that does not respond to medical treatment and who have large symptomatic lesions. Radiation therapy shows favorable results in 75% of cases but can have long-term complications, with the most common being growth restriction during schooling and the presence of radiation-induced secondary malignancies.[16] In the present case, the patient received RT treatment with a Varian CLINAC iX device, with a total dose of 45 Gy in 25 fractions of 1.8 Gy per day, using VMAT technique which has the objective to cause damage on DNA of irradiated cell seeking to stop the osteolytic and inflammatory process which seems to be the reason causing the pain and performance improvement. On the other hand, medical treatment given with bisphosphonates is not a therapeutic treatment but it is aimed to regulate calcium and phosphate serum values and its potential effects.

The progression of the disease is slow, and the prognosis is unpredictable. In the case of our patient, the subject continued medical follow-up 3 months later at his clinic.

CONCLUSION

GSD is characterized by massive osteolysis, mainly affecting the bones of the skull, shoulders and pelvic girdle. It is important to suspect the presence of this syndrome when there is bone pain that does not subside with analgesic treatment. An initial study with an X-ray will help us to infer the disease in search of bone deformity, and the computed tomography will help us to offer a timely diagnosis. Treatment depends on the characteristics of the lesion. Improving the quality of life of patients and offering a better prognosis. In our case, we describe the medical and surgical approach for our patient, and we also confirm what the most up-to-date literature reports on diagnostic and treatment methods in SDG. Offering a better quality of life to patients.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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