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Editorial

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The MACARENHA connection: a holistic approach to understand and fight the cardiometabolic epidemics that ravage Mexico

La conexión MACARENHA: un enfoque holístico para entender y combatir las epidemias cardiometabólicas que asolan México

GREHTA Group*:
Luis Alcocer Díaz-Barreiro, Alejandro Alcocer, Humberto Álvarez-López, Ana E Ancona-Vadillo, Neftalí Eduardo Antonio-Villa, Simón Barquera, Gabriela Borrayo-Sánchez, David Cardona-Müller, Ernesto Cardona-Muñoz, Emilia Cantoral-Farfán, José Ángel Cigarroa-López, Aníbal Cruz-Montalvo, Adolfo Chávez-Mendoza, Adolfo Chávez-Negrete, Guillermo Saturno-Chiu, Sergio Emmanuel Delgado-Félix, Enrique Díaz-Díaz, Miguel Ángel Díaz-Aguilera, Ernesto Díaz-Domínguez, Manuel Duarte-Vega, José Manuel Enciso-Muñoz, Xavier Escudero-Cañedo, Guillermo Enrique Ferrari, Abelardo Flores-Morales, Héctor Galván-Oseguera, Rafael García-Fernández, Rosalba García-Méndez, Sergio Moisés García-López, Enrique Gómez-Álvarez, Vidal José González-Coronado, Ángel Gracia-Ramírez, Juan Miguel Heredia-Lavín, Mauricio López-Meneses, Karina Lupercio-Mora, Alejandra Madrid-Miller, José Antonio Magaña-Serrano, Dania Heloneyda Martínez-Juárez, Eduardo Meaney-Mendiolea, Patricio Ortiz-Fernández, Silvia Palomo-Piñón, Juan José Parcero-Valdés, Fabiola Pazos-Pérez, Abel Alberto Pavía-López, Adriana Puente-Barragán, Ariadna Rechy-Rivera, Luis Rey-García, Alejandro Ricalde-Alcocer, Martín Rosas-Peralta, Miguel Ángel Santiago-Velázquez, Marissa Silva, Rosbel Toledo-Ortiz, Rodrigo Villaseñor-Hidalgo

In 1827, the British physician and scholar Richard Bright (1789-1858) described the association among edema, albuminuria, cardiac enlargement, «hard pulse» (later related to high blood pressure, HBP), uremia and neurological catastrophes like seizures, blindness, and coma.[1] Bright's disease, as it was named for many years, acute and chronic nephritis, was an early attempt to intertwin the clinical manifestations of pathologies affecting organs and systems anatomically distant from each other. Although several physicians had related HBP to cardiac hypertrophy, the British of Indian and Irish origin physician Frederick Henry Horatio Akbar Mahomed (1849-1874), measuring blood pressure with a primitive quantitative sphygmogram of his own (improved from Marey's invention), described HBP in the absence of kidney disease, but linked it with cardiac hypertrophy, aortic aneurysms, stroke, arteriolar fibrosis, and other cardiovascular (CV) outcomes.[2] In 2004, the term «cardiorenal syndrome» (CRS) was introduced by the National Heart, Lung, and Blood Institute Working Group, focused on describing the close interplay

* Group of Experts on Arterial Hypertension. GREHTA working group for MACARENHA connection.

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between the kidney and heart physiologies.[3] The concept has evolved, highlighting the hemodynamic, neurohumoral, biochemical, immunoinflammatory, and hematologic links between both organs.[4] As it is known, the four categories of CRS[4] describe the conditions in which the failure of one of these two organs adversely affects the other and vice versa.[4]

In 2023, the American Heart Association coined the term «cardiovascular-kidney-metabolic (CKM) syndrome», incorporating cardiovascular, renal, and metabolic conditions, foremostly diabetes and obesity (diabesity) in a single nosological entity.[5] This conceptual consolidation not only refers to the pathophysiological links between the different elements of the CMK syndrome but also applies principally to a more comprehensive diagnostic, preventive, and therapeutic management.[6]

From this evolutionary, modern, and holistic comprehension of HBP, which infrequently emerges as a solitary risk factor, the GRETHA Group, one of the sister medical associations of ANCAM, held a meeting at the end of the past year in Mexico City and launched the concept of MACARENHA connection. The acronym was composed with the following initials: MA, stands for **M**etabolic and **A**diposity; CA, for **C**ardiac and **A**rterial; R, for **R**enal, and EN for **E**ntero-**H**epatic, and HA, for **N**eurological-Behavioral, in **H**ypertension (HA in Spanish).

This concept underlines the physiopathology entanglement among the heart, the kidney, the arterial vessels, the metabolism (mainly carbohydrates and lipids), obesity or overweight, the intestine, and the nervous system. Furthermore, the connection (using a nice feminine name, also the title of a popular danceable song) will easily remind caregivers that diagnosis and treatment must encompass all the elements of the acronym. If HBP is found in a patient, it is mandatory to correct the weight problem; determine the serum concentration of glucose and the complete lipid profile (total cholesterol, high and low-density lipoproteins cholesterol, triglycerides, and all atherogenic indices); evaluate the heart, nervous system, and kidney statuses; and achieve, through an appropriate diet, healthy intestine function and microbiota. All risk factors must be diagnosed, treated, and controlled or reduced as soon as possible. The neurological-behavior component includes not only acute and chronic brain conditions (stroke, dementia, and lacunar infarcts) but also mood alterations such as anxiety and depression.

In the Mexican pathological and epidemiological scenario, the foundation stone on which rests the enormous load of type 2 diabetes and ischemic heart disease, the two leading causes of general mortality, in adults of both genders,[7] is the obesity/overweight (O/O) syndrome affecting almost 80% of the population over 20 years of age.[8] In most cases, O/O, through varied pathogenic mechanisms, detonates in the same patient the rise of blood pressure, dysglycemia (prediabetes and diabetes), and a lipid disturbance called lipid triad or atherogenic dyslipidemia.[9] More recently, the set of liver pathologies enclosed in the term «metabolic dysfunction-associated steatotic liver disease (MASLD)»[10] has surpassed the interest of gastroenterology and hepatology and is gaining general interest. Firstly, liver fat infiltration is a manifestation/cause of the binomial insulin resistance/hyperinsulinism syndrome, so the hepatic pathology is linked to dysglycemia, dyslipidemia, inflammation, and cardiovascular and cerebrovascular diseases. And secondly, rapidly, MASLD is converting into the leading cause of cirrhosis and hepatoma worldwide. Again, gastroenterologists, hepatologists, and internists who usually diagnose and treat this liver pathology must remember the ties with other dreadful extra gastrointestinal conditions. Finally, the intestine interplay in the MACARENHA connection via two players, the enterogastric hormones of the liver-gut-pancreas-hypothalamus axis influencing the cycle of hunger-satiety[11] and the energetic expenditure, and the intestinal microbiota and mucosa. Human intestinal microbiota, through diverse, complex mechanisms, plays essential roles in the genesis of obesity, insulin resistance, type 2 diabetes, MASLD, and HBP, among many other pathologic conditions.[12]

GRETHA will present an extensive document describing the MACARENHA connection in more detail, with the explicit purpose of putting in the minds of general practitioners, family physicians, specialists, decision makers, nurses,

nutritionists, and all those whose activity is related to health, this essential holistic approach to diagnose, prevent, and treat all the constitutive elements of this kaleidoscopic framework of cardiovascular, renal, cerebrovascular and hepatic-enteral diseases.

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Statement

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Statement from the Presidency of ANCAM and its Editorial Committee

Declaración de la Presidencia de la ANCAM y de su Comité Editorial

José Antonio Magaña-Serrano,* Eduardo Meaney‡

ANCAM and this journal, its official publication, are apolitical, inclusive, and tolerant. Our Association is an academic body dedicated exclusively to promoting the care and prevention of cardiovascular diseases and the dissemination of science. We do not intervene in political, religious, historical, or philosophical discussions (except those about bioethics). However, each member individually exercises the inalienable rights of thought, belief, religion, political activism, and expression.

However, recent events in international geopolitics compel us to unite. The risks we face go beyond potential economic consequences, as scientific knowledge and dissemination are compromised.

This situation compels us to close ranks and unite. Beyond individual ideology, institution, or personal medical practice, today, we must be united in the defense of science and truth, and our journal, the official publication of ANCAM, is the guarantor of the best scientific practices. This journal is the academic trench in which all of us can help our country.

In this sense, we invite all our members and the scientific community to join us in a crusade, contributing scientific content through original research, systematic and short reviews, meta-analyses, expert consensus, and presenting relevant cases.

Today, more than ever, WE ARE ALL ANCAM,
Remembering that «Prevention is our goal».

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ORIGINAL RESEARCH

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Inflammation indices in chronic stable coronary artery disease

Índices de inflamación en enfermedad arterial coronaria crónica estable

Juan Salazar,*,‡ Douglas Inciarte,* Soledad Briceño,* Mayela Bracho,* Carlos Esis,* Egle Silva,* Roberto Añez§

Keywords:
inflammation, chronic stable coronary artery disease, severity, systemic immune-inflammation index.

Palabras clave:
inflamación, enfermedad arterial coronaria crónica estable, severidad, índice inmunitario-inflamatorio sistémico.

ABSTRACT

Introduction: coronary artery disease (CAD) is a chronic inflammatory disorder of multifactorial origin, with inflammation being a key pathophysiological aspect. **Objective:** to determine the relationship between inflammatory indices and the severity of chronic CAD in subjects undergoing cardiac catheterization at the Institute of Cardiovascular Disease Research of the University of Zulia. **Material and methods:** the research was descriptive, cross-sectional, and correlational, with a non-experimental design. The sample was selected through simple random sampling, with subjects over 18 years of age with chronic coronary syndrome who had inflammatory indices quantified and the SYNTAX score determined to assess the severity of CAD. **Results:** of the 73 subjects evaluated, 50.7% (n = 37) were men, the overall average age was 59.5 ± 7.7 years, 83.6% (n = 61) were hypertensive, and 68.5% (n = 50) had a previous acute coronary syndrome. A higher average of platelets (376.1 ± 85.6 × 10^3/mm^3), platelet-lymphocyte ratio (PLR) (144.9 ± 54.7), and systemic immune-inflammation index (SIII) (703.2 ± 335.9) was observed in subjects with a SYNTAX score ≥ 33. A positive correlation was found between PLR and the SYNTAX score ($r = 0.61$; $p < 0.01$) and between the SIII and the SYNTAX score ($r = 0.55$; $p < 0.01$). In the multiple linear regression analysis, the SIII was the index most independently related to the SYNTAX score ($\beta = 0.64$; $p < 0.01$). **Conclusions:** the study found that the SIII was significantly associated with a higher severity of chronic CAD, as indicated by the SYNTAX score. This association was observed independently of other inflammatory and lipid factors.

RESUMEN

Introducción: *la enfermedad arterial coronaria (EAC) es una enfermedad inflamatoria crónica con un origen multifactorial, siendo la inflamación un aspecto fisiopatológico clave.* ***Objetivo:*** *determinar la relación entre los índices inflamatorios con la severidad de la EAC crónica en sujetos sometidos a cateterismo cardiaco en el Instituto de Investigaciones de Enfermedades Cardiovasculares de La Universidad del Zulia.* ***Material y métodos:*** *la investigación fue de tipo descriptiva, transversal, correlacional con un diseño no experimental. La selección de la muestra se realizó a través de un muestreo al azar simple en sujetos mayores de 18 años con síndrome coronario crónico a los cuales se les cuantificaron índices inflamatorios, y el puntaje SYNTAX para determinar la severidad de la EAC.* ***Resultados:*** *de los 73 sujetos evaluados, 50.7% (n = 37) fueron hombres, el promedio general de edad fue 59.5 ± 7.7 años, 83.6% (n = 61) fueron hipertensos y 68.5% (n = 50) tenían síndrome coronario agudo previo. Se observó un mayor promedio de plaquetas (376.1 ± 85.6 × 10^3/mm^3), índice plaquetas linfocitos (PLR) (144.9 ± 54.7) e índice inmunitario-inflamatorio sistémico (IIIS) (703.2 ± 335.9) en los sujetos con puntaje SYNTAX ≥ 33. Se obtuvo una correlación positiva entre el PLR y el puntaje SYNTAX ($r = 0.61$; $p < 0.01$), y entre el IIIS y el puntaje SYNTAX ($r = 0.55$; $p < 0.01$). En el análisis de regresión lineal múltiple, el IIIS fue el índice más relacionado de manera independiente con el puntaje SYNTAX ($\beta = 0.64$; $p < 0.01$).* ***Conclusiones:*** *el IIIS se asoció con un mayor grado de severidad de la EAC crónica según el puntaje SYNTAX, independientemente de otros factores inflamatorios y lipídicos.*

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Abbreviations:

BMI = Body Mass Index
CAD = Coronary Artery Disease
CCS = Chronic Coronary Syndrome
CRP = C-Reactive Protein
MLR = Monocyte-Lymphocyte Ratio
NLR = Neutrophil-Lymphocyte Ratio
PLR = Platelet-Lymphocyte Ratio
SIII = Systemic Immune-Inflammation Index

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INTRODUCTION

Various indices derived from cellular biomarkers inherent to the inflammatory process have been described, most of which originate from hematological values. Indices such as the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), or the monocyte-lymphocyte ratio (MLR) have been associated with increased negative outcomes, including mortality, in various cardiovascular scenarios.[1] Recently, it has been suggested that combining these hematological values could have better predictive value than other existing tools. As a consequence, the systemic immune-inflammation index (SIII) has been created, utilizing a combination of serum levels of neutrophils, lymphocytes, and platelets in a mathematical expression.[2,3]

Assessing the severity of coronary artery disease (CAD) is crucial for the classification of cardiovascular risk and, consequently, for the selection of therapeutic strategies to be implemented.[4] Thus, a cost-effective approach to predicting which subjects are more likely to have an acute coronary event is highly desirable. Among the multiple variables used for this purpose, biomarkers or inflammatory indices associated with the atherosclerotic process could be employed in low-resource settings. Thus, the objective of this study was to determine the relationship between inflammatory indices and the severity of chronic CAD in subjects undergoing cardiac catheterization at the Institute of Cardiovascular Disease Research of the University of Zulia.

MATERIAL AND METHODS

Study design and sample selection

A descriptive, cross-sectional, and correlational study with a non-experimental design was conducted on all patients of both genders diagnosed with chronic coronary syndrome (CCS) admitted for cardiac catheterization to the Hemodynamics Service of the Institute of Cardiovascular Disease Research of the University of Zulia (IECLUZ), located in the Municipality of Maracaibo, Zulia State, during the period from October 2022 to October 2023. The sample selection for this study was performed through simple random sampling of all admitted subjects who met the following criteria: patients of both genders, over 18 years of age, diagnosed with CCS. Subjects with pathologies that could affect laboratory parameters were excluded: evidence of acute or chronic infection, autoimmune or systemic inflammatory diseases, use of glucocorticoids during the previous 2 months, active neoplasms, hematological disorders, liver failure, renal failure, thyroid disorders, trauma or surgery within the previous month, acute coronary syndrome, previous revascularization (percutaneous intervention or coronary artery bypass grafting), decompensated heart failure, clinically significant valvular heart disease; patients who were incapacitated for or opposed to participating in the study were also excluded. After all the considerations, the final sample consisted of 73 patients.

Patient assessment

Each patient selected and included in the study was informed about the study being conducted and asked for their authorization to participate. Subsequently, they were administered a questionnaire based on direct patient interviews, where data such as gender, age, and educational level were investigated and classified as primary, secondary, or university studies. Their place of residence was categorized as urban or rural.

Regarding psychobiological habits and personal history, individuals who did not engage in any degree of physical activity were considered sedentary, and those currently smoking cigarettes were classified as smokers. Ex-smokers were defined as individuals who had quit smoking for over a year prior to the interview. Family history of CAD was only recorded if it had occurred in first or second-degree relatives at a premature age. The presence of hypertension, diabetes mellitus, and dyslipidemia was recorded if documented in medical records or if the patient was taking medications for these conditions.

Subsequently, each patient's weight and height were measured using a scale and a stadiometer (health o meter brand), and the body mass index (BMI) was calculated using the formula: BMI = weight/height^2. Additionally,

Table 1: General characteristic of the sample according to sex.

	Female n (%)	Male n (%)	Total n (%)
Clinical characteristics			
Secondary education	12 (32.4)	18 (50.0)	30 (41.1)
Urban origin	34 (91.9)	34 (94.4)	68 (93.2)
Sedentarism	33 (89.2)	28 (77.8)	61 (83.6)
Current smokers	3 (8.1)	6 (16.7)	9 (12.3)
Ex-smokers	17 (45.9)	13 (36.1)	30 (41.1)
Cardiovascular disease (FH)	21 (56.8)	14 (38.9)	35 (47.9)
Hypertension	32 (86.5)	29 (80.6)	61 (83.6)
Diabetes mellitus	11 (29.7)	12 (33.3)	23 (31.5)
Dyslipidemia	12 (32.4)	17 (47.2)	29 (39.7)
Prior ACS*	20 (54.1)	30 (83.3)	50 (68.5)
Drug use			
Nitrates*	15 (40.5)	25 (69.4)	40 (54.8)
ACEi or ARB	27 (73.0)	27 (75.0)	54 (74.0)
Single antiplatelet therapy	13 (35.1)	11 (30.6)	24 (32.9)
Dual antiplatelet therapy	16 (43.2)	21 (58.3)	37 (50.7)
Statins*	13 (35.1)	27 (75.0)	40 (54.8)
Antidiabetics	9 (24.3)	9 (25.0)	18 (24.7)
SGLT2i	4 (10.8)	3 (8.3)	7 (9.6)
Age (years)‡	60.4 ± 7.1	58.7 ± 8.3	59.5 ± 7.7
Total	37 (50.7)	36 (49.3)	73 (100.0)

ACEi = Angiotensin-Converting Enzyme inhibitor. ACS = Acute Coronary Syndrome.
ARB = Angiotensin Receptor Blocker. FH = Family History.
SGLT2i = Sodium-GLucose coTransporter-2 inhibitors.
* χ^2 test, $p < 0.01$.
‡ Data indicate mean ± standard deviation.

abdominal circumference was measured using a calibrated measuring tape, employing anatomical landmarks for accurate determination.

Laboratory analyses

Peripheral blood samples (5 mL) were obtained prior to angiographic procedures following a fasting period of at least 8 hours. A routine complete blood cell count was performed using a Mindray BC-2600 analyzer (China). Analysis of glucose, urea, creatinine, total cholesterol, HDL, triglycerides, and C-reactive protein (CRP) was enzymatically conducted using commercial kits with the BT-3000 auto-analyzer (Biotechnica, Rome, Italy). LDL levels were determined using the Friedewald formula when serum triglyceride levels were below 400 mg/dL. Blood samples were collected in standardized EDTA tubes for cell counting, and serum measurements were performed immediately after collection.

The NLR and PLR were calculated using the formulas absolute neutrophil count/absolute lymphocyte count and absolute platelet count/absolute lymphocyte count, respectively. The systemic immune-inflammation index (SIII) was determined using the formula: absolute platelet count × (absolute neutrophil count / absolute lymphocyte count).[5]

Angiographic analysis

Coronary angiography was performed using the standard Judkins technique, with at least two projections taken for all coronary arteries. Anatomical severity was evaluated qualitatively and quantitatively by two interventional cardiologists using the SYNTAX I score, which was calculated through the virtual platform (www.syntaxscore.com). Results were divided into three categories (SYNTAX < 23, SYNTAX 23-32, and SYNTAX ≥ 33).[6]

Statistical analysis

After data collection, a tabulation sheet was designed to facilitate data entry and analysis. Results were expressed as descriptive measures of central tendency (mean), dispersion (standard deviation), as well as absolute and relative values. The χ-square test was used for evaluation between qualitative variables, the t-test was used for comparisons between quantitative variables, and Pearson's correlation coefficient was used to assess correlation between variables. Additionally, a multiple linear regression analysis was conducted with the SYNTAX score as the dependent variable, using the backward elimination method for variable selection in the model. The alpha level was set at 0.05. All analyses were performed using SPSS version 20 for Windows (Chicago, IL).

RESULTS

Out of the 73 evaluated subjects, 50.7% (n = 37) were male, with a mean age of 59.5 ± 7.7

years. According to the sociodemographic characteristics, the predominant groups were those with secondary education (41.1%; n = 30), urban residence (93.2%; n = 68), sedentary lifestyle (83.6%; n = 61), and ex-smokers (41.1%; n = 30). Regarding medical history, hypertension (83.6%; n = 61) and previous acute coronary syndrome (ACS) (68.5%; n = 50) were the most predominant, with ACS being more frequent in males (men: 83.3% vs women: 54.1%; p < 0.01). ACE inhibitors/ARBs were the most commonly used medications (74%; n = 54), followed by statins and nitrates (54.8%; n = 40), with a higher frequency of use in males for these pharmacological groups *(Table 1)*.

Table 2: Clinical and laboratory characteristics of the sample according to sex.

	Female Mean ± SD	Male Mean ± SD	Total Mean ± SD
BMI (kg/m^2)	28.9 ± 5.3	29.1 ± 7.5	29.0 ± 6.7
Abdominal circumference (cm)	101.7 ± 8.2	100.3 ± 10.1	101.0 ± 9.1
Systolic blood pressure (mmHg)	144.2 ± 19.4	139.8 ± 16.8	142.0 ± 18.2
Diastolic blood pressure (mmHg)	79.5 ± 10.0	82.2 ± 8.8	80.8 ± 9.5
Leukocytes (× 10^3/mm^3)	7.8 ± 1.9	7.5 ± 2.3	7.7 ± 2.1
Neutrophils (× 10^3/mm^3)	4.8 ± 1.4	4.6 ± 1.8	4.7 ± 1.6
Lymphocytes (× 10^3/mm^3)	3.0 ± 0.7	2.9 ± 0.8	2.9 ± 0.8
Platelets (× 10^3/mm^3)	256.6 ± 85.5	306.7 ± 95.6	281.3 ± 93.4
NLR	1.64 ± 0.46	1.63 ± 0.61	1.63 ± 0.53
PLR	91.31 ± 44.7	112.8 ± 46.5	101.9 ± 46.6
SIII	425.0 ± 206.3	515.2 ± 298.7	469.5 ± 258.3
Hemoglobin (g/dL)*	12.1 ± 1.1	13.3 ± 1.2	12.7 ± 1.3
Hematocrit (%)*	37.4 ± 4.3	40.4 ± 4.6	38.9 ± 4.7
Glycemia (mg/dL)	114.6 ± 39.3	117.7 ± 55.5	116.1 ± 47.7
Creatinine (mg/dL)*	0.9 ± 0.2	1.0 ± 0.1	1.0 ± 0.2
Urea (mg/dL)	37.4 ± 13.7	37.7 ± 9.2	37.6 ± 11.6
Total cholesterol (mg/dL)*	186.2 ± 56.3	158.4 ± 44.0	172.5 ± 52.2
LDL-C (mg/dL)*	114.5 ± 52.4	91.6 ± 40.7	103.2 ± 48.1
HDL-C (mg/dL)	45.2 ± 7.0	44.0 ± 6.0	44.6 ± 6.5
Triglycerides (mg/dL)	157.9 ± 108.3	123.5 ± 60.0	140.9 ± 89.0
VLDL-C (mg/dL)	31.1 ± 21.2	24.4 ± 12.6	27.8 ± 17.7
C reactive protein (mg/L), median [P25-P75]	5 [3-10.2]	3.4 [3-5]	4 [3-7.1]
SYNTAX score, median [P25-P75]‡	8 [1-22]	22 [11-39.3]	14 [1-35]
Total	37 (50.7)	36 (49.3)	73 (100.0)

BMI = Body Mass Index. HDL-C = High-Density Lipoprotein Cholesterol. LDL-C = Low-Density Lipoprotein Cholesterol. NLR = Neutrophils-Lymphocytes Ratio. PLR = Platelet-Lymphocytes Ratio. SD = Standard Deviation. SIII = Systemic Immune-Inflammation Index. VLDL-C = Very Low-Density Lipoprotein Cholesterol. * Student's t-test, p < 0.05. ‡ Mann Whitney's U test, p < 0.05.

Table 2 displays clinical and laboratory characteristics by sex. There were no significant differences in mean scores of inflammatory indices between sexes; however, higher levels of hemoglobin, hematocrit, creatinine, and SYNTAX scores were observed in males, while mean total cholesterol and LDL levels were higher in females.

In terms of subject distribution according to the severity of CAD, 28.8% (n = 21) had no CAD; 32.9% (n = 24) had SYNTAX score < 23; 28.8% (n = 21) had SYNTAX score ≥ 33; and 9.6% (n = 7) had SYNTAX score 23-32. When assessing inflammatory indices according to SYNTAX score, higher mean platelet counts (376.1 ± 85.6 × 10^3/mm^3), PLR (144.9 ± 54.7), and SIII (703.2 ± 335.9) were observed in subjects with SYNTAX score ≥ 33 *(Table 3)*.

Figure 1 shows the degree of correlation between inflammatory indices and the SYNTAX score, *Figure 1A* shows no correlation between Syntax score and NLR, likewise a positive correlation between PLR, and the SYNTAX score (r = 0.61; p < 0.01) *(Figure 1B)* and between the SIII and the SYNTAX score (r = 0.55; p < 0.01) *(Figure 1C)*. Finally, a multiple linear regression model was performed, where the SIII was independently most associated with the SYNTAX score (β = 0.64; p < 0.01), with the final adjustment shown in *Table 4*.

DISCUSSION

Atherosclerosis plays a pivotal role in the development and progression of CAD, associated with a low-grade inflammatory response typical of the cardio-metabolic continuum. Elevated levels of inflammatory markers such as CRP, interleukins, and tumor necrosis factor have been reported in subjects with atherosclerotic cardiovascular disease. Furthermore, various

Table 3: Inflammatory indices according to SYNTAX score.

Inflammatory indices	Normal coronary arteries (A) Mean ± SD	SYNTAX Score < 23 (B) Mean ± SD	SYNTAX Score 23-32 (C) Mean ± SD	SYNTAX Score ≥ 33 (D) Mean ± SD	p*
Neutrophils (× 10^3/mm^3)	4.8 ± 1.5	4.6 ± 1.4	4.1 ± 1.0	5.0 ± 2.1	0.60
Lymphocytes (× 10^3/mm^3)	3.1 ± 0.9	2.9 ± 0.7	3.1 ± 0.3	2.8 ± 0.8	0.43
Platelets (× 10^3/mm^3)	244.3 ± 63.6	232.4 ± 71.3	275.6 ± 39.7	376.1 ± 85.6	< 0.01
Neutrophils-lymphocytes ratio	1.56 ± 0.39	1.61 ± 0.49	1.33 ± 0.36	1.84 ± 0.70	0.12
Platelet-lymphocytes ratio	81.9 ± 27.3	85.3 ± 32.9	90.3 ± 16.5	144.9 ± 54.7	< 0.01
SIII	381.5 ± 133.6	372.5 ± 149.5	365.2 ± 102.9	703.2 ± 335.9	< 0.01
Total, n (%)	21 (28.8)	24 (32.9)	7 (9.6)	21 (28.8)	73 (100.0)

SD = Standard Deviation. SIII = Systemic Immune-Inflammation Index.
* ANOVA test.

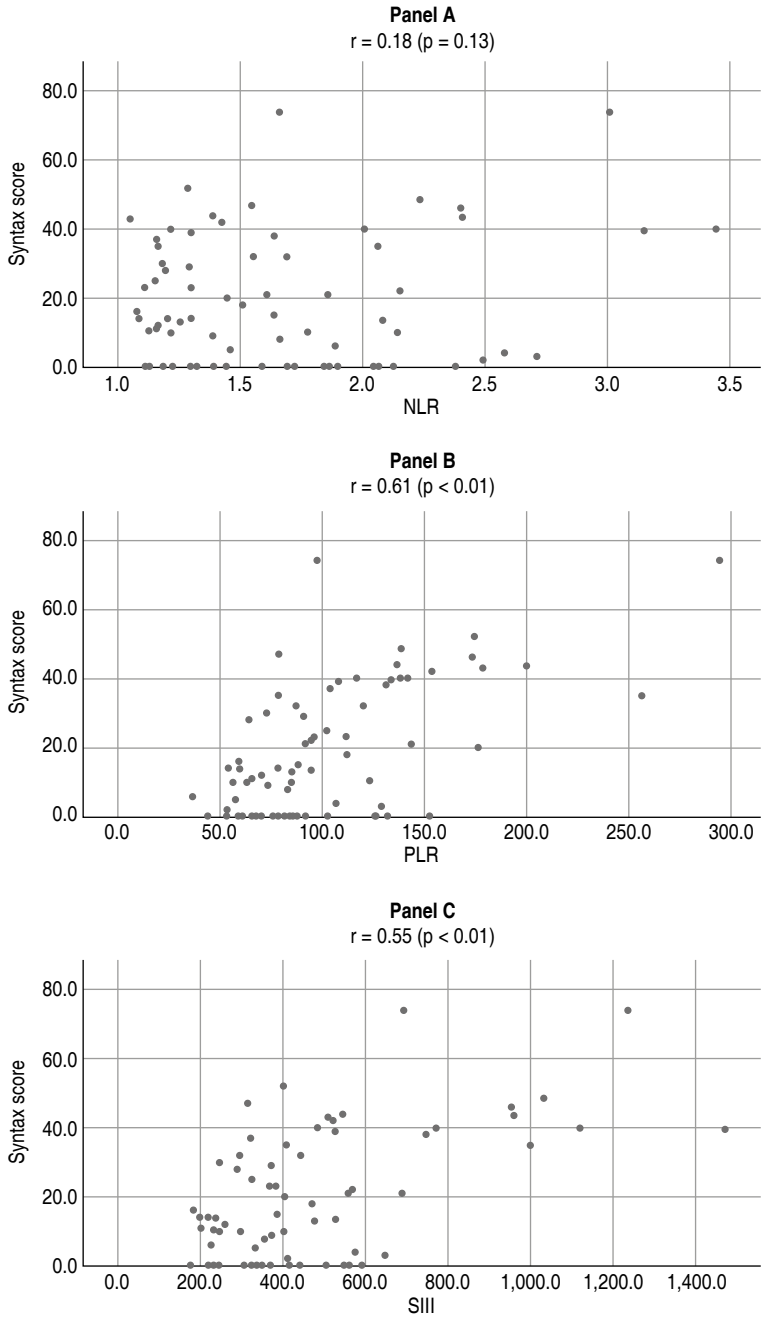
indices derived from cellular biomarkers involved in the inflammatory process and obtained from hematologic values are able to predict severity and outcomes in these patients. This report aims to determine the relationship between inflammatory indices and the severity of chronic CAD in subjects undergoing cardiac catheterization at a specialized cardiovascular institute in Maracaibo, Venezuela.

The key finding of the study is the observed association between the SIII and increased severity of CAD, independent of other risk factors, and showing far superior results than other inflammatory indices. Therefore, the combination of these easily accessible laboratory parameters, such as the three major cellular lines, could potentially serve as a tool to assess inflammatory status in patients with CCS, particularly in primary care settings and outpatient follow-up.

These findings align with those presented by Candemir et al.,[7] who, in a retrospective study of 669 subjects in Turkey, demonstrated a positive correlation between the SIII and the SYNTAX score (Rho: 0.630, p = 0.001). In their multivariate analysis, the SIII emerged as an independent predictor of high SYNTAX score (Odds Ratio: 1.004; 95% CI: 1.001-1.007; p = 0.015). Similarly, in 5,602 patients undergoing percutaneous coronary intervention, Yang et al.,[8] found that an SIII value ≥ 694.3 was independently associated with an increased risk of cardiac death (HR: 2.02; 95% CI: 1.43-2.86), non-fatal myocardial infarction (HR: 1.42; 95% CI: 1.09-1.85), non-fatal stroke (HR: 1.96; 95% CI: 1.28-2.99), and major cardiovascular events (HR: 1.65; 95% CI: 1.36-2.01). In addition, Ma & Li,[9] using multivariate logistic regression analysis of NHANES data from 2009-2018, observed that higher SIII levels could be associated with a greater incidence of CAD, particularly in men.

Remarkably, the other inflammatory index associated with CAD severity was PLR, albeit only in univariate analysis, highlighting the role of platelets in the atherosclerotic process as an essential element in prothrombotic phenomena through interactions between the endothelium and other components of the inflammatory cascade.[10] In contrast, NLR did not show a relationship with CAD severity in our study. This finding may be attributed to the chronic nature of the evaluated cardiovascular disease, with reduced plaque vulnerability and consequently lesser involvement of neutrophils in this stage of the disease's natural history. Nonetheless, these findings differ from those reported by Rodríguez et al.,[11] who analyzed

511 consecutive patients undergoing coronary angiography at the Hermanos Ameijeiras Hospital (Cuba) and found that an elevated neutrophil-to-lymphocyte ratio prior to invasive coronary angiography was associated with greater severity of coronary artery disease.



NLR = Neutrophils-Lymphocytes Ratio. PLR = Platelet-Lymphocytes Ratio. SIII = Systemic Immune-Inflammation Index.

Figure 1: Correlation between inflammatory indices and SYNTAX score.

It is imperative to highlight that this association between the previous indices, specifically the SIII, with the severity of CAD is independent of other proinflammatory factors such as CRP and lipid variables such as LDL. Therefore, it would be interesting to know the anti-inflammatory efficacy of pharmacological agents with the SIII, in particular regarding medium to long-term outcomes. Prime candidates in this regard would be monoclonal antibodies, enzyme regulators, or colchicine. Such data would allow them to standardize their determination and routine evaluation not only from the practical standpoint but also in clinical research.

Regarding population characteristics, it is essential to note that a considerable amount of the subjects were not under optimal pharmacological treatment, as no pharmacologic family had a usage rate higher than 80%, which translates to mean values of certain variables and risk factors above the suggested goal for patients with CCS. The above demonstrates the imperative need to encourage secondary prevention strategies and to emphasize the relevance of adequate treatment adherence from the patient's perspective to decrease recurrent events and, thus, higher morbimortality and disability rates. Optimal intervention in diverse cardiometabolic risk factors could make a positive impact on low-grade inflammation and, therefore, the evaluated inflammatory indices.[12-14]

Among the study limitations, the most notable was the sample size, which complicates the generalization of results to the entire population, and the cross-sectional design, which does not allow the establishment of causality. Additionally, the lack of analysis of other more specific inflammatory mediators, such as interleukins and tumor necrosis factor, due to their limited availability in our context is another constraint.

CONCLUSIONS

The SIII was associated with a higher degree of severity of chronic CAD according to the SYNTAX score, independent of other inflammatory and lipid factors in a group of Venezuelan patients. Additionally, subjects

Table 4: Linear regression model for inflammatory indices and SYNTAX score.

	Dependent variable: SYNTAX score (Log)*			
	Non-standardized β	Standard error	Standardized β	p
NLR	−13.3	3.6	−0.38	0.09
PLR	0.7	0.4	0.17	0.07
SIII	0.5	0.1	0.64	< 0.01

NLR = Neutrophils-Lymphocytes Ratio. PLR = Platelet-Lymphocytes Ratio. SIII = Systemic Immune-Inflammation Index.
* Model created using the backwards method selection, adjusted for age, nitrates usage, ACE/ARB usage, single antiplatelet therapy usage, glycemia, creatinine, LDL, triglycerides, C-reactive protein (log).

with greater CAD severity showed higher average SIII, PLR, and platelet levels, correlating directly with the SYNTAX score. Therefore, it is important to routinely assess inflammatory indices such as the SIII and PLR in patients with chronic CAD, as they may be linked to greater disease severity, allowing for the selection of subjects for more intensive anti-ischemic management. This also ensures appropriate antithrombotic treatment tailored to each patient's characteristics, highlighting the pivotal role of platelets in inflammatory processes.

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Declaration of patient consent: the authors confirm that they have complied with the relevant workplace protocols for the use of patient data. Furthermore, the authors confirm that the patient has been duly informed and has provided written informed consent for the publication of their images and other clinical information in the journal without any identifying details in order to safeguard their right to privacy. Additionally, the authors attest that no form of generative artificial intelligence was employed in the preparation of this manuscript or the creation of figures, graphs, tables, or their corresponding captions or legends.

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Observational Registry for Cardiac Ablation in Atrial Fibrillation in Mexico (ORCA-AF)

Registro Observacional Mexicano para Ablación Cardiaca en Fibrilación Auricular (ROMA-FA)

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Keywords:
atrial fibrillation, pulmonary vein isolation, radiofrequency, antiarrhythmic treatment, CARTO 3.

Palabras clave:
fibrilación auricular, aislamiento de venas pulmonares, radiofrecuencia, tratamiento antiarrítmico, CARTO 3.

ABSTRACT

Introduction: Atrial Fibrillation (AF) is a prevalent chronic arrhythmia that affects approximately 4% of the Mexican population. AF correlates with an elevated risk of myocardial infarction, increased rate of hospitalizations, and mortality. In recent years, radiofrequency Pulmonary Vein Isolation (PVI) for cardiac ablation has emerged as the frontline intervention for symptomatic AF. **Material and methods:** a retrospective observational study was conducted at General Hospital «Tacuba» ISSSTE to evaluate the clinical characteristics and antiarrhythmic management of patients with AF undergoing PVI utilizing the CARTO 3 three-dimensional electromagnetic mapping system with follow-up assessments conducted at 3, 6, and 12 months post-PVI. **Results:** the median time for patients to discontinue antiarrhythmic treatment post-PVI was three months. Amiodarone was the most prescribed antiarrhythmic drug. A significant reduction in the percentage of patients on antiarrhythmic treatment was observed post-PVI. The study showed a 95.9% success rate for radiofrequency PVI cardiac ablation procedures. **Conclusion:** the study suggests that radiofrequency PVI is an effective and safe treatment for AF in protocolized patients, where ablative therapy has shown the most significant impact on disease control and clinical and likely economic positive effects in reducing the disease burden.

RESUMEN

Introducción: *la fibrilación auricular (FA) es la arritmia crónica más común que afecta aproximadamente a 4% de la población mexicana. La FA se asocia con un mayor riesgo de infarto miocárdico, hospitalizaciones y muerte. En los últimos años el aislamiento de venas pulmonares (AVP) con radiofrecuencia, como parte del manejo ablativo de la enfermedad, se ha establecido como el tratamiento de primera línea para pacientes con FA sintomática.* ***Material y métodos:*** *se realizó un estudio observacional retrospectivo en el Hospital General «Tacuba» ISSSTE para evaluar las características y el tratamiento antiarrítmico de los pacientes con FA sometidos a AVP con radiofrecuencia con sistema de mapeo tridimensional electromagnético CARTO 3 a 3, 6 y 12 meses de seguimiento post-AVP.* ***Resultados:*** *el tiempo promedio para descontinuar el tratamiento antiarrítmico post-AVP fue de tres meses. La amiodarona fue el tratamiento antiarrítmico más prescrito. Se observó una reducción significativa de tratamiento antiarrítmico post-AVP. El estudio demostró que el procedimiento de ablación cardiaca mediante AVP con radiofrecuencia es efectiva con una tasa de éxito del 95.9%.* ***Conclusiones:*** *el estudio sugiere que el procedimiento de ablación cardiaca mediante AVP con radiofrecuencia de alto poder es un tratamiento exitoso y seguro para el control de la FA, en los pacientes debidamente protocolizados y en los que la terapia ablativa ha demostrado mayor impacto en control de la enfermedad y un impacto positivo en la reducción de la carga clínica y seguramente económica de la enfermedad.*

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Abbreviations:
ACT = Activated Clotting Time
AF = Atrial Fibrillation
AT = Atrial Tachycardia
LAD = Left Atrial Diameter
LVEF = Left Ventricular Ejection Fraction
NYHA = New York Heart Association
PRIS = Propofol Infusion Syndrome
PVI = Pulmonary Vein Isolation
SD = Standard Deviation

INTRODUCTION

Atrial Fibrillation (AF) stands as the most prevalent sustained chronic arrhythmia globally, affecting approximately 1-2% of the worldwide population[1,2] and approximately 4% of Mexico's population.[3] Its incidence is notably higher among men and escalates with advancing age, with a discernible rise in occurrence observed from age 40 onwards. Moreover, AF's prevalence amplifies in tandem with predisposing conditions, including obesity, type 2 diabetes, systemic arterial hypertension, obstructive sleep apnea, coronary artery disease, and habits such as tobacco or alcohol consumption.[1,4] AF correlates with an elevated risk of myocardial infarction, heightened hospitalization rates, and increased mortality.[5,6] The aging demographic and improved survival rates amidst chronic ailments further forecast a surge in AF prevalence in the forthcoming years,[1,4] accentuating the need for intensified research endeavors aimed at comprehending this pathology and refining its therapeutic modalities.

In recent years, Pulmonary Vein Isolation (PVI) via radiofrequency ablation has emerged as the frontline intervention for managing symptomatic AF –both paroxysmal and persistent– particularly in refractory or intolerance to antiarrhythmic pharmacotherapy.[2,7] Despite the expanding use of PVI with radiofrequency in clinical practice, there is scarce epidemiological data on AF and its treatment landscape in the Mexican population.[3,6,8] Additionally, no comprehensive records documenting patient outcomes after the ablation procedure are available.

A retrospective observational registry was undertaken at the Cardiac Electrophysiology Service of the General Hospital «Tacuba» of the «Instituto de Seguridad Social y Servicios de los Trabajadores del Estado» (ISSSTE) to bridge this knowledge gap. Patient referrals to this center originate from primary care medical units through routine referral systems or direct patient presentations facilitated through institutional channels. Cases were meticulously evaluated, and candidates deemed suitable for ablation were scheduled for PVI employing a radiofrequency catheter equipped with a contact sensor and the CARTO 3 electromagnetic 3D mapping system.

Consequently, the primary objective of this investigation was to delineate and assess the clinical characteristics and antiarrhythmic management of patients afflicted with AF undergoing PVI utilizing the CARTO 3 electromagnetic 3D mapping system with follow-up assessments conducted at 3, 6, and 12 months post-PVI.

MATERIAL AND METHODS

An observational, longitudinal, retrospective, and single-center study was carried out, including all patients with paroxysmal or persistent AF undergoing PVI with radiofrequency between August 2017 and February 2022 at the Cardiology Service of the General Hospital «Tacuba» ISSSTE.

A review of the medical records of all patients was conducted, and relevant information was recorded in a structured database. The collected information included:

1. Sociodemographic and clinical data: age, sex, date of AF diagnosis, type of AF, presence of arterial hypertension, Left Ventricular Ejection Fraction (LVEF), Left Atrial Diameter (LAD), and New York Heart Association (NYHA) functional classification.
2. Specific data on PVI include the date of the procedure, type of sedation, average power used in the procedure, complications during the procedure, and length of hospital stay.
3. Clinical data at 3, 6, and 12 months post-PVI: prescription of antiarrhythmic treatment, date of last intake of antiarrhythmic therapy (if any), transient ischemic attack, acute myocardial infarction, heart failure, ischemic stroke, recurrence of AF/atypical

flutter/Atrial Tachycardia (AT), typical flutter, resumption of antiarrhythmic treatment, progression from paroxysmal to persistent AF, admission to the Emergency Department, reintervention, and death.

Recurrences were distinguished as follows:

1. AF: appearance of arrhythmia characterized by atrial cycle length < 200 bpm, non-discernible P-wave, and variable RR interval in the absence of atrioventricular block, of sufficient duration to be detected in a surface electrocardiogram or at least 30 s in a Holter recording.[9]
2. Atypical flutter: appearance of re-entrant arrhythmia characterized by continuous, uniform, and regular atrial electrocardiographic pattern, with frequency ≥ 240 bpm (re-entrant tachycardia) related to PVI.[10]
3. AT: appearance of arrhythmia characterized by the electrocardiographic pattern with well-defined P-waves separated by isoelectric lines with frequency ≤ 240 bpm.[10]

Recurrence of AF/atypical flutter/AT was only considered if reported after 3 months post-PVI (6- and 12-month follow-up).

Post-PVI events considered were as follows: resumption of antiarrhythmic treatment, progression from paroxysmal to persistent AF, recurrence of AF/atypical flutter/AT, admission to the Emergency Department, reintervention, typical flutter, transient ischemic attack, acute myocardial infarction, heart failure, ischemic stroke, and death.

Based on the collected information, the time elapsed between the diagnosis of AF and the performance of PVI and between the procedure and the last intake of antiarrhythmic treatment was calculated.

PVI procedure

Before the procedure, the patient was referred to the Hospital in two possible ways: routine and personalized.

The most common routine referral was made through an institutional medical referral system, where the patient entered the Health System through evaluation by the general practitioner in a primary care Medical Unit, where symptoms were documented, and diagnostic studies were extended to corroborate the presence of AF. Subsequently, having these studies, the patient was sent to the second level of care, provided by the Cardiology and Cardiac Electrophysiology services, where a specific diagnostic protocol was performed with ambulatory electrocardiographic monitoring and echocardiogram if required. Once the diagnosis of AF was confirmed and the criteria to be a candidate for ablation procedure were met, the patient was scheduled for PVI.

In the personalized referral, data of the patient with a confirmed diagnosis was sent to the institutional email of the Electrophysiology Service of the General Hospital «Tacuba» ISSSTE, which analyzed the case and contacted the patient to provide a date for arrhythmia clinic evaluation with an average attention time of one week. Complementary studies were evaluated, and if the patient was a candidate for an ablation procedure, the patient was scheduled for PVI.

Unlike other protocols, patients did not discontinue anticoagulant or antiarrhythmic treatment in the pre-procedure period *(Figures 1 and 2)*.

Procedures were performed under general sedation. A bilateral femoral vein approach was performed: Sterile drapes were placed before asepsis and antisepsis of both inguinal regions, and 2% lidocaine was infiltrated into the areas of interest. Two venous punctures were performed in the right groin and a single venous puncture in the left groin, placing vascular accesses of 8 Fr, 8 Fr, and 10 Fr, respectively. Through the 8 Fr sheath on the right side, a decapolar catheter was introduced into the coronary sinus, and through the 10 Fr sheath on the left side, an intracardiac ultrasound probe was introduced for intracardiac mapping. The 8 Fr vascular access was exchanged for a preformed FastCath sheath. Subsequently, a transeptal puncture was performed with a BRK needle under continuous visualization by intracardiac echocardiogram (ICE). Once the transeptal puncture was performed, unfractionated heparin was administered at 100 IU per kg of body weight, which was

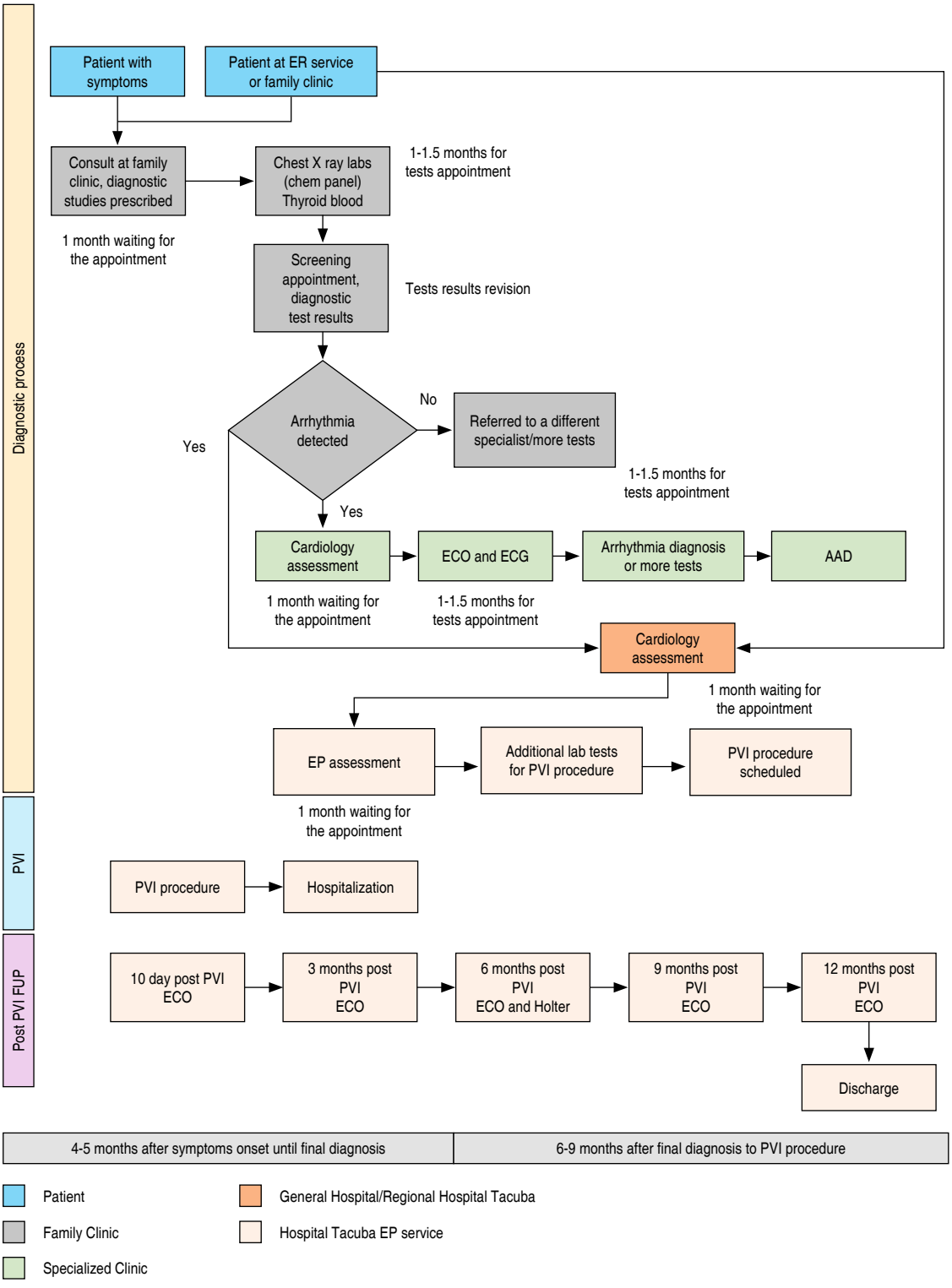

Figure 1: Patient pathway ISSSTE west zone.
AAD = antiarrhytmic drug. ECG = electrocardiogram, ECO = echocardiogram. EP = electrophysiology. ER = emergency room. FUP = follow up. PVI = Pulmonary Vein Isolation.

adjusted to maintain Activated Clotting Time (ACT) between 300-350 s during the procedure, every 30 min. The transeptal puncture sheath was exchanged for a bidirectional guiding sheath (MOBICATH® or CARTO VIZIGO®). A PENTARAY® multielectrode mapping catheter was introduced, and a voltage map was performed to document the connection of the pulmonary veins and fibrotic areas in the atrial body. The PENTARAY® catheter was then exchanged for a radiofrequency ablation catheter, THERMOCOOL SMARTTOUCH® or THERMOCOOL SMARTTOUCH SF®, and pulmonary vein isolation was performed. In cases where fibrosis was observed in the posterior wall, isolation of that zone (BOX technique) was considered. Finally, a voltage map was performed to document the isolation of the four pulmonary veins post-procedure and stimulation within each pulmonary vein to confirm the exit block. The approximate duration of each procedure was two hours. At the same time, fluoroscopy time varied between 1.5-2.5 min, and the ablation index was 420 anterior and 400 posterior in patients who used the Ablation Index module of CARTO 3.

Following the PVI, the patient was transferred to the Coronary Care Unit, where they were monitored, and vascular access was evaluated continuously for 21 hours by nursing staff and cardiologists. If the patient did not present procedure complications during this period, they were discharged home with precise instructions (look for bleeding at the puncture site, changes in lower limb coloration, dyspnea, chest pain, and palpitations, among others). If complications occurred during home follow-up, the patient was instructed to visit the emergency department.

Suspension of antiarrhythmic treatment was indicated 3 months post-PVI and an appointment was scheduled for follow-up evaluation by the Cardiac Electrophysiology Service, including 24-hour electrocardiographic monitoring (24-hour Holter). Anticoagulant treatment was discontinued at the 3-month follow-up visit based on electrocardiographic monitoring results, symptomatology (absence of palpitations for more than 30 s), or electrocardiogram. The patient was also evaluated at 6 and 12 months post-PVI.

Statistical analysis

The statistical analysis was performed using R software (version 4.2.2).[11]

Quantitative variables with normal distribution were described as mean ± Standard Deviation (SD), and variables with non-normal distribution were expressed as median (minimum-maximum). Data normality was determined using the Shapiro-Wilk test. Qualitative variables were described as absolute and relative frequencies according to the number of patients with recorded information. Statistical

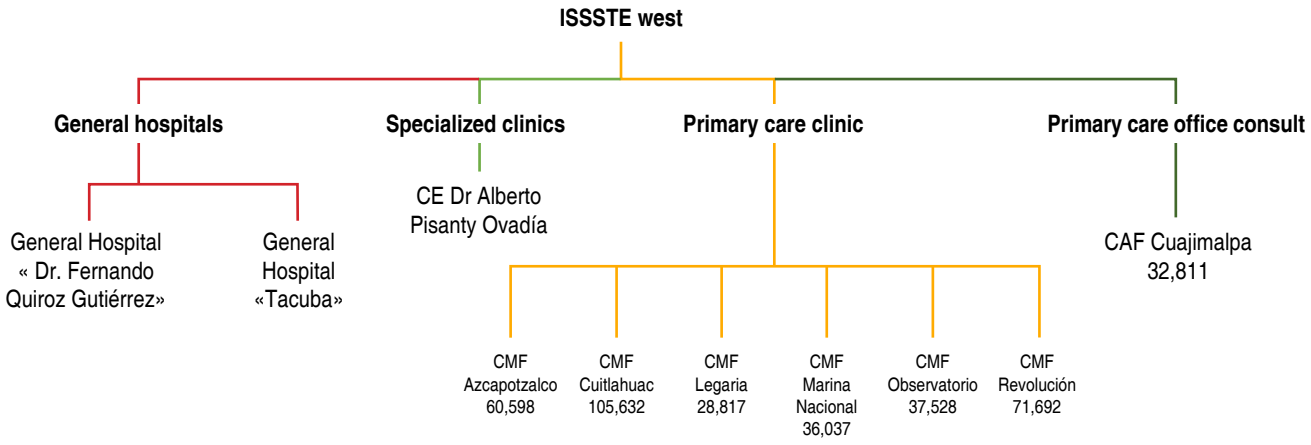

Figure 2: Medical division ISSSTE updated in 2021. Health regulatory authority.
CAF = consultorio de atención familiar. CE = clínica de especialidades. CMF = clínica médica familiar.

Table 1: Baseline characteristics. N = 74.

Variables	n (%)
Sociodemographic characteristics	
Age (years)	64.0 [27.0-84.0]
Gender	
Male	47 (63.5)
Female	27 (36.5)
Clinical characteristics	
Time since AF diagnosis (months)	6.1 [0.1-185.7]
AF type	
AF paroxysmal	53 (71.6)
AF persistent	21 (28.4)
CV risk factors	
Hypertension	32 (43.2)
NYHA (N = 71)	
Class I	42 (60.0)
Class II	25 (35.7)
Class III	3 (4.3)
Left atrial diameter (mm) (N = 71)	45.6 ± 7.2
LVEF (%)	60.0 [25.0-77.0]

Qualitative variables are shown as n (%), mean ± standard deviation for quantitative variables with normal distribution or median [min-max] for non-normal quantitative variables distribution.
AF = Atrial Fibrillation. LVEF = Left Ventricular Ejection Fraction. NYHA = New York Heart Association.

comparisons of qualitative variables were made using the Cochran Q test for comparing three follow-up points or the McNemar test for comparing two follow-up points. A p-value of ≤ 0.05 was considered significant.

The total rate of post-PVI events at 12 months was calculated by dividing the total number of patients who presented resumption of antiarrhythmic treatment, progression from paroxysmal to persistent AF, recurrence of AF/atypical flutter/AT, admission to the Emergency Department, reintervention, typical flutter, transient ischemic attack, acute myocardial infarction, heart failure, ischemic stroke, and/or death during the entire follow-up period by the total number of patients included in the study.

The success rate of PVI at 12 months was calculated by dividing the total number of patients without recurrence of AF/atypical flutter/AT during the entire follow-up period by the total number of patients included in the study.

RESULTS

Between August 2017 and February 2022, at the Cardiology Service of the General Hospital «Tacuba» ISSSTE, 76 patients underwent cardiac ablation procedures using PVI with radiofrequency to treat paroxysmal or persistent AF. Two patients were excluded from the study: one patient died during the follow-up period due to causes unrelated to AF or PVI, and another patient had auricular involvement of more than 90% during intracardiac mapping, leading to the diagnosis of progression from persistent to permanent AF, and did not undergo the PVI procedure. Statistical analysis was conducted with information from 74 patients.

Patients

The baseline sociodemographic and clinical characteristics of the 74 patients included in the study are presented in *Table 1*. The median age of the patients was 64 years (27-84 years), and 63.5% were men. Regarding AF, 71.6% of patients had paroxysmal AF, and 28.4% had persistent AF. 43.2% of patients had arterial hypertension. Only 71 patients had records of the NYHA functional classification of heart failure, of which 60% were assigned to class I, 35.7% to class II, and 4.3% to class III. The median LVEF was 60% (25.0-77.0%), and the mean LAD, reported for only 72 patients, was 45.6 ± 7.2 (SD).

Table 2 presents the characteristics of the PVI procedure. The time elapsed between the diagnosis of AF and the performance of PVI was obtained for all 74 patients, with a median of 6.1 months (0.1-185.7 months). All patients underwent general sedation during the procedure, and the power used was 45.0 Watts (W) (36.0-53.0 W). Five patients (6.8%) experienced complications during the procedure, one patient (1.4%) experienced propofol infusion syndrome (PRIS), and four patients experienced vascular complications. These five patients remained hospitalized for more than 24 hours.

Follow-up post-PVI

Table 3 shows the post-PVI events experienced by patients at 3, 6, and 12 months of follow-up. The total rate of post-PVI events at 12 months

was 6.8% (5 out of 74). The reported events are described below.

At the 3-month follow-up, one patient (1.4%) experienced an ischemic stroke, in addition to typical flutter, leading to admission to the Emergency Department and undergoing reintervention of cardiac ablation using PVI. At the 6-month follow-up, one patient (1.4%) presented typical flutter, leading to admission to the Emergency Department and undergoing reintervention of cardiac ablation using PVI; one patient (1.4%) met criteria for recurrence in AF; and another patient (1.4%) discontinued antiarrhythmic treatment at 3 months post-PVI, however, had to resume it during the 6-month follow-up period, and at the 12-month follow-up, presented typical flutter. At the 12-month follow-up, two more patients (2.7%) experienced recurrence in AF, one of whom had already been classified with recurrence since the 6-month follow-up.

Regarding the procedure's success, 72 out of 74 patients did not experience recurrence of AF/atypical flutter/AT post-PVI, resulting in a procedure success rate of 97.3% at 12 months *(Table 4)*.

Table 2: Characteristics of pulmonary vein isolation with radiofrequency.

Variables	n (%)
Sedation	
General	74 (100.0)
Average power used during the procedure (W)	45.0 [36.0-53.0]
Complications during the procedure	5 (6.8)
Propofol induced syndrome	1 (1.4)
Vascular complications	4 (5.4)
Post-procedure hospitalization stays	
24 h	69 (93.2)
48 h	5 (6.8)

Qualitative variables are shown as n (%) qualitative variables or median [min-max] for quantitative variables with non-normal distribution.

Sinus rhythm and antiarrhythmic drug treatment post-PVI

The number of individuals in sinus rhythm and the use of antiarrhythmic drug treatment are shown in *Table 4*. The percentage of patients in sinus rhythm at 12 months post-PVI was 95.9% (71 out of 74).

Table 3: Follow-up findings post pulmonary vein isolation.

Variables	3 months ± 1 month n (%)	6 months ± 1 month n (%)	12 months ± 1 month n (%)
Resumption of antiarrhythmic treatment	0 (0)	1 (1.4)	0 (0)
AF progression paroxysmal to persistent	0 (0)	0 (0)	0 (0)
AF recurrence*	–	1 (1.4)	2 (2.7)
Atypical flutter recurrence*	–	0 (0)	0 (0)
Atrial tachycardia recurrence*	–	0 (0)	0 (0)
ER service admission	1 (1.4)	1 (1.4)	0 (0)
Reintervention	1 (1.4)	1 (1.4)	0 (0)
Typical flutter	1 (1.4)	1 (1.4)	1 (1.4)
Transient ischemic attack	0 (0)	0 (0)	0 (0)
MI	0 (0)	0 (0)	0 (0)
Heart failure	0 (0)	0 (0)	0 (0)
Ischemic stroke	1 (1.4)	0 (0)	0 (0)

The information is shown as n (%), stroke, AF, and atrial tachycardia.
AF = atrial fibrillation. ER = emergency room. MI = myocardial infarction.
* Was considered as recurrence only if reported in the 6- and 12-months follow-up.

Table 4: Sinus rhythm and antiarrhythmic drug treatment post-PVI.

Variables	3 months ± 1 month n (%)	6 months ± 1 month n (%)	12 months ± 1 month n (%)
Subjects in sinus rhythm	74 (100.0)	74 (100.0)	71 (95.9)
Subjects with antiarrhythmic treatment	74 (100.0)	30 (40.5)	15 (20.3)
Antiarrhythmic treatment			
Amiodarone	63 (85.1)	23 (76.7)	12 (80.0)
Propafenone	8 (10.8)	5 (16.7)	2 (13.3)
Dronedarone	1 (1.4)	1 (3.3)	0 (0)
Metoprolol	2 (2.7)	1 (3.3)	1 (6.7)

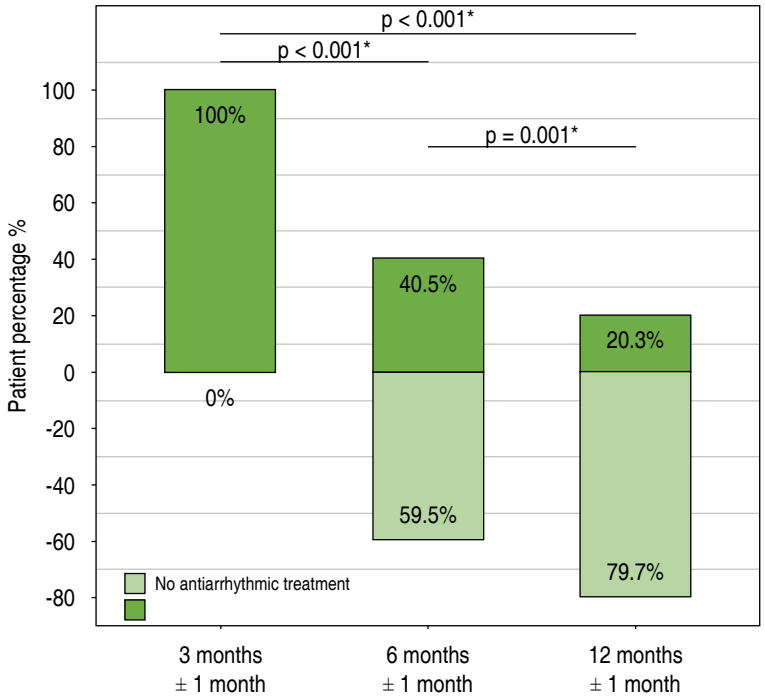

Figure 3: Difference in the percentage of patients with antiarrhythmic treatment post-PVI. The image shows how the percentage of patients with antiarrhythmic treatment decreased after 3, 6, and 12 months of post-PVI follow-up. The p-values were calculated using the McNemar test and adjusted using the FDR method for multiple comparisons.
PVI = Pulmonary Vein Isolation. FDR = False Discovery Rate.
* Statistically significant value, $p \leq 0.001$.

The use of antiarrhythmic drug treatment was recorded for all 74 patients included in the study. The therapy was definitively discontinued in sixty patients and did not resume, with a median time of 3 months (1.6-10.6 months). Of the remaining 14 patients, in one patient, antiarrhythmic drug treatment was discontinued at 3 months post-PVI. However, treatment had to be resumed after approximately four months (at the 6-month post-PVI follow-up), while in the other 13 patients, treatment was not discontinued during the follow-up period.

The percentage of patients with antiarrhythmic drug treatment significantly changed at the three follow-up points (Cochran's Q test, $p < 0.001$), progressively and significantly decreasing between three and six months post-PVI (McNemar's test, adjusted $p < 0.001$), and 12 months post-PVI (McNemar's test, adjusted $p < 0.001$, compared to 3 months; McNemar's test, adjusted $p = 0.001$, compared to 6 months) as shown in *Table 4 and Figure 3*. The most used drug during the follow-up period was amiodarone (76.7-85.1%), followed by propafenone (10.8-16.7%), dronedarone (0-3.3%), and metoprolol (2.7-6.7%), as shown in *Table 4*. Only one patient was recorded to be on a combination of two different antiarrhythmic drugs (metoprolol and amiodarone) at the 3-month follow-up.

DISCUSSION

The General Hospital «Tacuba» of the ISSSTE is a public sector hospital where the Electrophysiology Service was established recently, starting its functions in 2017. Initially, the service was characterized by low-risk procedures using conventional tools (without three-dimensional mapping, using polygraphy and fluoroscopy) with low productivity. In 2018, electroanatomic

mapping tools (CARTO 3) were obtained, allowing the first procedure of catheter ablation with Pulmonary Vein Isolation (PVI) to be performed in the Service. Although productivity was low during that year, it increased considerably by 2019. However, with the arrival of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, treatment for patients with Atrial Fibrillation (AF) was limited in the Service due to the prioritization of coronavirus disease 2019 (COVID-19) patients, as was the case across the country, with normal functions resuming by late 2021.

Since 2019, efforts have been made to establish a structured protocol for the rapid and effective care of referred patients with AF, which has been improved over the years based on hospital experience. This experience includes, particularly in our service, the high rate of referred patients from primary care units and a low rate of first-contact patients in the hospital's Emergency Department.

Considering the growing experience in AF treatment, the fact that radiofrequency catheter ablation with PVI has become a standard treatment for this condition,[12] and the lack of studies evaluating the progression of patients during and after the procedure in Mexico,[8,13] a retrospective registry was decided upon.

It is known that AF is the most common sustained chronic arrhythmia worldwide, with a prevalence higher in men and increasing proportionally with age.[1,6,14] These epidemiological data are reflected in the present registry, where the median age of the patients was 64 years, and 63.5% were men. Additionally, 43.2% of the patients had hypertension, a disease that, due to its high prevalence in the population, is considered the primary cardiovascular risk factor for the development of AF.[1,14,15]

Catheter ablation with PVI has become a standard treatment for AF. The success rate of this procedure depends directly on the timing of application; in other words, the earlier the procedure is performed, the better the outcome. However, in Mexico's healthcare context, the prolonged time between diagnosis and referral for catheter ablation with PVI continues to be a barrier to AF control. In our unit, the referral time was an average of 6.1 months (0.1 and 185.7 months), mainly due to the lack of timely referral to perform the procedure. Addressing this need, the Cardiac Electrophysiology Service has been structuring a protocol for rapid reference and evaluation of candidates over the years to shorten the time between diagnosis and the performance of catheter ablation with PVI.

However, there are other significant barriers to care, such as the limited number of specialists in cardiac electrophysiology and the limited availability of the Hemodynamics room, limiting the possibility of treating patients with AF.

Regarding the complications of the catheter ablation with the PVI procedure, five patients with complications during the procedure were reported. One patient had Propofol infusion syndrome (PRIS); while propofol is one of the most used anesthetics in ablation procedures,[16] this syndrome is a rare complication and not directly related to AF[17] or the PVI technique. The other four (5.4%) patients who required hospitalization for more than 24 hours had vascular complications, specifically hematomas, a percentage like that reported in other studies between 2-6%.[18] In all five cases, the patients remained hospitalized for 48 hours post-PVI and were discharged after that time.

AF is associated with a fivefold increased risk of ischemic stroke, a threefold increased risk of heart failure, an increased risk of cognitive impairment (dementia), prolonged hospitalization, higher healthcare costs, and increased mortality. Therefore, the main objective of catheter ablation with PVI for the treatment of AF is to improve the patient's quality of life and reduce the risks and costs associated with managing the disease (use of antiarrhythmic drugs and necessary medical consultations due to AF control).[9,18-21]

In this regard, our experience suggests that catheter ablation with PVI is a safe procedure for treating AF, with a post-PVI event rate of 6.8%, similar to that reported in other studies where it ranges between 3-6%.[22-26] The post-PVI events reported were the resumption of antiarrhythmic treatment, recurrence of AF, typical flutter, ischemic stroke, admission to the Emergency Department, and reintervention of the ablation procedure. No deaths related to AF or the procedure were reported.

Furthermore, it was observed that catheter ablation with PVI is an effective procedure for treating AF, with a success rate of 97.3%, similar to previous values reported between 74-91%.[27-29] Only two patients experienced AF recurrence: one had recurrence at 6 and 12 months post-PVI, while the other only had recurrence at 12 months post-PVI.

On the other hand, 95.9% of the patients remained in sinus rhythm at 12 months post-PVI. Sinus rhythm loss was observed in three patients. One of these patients resumed their antiarrhythmic treatment at 6 months post-PVI and subsequently presented typical flutter at the 12-month follow-up, while another had AF recurrence at the 12-month follow-up.

The median time for patients to discontinue antiarrhythmic treatment after PVI was three months, ranging from 1.6 to 10.6 months. Typically, at our institution, antiarrhythmic treatment is discontinued 3 months after PVI.

A significant decrease in the percentage of patients on antiarrhythmic treatment was observed, indicating that cardiac ablation via PVI reduces the use of antiarrhythmic drugs for AF treatment.[30-32]

Finally, as a result of the extensive and growing experience in AF treatment at the Cardiac Electrophysiology Service of the General Hospital "Tacuba" of the ISSSTE, as well as findings from this study, measures have been initiated to disseminate knowledge on the comprehensive and timely management of AF patients to Family Medicine Units. These measures include the implementation of in-person or online talks with primary care physicians and subspecialists, focusing on diagnostic methods, indications, and treatment therapies, aiming to shorten diagnostic periods and better profile patients suitable for PVI cardiac ablation procedures. Additionally, there is an intention to set up patient information modules in outpatient waiting areas, explaining the concept of AF, its symptoms, and treatment to raise public awareness about the disease and promote timely treatment.

Limitations

This was a retrospective observational study conducted at a single center involving patients of varying ages diagnosed with paroxysmal or persistent AF undergoing PVI. Before the PVI procedure, a protocol was established and followed to determine patient suitability for ablative therapy based on echocardiographic analysis. Despite adhering to this protocol, the SARS-CoV-2 pandemic and related prevention measures were the primary limitations for conducting this retrospective study, as in some cases, it was not feasible to carry out in-person follow-up of patients undergoing PVI in the Cardiology Service, resulting in a lack of close monitoring and non-compliance with post-PVI antiarrhythmic and/or anticoagulant treatment suspension protocols. However, patients were followed up personally, with variations in timing, but compliance was achieved in most cases.

CONCLUSIONS

The authors confirm they have complied with the relevant workplace protocols for patient data use. Furthermore, the authors confirm that the patient has been duly informed and provided written informed consent to publish their images and other clinical information in the journal without identifying details to safeguard their right to privacy. Additionally, the authors attest that no form of generative artificial intelligence was employed in preparing this manuscript or creating figures, graphs, tables, or corresponding captions or legends.

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Declaration of confidentiality and patients consent: the authors confirm they have complied with the relevant workplace protocols for patient data use. Furthermore, the authors confirm that the patient has been duly informed and provided written informed consent to publish their images and other clinical information in the journal without identifying details to safeguard their right to privacy. Additionally, the authors attest that no form of generative artificial intelligence was employed in preparing this manuscript or creating figures, graphs, tables, or corresponding captions or legends.

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Coronary artery to right pulmonary artery fistula in an adolescent

Fístula coronaria a la rama derecha de la arteria pulmonar en un adolescente: reporte de caso

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Keywords:
coronary fistula, right coronary artery, color Doppler echocardiography, multidetector-row computed tomography, right branch of the pulmonary artery.

Palabras clave:
fistula coronaria, arteria coronaria derecha, ecocardiografía Doppler color, tomografía computada multidetector, rama derecha de la arteria pulmonar.

ABSTRACT

Coronary artery fistulas (CAF) represent a rare category of congenital anomalies that are frequently underdiagnosed due to the absence of early-life symptomatology. Most cases of CAF are incidentally discovered during imaging examinations conducted for unrelated medical issues. Given the diverse presentation and potential severity of CAF progression, early screening is warranted, as irreversible cardiac remodeling may occur. Some fistulas may be large in the newborn period, but others may increase in size over time. The most substantial shunts typically occur in those fistulas where the coronary artery communicates with the right side of the heart rather than the left, which may result in symptoms of congestive heart failure, particularly in infants and occasionally in newborns. Furthermore, there have been instances of similar presentations in the elderly. Additionally, there exists a risk of thrombosis within these fistulas, which can lead to severe complications such as acute myocardial infarctions, paroxysmal fibrillation, and ventricular arrhythmias. A multimodal evaluation is crucial for achieving an accurate diagnosis at an earlier stage in life. This report presents the case of a 13-year-old female gymnast who sought medical evaluation due to palpitations.

RESUMEN

Las fístulas de las arterias coronarias (FAC) representan una categoría poco frecuente de anomalías congénitas que con frecuencia no se diagnostican debido a la ausencia de sintomatología en etapas tempranas de la vida. La mayoría de los casos de FAC se descubren de forma incidental durante un examen diagnóstico por problemas médicos no relacionados. Dada la diversidad en su presentación clínica y la posible gravedad de la progresión, se justifica la detección temprana, ya que puede producirse una remodelación cardiaca irreversible. Algunas fístulas pueden ser grandes en el periodo neonatal, pero otras pueden aumentar de tamaño con el tiempo. Los cortocircuitos significativos suelen producirse en aquellas fístulas en las que la arteria coronaria se comunica con el lado derecho del corazón en lugar del izquierdo, lo que puede provocar síntomas de insuficiencia cardiaca congestiva, en particular en lactantes y, ocasionalmente, en recién nacidos. Asimismo, ha habido casos de presentaciones similares en adultos. Además, existe un riesgo de trombosis dentro de estas fístulas, que puede provocar complicaciones graves, como infartos agudos del miocardio, fibrilación paroxística y arritmias ventriculares. La evaluación multimodal es fundamental para lograr un diagnóstico preciso en una etapa temprana de la vida. En este reporte se presenta el caso de una gimnasta de 13 años que acudió a una evaluación médica debido a palpitaciones.

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Abbreviations:
AO = Aorta
CAF = Coronary Artery Fistula
CC = Catheter Closure
CPAF = Coronary to pulmonary Artery Fistula
ECG = Electrocardiogram
LAD = left anterior descending artery
LCA = left coronary artery
LBPA = Left Branch of the Pulmonary Artery
MDCT = Multidetector-row Computed Tomography
RBPA = Right Branch of the Pulmonary Artery
RCA = Right Coronary Artery
SI = Surgical Intervention
TTE = Transthoracic Echocardiogram

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INTRODUCTION

Coronary artery anomalies encompass a group of congenital malformations characterized by alterations in the origin, course, or termination of one of the three primary epicardial arteries. Among these anomalies, coronary arteriovenous fistulas (CAF) are classified as termination anomalies. They represent abnormal direct connections between a coronary artery and a cardiac chamber, great vessel, or other vascular structures.[1] Bypassing the myocardial capillary network carries the potential to produce myocardial ischemia via the coronary steal phenomenon. The resulting left-to-right shunt may lead to volume overload, thereby increasing the risk of subsequent heart failure.[2] Coronary Arteriovenous Fistulas (CAF) are categorized as either congenital or acquired, with congenital fistulas constituting the majority of cases. Acquired CAF may develop due to intracardiac congenital heart operations, traumatic injuries to the heart, or complications arising from interventional cardiac procedures. Most presentations of CAF are isolated; however, they can also occur in conjunction with other congenital heart diseases, including atrial septal defects, ventricular septal defects, or Tetralogy of Fallot.[3] The prevalence of CAF is relatively low, occurring in approximately 0.2-0.4% of individuals with congenital heart disease. Among pediatric patients undergoing echocardiography, the prevalence is estimated at 0.06%, while in adults undergoing coronary angiography, the prevalence ranges from 0.13-0.22%.[4]

Nevertheless, advancements in imaging technology, such as multidetector-row computed tomography (MDCT), have enhanced the detection rate, leading to an overall prevalence of up to 0.9%.[5] Coronary-to-pulmonary artery fistulas represent the most common type, found incidentally on MDCT, accounting for 15-30% of the total population of CAF. Notably, 89% of these fistulas drain into the pulmonary trunk rather than into other segmental pulmonary arteries.[6]

The predominant embryologic explanation for a coronary-to-pulmonary artery fistula (CPAF) is the Hackensellner involution-persistence hypothesis. CPAF originating from the left coronary artery (LCA) represents 84% of cases, significantly outnumbering those that originate from the right coronary artery (RCA), which accounts for 38% of cases. According to the findings of Verdini et al., there are two distinct types of CPAF. The first type is characterized by a single prominent fistulous connection between either the left anterior descending artery (LAD) or the RCA and the main pulmonary trunk. The second type encompasses multiple small-caliber fistulous connections from the LAD or RCA that drain into the main pulmonary trunk.

Fistulas exhibiting a single connection are more likely to result in hemodynamic disturbances and associated symptoms compared to those with multiple connections. Although CPAF may be identified incidentally and may not be clinically significant, there exist cases with substantial hemodynamic consequences that necessitate intervention. It is important to note that the majority of CPAF have been documented solely in a limited number of case reports —there are only 22 reported pediatric cases in the existing literature— or have been discussed in relation to other congenital fistulas in larger studies.[6]

CASE PRESENTATION

A 13-year-old female gymnast presented for evaluation with complaints of palpitations, dizziness, pallor, and near-syncope. Her recorded weight was 42.7 kg (94.17 lb), height 152 cm (4 feet 11 inches), heart rate (HR) 68 beats per minute, and blood pressure (BP) 109/68 mmHg. The physical examination yielded unremarkable findings. An electrocardiogram (ECG) revealed a normal sinus rhythm without evidence of hypertrophy or alterations in repolarization. A 24-hour Holter monitor displayed normal results. The echocardiogram indicated a normal segmental relationship and chamber sizes consistent with levocardia. Both color and spectral Doppler flow assessments were normal across longitudinal and transverse views at the subcostal, parasternal, and apical levels.

The parasternal short-axis view of the aortic root showed the right coronary artery (RCA) and left coronary artery (LCA) in their appropriate anatomical positions, with the proximal segment of the RCA exhibiting a Z score of 0.2 *(Figure 1)*. However, the suprasternal longitudinal view identified an abnormal vascular structure with anterograde flow descending into the right branch of the pulmonary artery (RBPA) *(Figure 2)*. The suprasternal short-axis view illustrated an anastomosis at the proximal segment of the RBPA, characterized by continuous, pulsatile flow, a maximum recorded velocity of 2.8 m/s, and a maximum gradient of 31 mmHg *(Figure 3)*.

Based on the clinical findings and echocardiographic results, the differential diagnoses included a systemic-to-pulmonary collateral artery and/or a coronary artery fistula (CAF). However, given the normal pulmonary pressure, the coronary artery fistula was considered the primary diagnosis. A multidetector-row computed tomography (MDCT) scan was subsequently performed to establish a definitive diagnosis, revealing a coronary-to-pulmonary artery fistula originating from the sinus node artery (a branch of the proximal right coronary artery) with an anastomosis at the anterior wall of the RBPA *(Figure 4)*.

After conducting a comprehensive analysis of the case and discussing various strategies with the mother, the family concluded that the patient would continue to undergo annual reviews without pharmacotherapy.

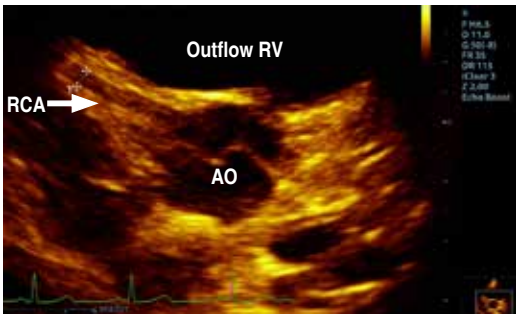

Figure 1: Parasternal short-axis 2D view from TTE, the transducer tilted superiorly and rightward in order to visualize RCA (arrow): the origin of the Right Coronary Ostium and Right Coronary Artery (RCA).

DISCUSSION

The progress in non-invasive diagnostic techniques has facilitated the early identification of incidental findings in asymptomatic pediatric patients. This advancement allows for the formulation of treatment protocols before conditions advance to irreversible cardiac remodeling. Some fistulas may be large in the newborn period, but others may increase in size over time. The most substantial shunts typically arise when a coronary artery connects to the right side of the heart instead of the left, which may result in symptoms of congestive heart failure, particularly during infancy and, on occasion, in the neonatal period. Furthermore, cases of heart failure associated with large fistulas have also been documented in the elderly population.

The occurrence of thrombosis within the fistula can lead to serious complications, including acute myocardial infarction (specifically when there is drainage to the coronary sinus) and paroxysmal atrial fibrillation (more frequently observed when the connection is to the right atrium). The most prevalent symptoms and complications observed in adults include angina, particularly in the setting of concomitant coronary artery disease. Additionally, individuals may experience myocardial infarction, heart failure, and ventricular arrhythmias.[7] Previous case reports have indicated instances of bacterial endocarditis, the formation of aneurysms, and rupture of coronary fistulas.[8]

Eighty percent of pediatric patients diagnosed with coronary artery fistulas remain asymptomatic until they reach their second decade of life. At this point, clinical symptoms may emerge, including fatigue, dyspnea, angina, and/or heart failure. A significant physical finding that typically prompts referral to a pediatric cardiologist is the detection of an asymptomatic continuous murmur over the precordium. This murmur resembles that of a patent ductus arteriosus; however, it is crucial to distinguish between the two conditions. The murmur associated with CAF is generally audible over the left lower sternal border, in contrast to the location beneath the left clavicle typically associated with murmurs originating

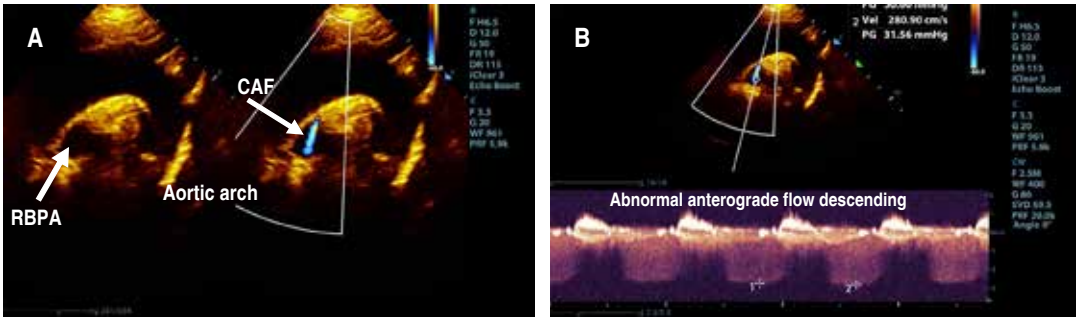

Figure 2: A) Suprasternal long-axis 2D, the transducer tilted anterior (aortic arch to the left and continuous color Doppler): view of abnormal anterograde flow descending in the RBPA (arrow). **B)** Suprasternal long-axis 2D (aortic arch to the left with continuous Doppler): view of abnormal continuous anterograde flow descending into the RBPA with Vmax: 2.8 m/s.

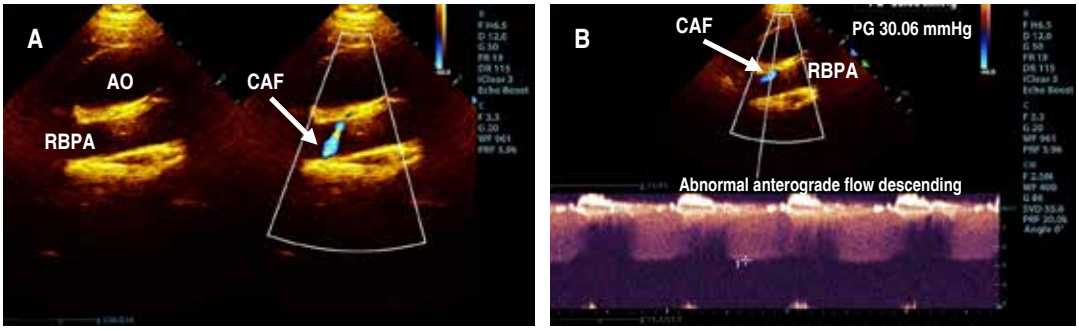

Figure 3: A) Suprasternal short-axis 2D color Doppler, the transducer tilted from anterior to posterior: view of abnormal anterograde flow descending into the proximal segment of RBPA (arrow). **B)** Suprasternal short-axis 2D with continuous Doppler: view of abnormal anterograde flow at the level of the proximal segment of RBPA with Vmax: 2.8 m/s.

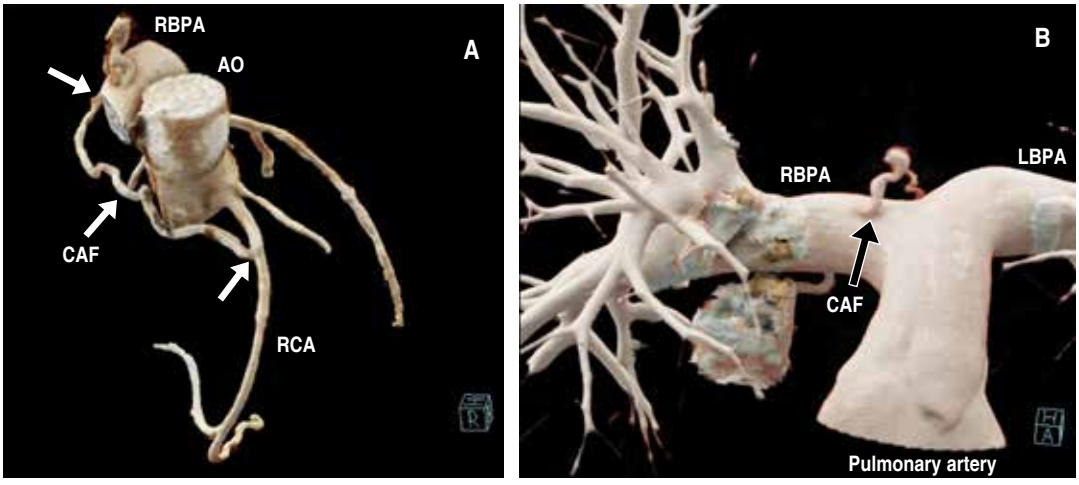

Figure 4: A) AngioTAC: view of CAF (arrow) origin at the level of the sinus node branch with distal anastomosis of the RBPA. **B)** AngioTAC: view of the CAF with distal anastomosis (arrow) in the superior wall of the proximal segment of RBPA.

from the patent arterial duct. Furthermore, the murmur typically peaks in mid-diastole rather than in systole.

Electrocardiographic findings may indicate signs of volume overload affecting both sides of the heart, as well as myocardial ischemia patterns. Chest radiographs can either appear normal or exhibit mild cardiomegaly and signs of pulmonary congestion.

Transthoracic echocardiography (TTE) may reveal CAF when the proximal coronary artery that feeds the fistula is dilated and tortuous in the presence of a large shunt. TTE is helpful in making an accurate diagnosis. In cases where the fistula and resulting shunt are small, color Doppler imaging may be diagnostic, as it effectively visualizes the chamber or vessel into which the fistula drains. Conventional pulse and continuous wave Doppler techniques can subsequently confirm the presence of high-velocity flow through the fistula.

For patients with higher body mass, multidetector computed tomography (MDCT) has proven to be more effective than echocardiography, providing precise identification of obstructions and superior anatomical delineation. Nevertheless, coronary angiography remains the gold standard for confirming the diagnosis of CAF.[9]

Congenital coronary artery anomalies present a significant risk for sudden cardiac death; however, only a select few subtypes are associated with an increased likelihood of myocardial ischemia with exertion. The most prevalent anomaly occurs when the coronary artery arises from an inappropriate sinus of Valsalva and follows an intra-arterial and intramural course. Notably, the anomalous left coronary artery originating from the right aortic sinus is recognized as carrying the highest risk, particularly among young high-endurance athletes.[10] Consequently, it is imperative to establish comprehensive screening protocols for this population.

Moreover, the clinical progression of CAF remains largely undefined, resulting in existing management guidelines being based on limited scientific evidence. According to the American College of Cardiology and the American Heart Association guidelines published in 2008, surgical intervention is classified as a class I C recommendation for large CAF, irrespective of symptomatology. For symptomatic small- to medium-sized fistulas, intervention is warranted in the presence of documented myocardial ischemia, arrhythmia, unexplained ventricular systolic or diastolic dysfunction, or endarteritis.[11] Similarly, European guidelines introduced in 2020 advocate percutaneous or surgical closure in symptomatic patients or cases involving significant shunting.[12]

The treatment options for CAF encompass both surgical intervention (SI) and catheter closure (CC). The considerable heterogeneity in size, symptomatology, and age at presentation presents a substantial challenge in determining the optimal management strategy. Recent advancements in delivery systems, microcatheters, and enhanced devices have positioned percutaneous transcatheter embolization as a safe and effective alternative in cases where anatomical conditions permit. In instances involving large aneurysmal dilations of the fistula, surgical intervention provides the opportunity for excision or reduction of the aneurysm's size.

Gowda et al. categorize CAF into two distinct types: proximal and distal. Proximal CAF originate from the central region of the proximal major epicardial artery and are generally classified as low risk for coronary events following closure because there are no normal nutritive coronary branches arising from the residual fistula segment. Conversely, distal CAF arise from the distal major epicardial coronary artery; the proximal conduit coronary artery is either tortuous or dilated and also has normal coronary artery branches supplying the myocardium.[13]

It is recommended that small-sized proximal and distal CAF undergo medical observation without intervention. All proximal CAF categorized as moderate to large, regardless of the presence of symptoms, should be closed (SI or CC) nearest to the origin of the fistula from the coronary tree as feasible, supplemented by one year of antiplatelet therapy. The decision to intervene in patients with medium to large distal CAF remains a topic of ongoing debate. Intervention at a younger age for medium-sized distal CAFs may be advisable due to favorable

remodeling mechanisms, also accompanied by one year of antiplatelet therapy.[13]

However, large distal CAF associated with significantly dilated conduit coronary arteries, irrespective of age, are considered to carry a high risk of adverse coronary events following intervention. Gowda et al. classify the treatment of larger fistulas into two distinct categories: symptomatic and asymptomatic. In cases of larger symptomatic fistulas related to heart failure, endocarditis, or hemodynamically significant runoff, the recommended approach is to undertake either SI or CC. Furthermore, it is advisable to implement a rigorous post-closure anticoagulation regimen, which should begin with intravenous heparin, followed by the administration of either warfarin or low-molecular-weight heparin for a period of six to 12 months. Additionally, antiplatelet therapy is warranted for a duration of one year or may be extended indefinitely in the presence of residual coronary dilatation.[13] The management of asymptomatic patients can be categorized into two distinct approaches. The first approach entails continuous observation accompanied by indefinite antiplatelet therapy. The second approach employs SI or CC, following the same post-closure treatment plan for large symptomatic fistulas. Regardless of the selected therapeutic approach, follow-up anatomical evaluation of the CAF at six to 12 months should elucidate remodeling sequelae that will further determine the type and duration of anticoagulant management.[13]

Mavroudis et al. advocate for elective coil occlusion in patients who meet specific criteria: absence of multiple fistulae, presence of a single narrow drainage site, absence of large branch vessels, and safe accessibility to the coronary artery supplying the fistula.[14] Therefore, early intervention in the pediatric population may be a viable option for the management of CAF, even in asymptomatic patients.[15-17]

This case presents a divergence from the existing literature, as the patient does not exhibit a murmur, a finding reported in only 12% of similar cases. Furthermore, the anastomosis was identified in the right branch of the pulmonary artery (only three cases were reported in the literature, and all were adults). Following an extensive investigation, we observed several key morphological characteristics, including a small proximal fistula and a hemodynamic circulation demonstrating a QP/QS ratio of 1.2:1. Importantly, there was no evidence to suggest that the symptoms were associated with the fistula. Consequently, the decision was made to implement annual surveillance as the appropriate management approach.

Pharmacological agents such as beta-blockers, calcium channel blockers, antiplatelet agents, or anticoagulants are often recommended for conservative management. However, many of these treatment strategies are still debated, as they are primarily founded on anecdotal evidence or a limited number of retrospective studies. A standardized protocol for the management of CPAF has yet to be established, mainly due to the infrequency of such cases and the variability in their specific anatomy and clinical presentation. Consequently, there is a pressing need for an objective tool to assess hemodynamic instability in patients with CAF.

CONCLUSIONS

Coronary artery fistulas (CAF) represent a form of heart disease that is frequently underdiagnosed, particularly during the early stages of life, as many individuals remain asymptomatic. Given the variability in presentation and the severity of CAF progression, early screening is essential to mitigate the risk of irreversible cardiovascular remodeling. A multimodal approach to evaluation facilitates the establishment of a precise diagnosis at an earlier age.

This case represents a departure from current literature, as the anastomosis is located in the right branch of the pulmonary artery, with only three such cases documented in adults to date. CPAF can be found incidentally and not be clinically significant; however, some cases can lead to substantial hemodynamic issues necessitating intervention. CPAF have been described in limited numbers of case reports or referenced within broader studies detailing other CAF. Currently, definitive treatment guidelines for CPAF remain underdeveloped. Therefore, there is a need for an objective tool to evaluate hemodynamic instability in patients presenting with CPAF.

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Consent statement: the authors declare that since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

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REVIEW

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Prophylactic use of intravascular balloon occlusion in elective general non-cardiac surgery. Systematic review and meta-analysis of the literature

Uso profiláctico de balón de oclusión intravascular en cirugía general no cardiaca electiva. Revisión sistemática y metaanálisis de la literatura

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Keywords:
intravascular balloon occlusion, hemorrhage, elective surgery.

Palabras clave:
balón de oclusión intravascular, hemorragia, cirugía electiva.

ABSTRACT

Introduction: the use of endovascular occlusion balloon in elective non-cardiac surgery has emerged as an effective strategy to prevent intraoperative bleeding, a significant complication that can impact both surgical outcomes and patient recovery. This device, which selectively occludes large blood vessels, allows for precise control of blood flow, thereby minimizing the risk of hemorrhage and improving visibility in critical surgical areas. **Material and methods:** a search was performed across three major databases (PubMed, Ovid, and Embase), in addition to Google Scholar as a source of gray literature and the National Institute of Health (NIH) as a national database, covering the period from 2014 to 2024. **Results:** this systematic review included 17 articles; two showed a moderate risk of bias, while the others demonstrated good quality and low risk of bias. A total of 3,379 patients were analyzed, 95.3% women. The primary indication for the use of endovascular occlusion balloons was surgical procedures related to abnormal placentation in 67.5% of cases, with an average blood loss of 1,256 mL (SD: 699.9). The application of the balloon resulted in a significant reduction in blood loss of 856 mL (OR −3.43; 95% CI −6.22 to −0.63), with no significant differences observed in age, gender, or surgical duration. **Conclusion:** the use of intravascular balloon occlusion in elective non-cardiac general surgical procedures with a high risk of hemorrhage demonstrates effectiveness in reducing intraoperative blood loss. The most frequently observed complications include transient arterial thrombosis and localized issues at the puncture site. While various clinical scenarios for its application have been described, the strongest evidence supports its use in obstetric procedures, particularly those related to abnormal placentation.

RESUMEN

Introducción: *el uso de un balón de oclusión endovascular en cirugía electiva no cardiaca se ha revelado como una estrategia eficaz para prevenir las hemorragias intraoperatorias, una complicación importante que puede afectar tanto a los resultados quirúrgicos como a la recuperación del paciente. Este dispositivo, que ocluye selectivamente grandes vasos sanguíneos, permite un control preciso del flujo sanguíneo, minimizando así el riesgo de hemorragia y mejorando la visibilidad en zonas quirúrgicas críticas.* ***Material y métodos:*** *se realizó una búsqueda en tres bases de datos principales (PubMed, Ovid y Embase), además de Google Scholar como fuente de literatura gris y el Instituto Nacional de Salud (NIH) como base de datos nacional, abarcando el periodo de 2014 a 2024.* ***Resultados:*** *esta revisión sistemática incluyó 17 artículos; dos mostraron un riesgo moderado de sesgo, mientras que los demás demostraron buena calidad y bajo riesgo de sesgo. Se analizaron un total de 3,379 pacientes, de los cuales 95.3% fueron mujeres. La principal indicación para el uso de balones de oclusión endovascular fueron procedimientos quirúrgicos relacionados con la placentación anormal en 67.5% de los casos, con una pérdida sanguínea promedio de 1,256 mL (DE: 699.9). La aplicación del balón resultó en una reducción significativa de la pérdida de sangre de 856 mL (OR −3.43; IC95% −6.22 a −0.63), sin diferencias significativas observadas en edad, género o duración quirúrgica.* ***Conclusión:*** *el uso de oclusión con balón intravascular en procedimientos quirúrgicos generales electivos no cardiacos con alto riesgo de hemorragia demuestra efectividad en la reducción de la pérdida de sangre intraoperatoria. Las complicaciones más frecuentemente observadas incluyen trombosis arterial transitoria y problemas localizados en el sitio de punción. Aunque se han descrito diversos escenarios clínicos para su aplicación, la evidencia más sólida apoya su uso en procedimientos obstétricos, particularmente aquellos relacionados con la placentación anormal.*

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INTRODUCTION

The endovascular balloon occlusion is a method that has been introduced as a concept for more than 70 years, a result of the Korean War,[1] and since then, it has been put into sequential study and applied in the context of patient victims of military traumatic injuries and civilians. This has advanced to the point of becoming an endovascular technique that is easily applicable in the emergency department and in surgery rooms.[2] However, in search of making better use of this resource, in recent years, the concept of intravascular occlusion in the arterial and/or venous system has been applied in elective surgery as a complement in the treatment of various medical-surgical conditions in search of explored new strategies to prevent and control intra- and postoperative hemorrhagic events.

Historically, one of the main and most feared complications related to fatal outcomes is massive bleeding and secondary hypovolemic shock. Numerous efforts have been directed towards creating devices and interventional techniques to reduce or even prevent bleeding. Since its first application by Hughes on two wounded soldiers in the Korean War,[1] large blood vessel endovascular occlusion devices have opened multiple doors, leading to two main objectives. The first is bleeding control, such as in cases of severe trauma associated with non-compressible bleeding, ruptured abdominal aortic aneurysms, postpartum hemorrhage, etc., where the goal is to control an already established hemorrhage.[3] The second is the prevention of bleeding, which is the focus of more recent research, implementing these devices in elective (non-urgent) pelvic-obstetric, renal, hepatobiliary, and gastrointestinal procedures to avoid hemorrhage and its associated complications.

Effective management of intraoperative bleeding is essential for the success of any surgical procedure and remains a significant concern worldwide and locally, as hemorrhagic complications continue to impact the outcomes of certain types of procedures negatively, increasing reinterventions, massive transfusions, organ or multi-organ dysfunction, and in some situations, even death.[4]

In recent decades, technological advancements have led to the development of innovative endovascular techniques and devices to control hemorrhage during surgery. One of these significant advancements has been the introduction and use of intravascular occlusion balloons in adult patients undergoing elective surgery.[3,4] Initially, these devices were used in the trauma context to control massive bleeding, either through open or closed methods, but their application has expanded to non-traumatized adult patients undergoing major elective surgical procedures with significant bleeding risk.[5]

The implementation of these occlusion devices at the aortic and vena cava levels has demonstrated substantial benefits in terms of improved survival rates and fewer post-surgical hemorrhagic complications in patients who have experienced open or closed accidents.[6,7] This initial success has led to the exploration of their preventive use in elective surgeries, where a high risk of potentially fatal intraoperative bleeding is anticipated.[8]

Despite the growing popularity of this technique and several isolated studies, there is little evidence in the scientific literature regarding its indications, efficacy, safety, impact on the magnitude of bleeding, blood component polytransfusion, and mortality in the context of elective surgeries. Moreover, its current use is justified by isolated studies with diverse methodologies and results, often based on local experiences. Therefore, it is crucial to address this knowledge gap in an organized and systematic manner so that the available data can be collected, analyzed, and interpreted, and based on this, establish guidelines based on the best evidence to optimize bleeding outcomes for patients undergoing elective surgical procedures.

This systematic literature review aims to provide a specific response by thoroughly evaluating existing studies on the use of intravascular occlusion balloons in elective surgeries concerning the amount of intraoperative bleeding. By doing so, it seeks to provide a more synthesized and concrete view of the actual effectiveness of this technique in the context of non-traumatic surgical procedures based on the literature available to date.

The results of this review could have significant implications for clinical practice. If intravascular occlusion balloons are confirmed to be effective in reducing intraoperative bleeding in elective surgeries, this could support their prophylactic use and lead to a substantial reduction in bleeding-related complications. Additionally, by providing evidence-based guidance, this review can serve as a foundation for developing local, national, and international clinical protocols and help scientific communities generate recommendations on the implementation of this technique.

MATERIAL AND METHODS

Methodology

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[9]

The inclusion criteria for the review encompassed studies involving adult patients over 18 years of age undergoing elective surgery where intravascular occlusion balloons were used. The types of interventions considered included intravascular occlusion with arterial or venous balloons in elective surgery. The primary outcome of interest was the amount of intraoperative hemorrhage when intravascular balloon occlusion was utilized. Eligible studies included observational, analytical, and descriptive types and only those reported in English and Spanish were considered.

The exclusion criteria for the review included studies carried out in animal models or species other than humans, as well as those focused on emergency surgery. Studies were also excluded if they used devices other than intravascular, temporary, or definitive occlusion balloons in elective surgery or if they presented unrelated results that did not provide relevant and clear information on the reduction of intraoperative hemorrhage with intravascular occlusion balloons. Duplicate studies were excluded, retaining only the most complete and detailed version. Additionally, publications not subject to review by both researchers were excluded.

The search was carried out in three main databases: PubMed, Ovid, Embase, and Google Scholar, which is a gray literature database, and the National Institute of Health (INS) as a national database. Articles written in English and/or Spanish were accepted and published in the last 10 years until April 2024. The search result was stored in Mendeley and Rayyan© as organizer and reference manager, respectively. Additionally, bibliographic references of the included studies were searched and compiled to ensure a comprehensive review of the literature.

The searches were executed with the keywords in terms Mesh (Medical Subject Headings) Thesaurus on the health sciences of the National Library of Medicine (NLM); Vena Cava, Superior, Vena Cava, Inferior, Aorta, Aorta, Thoracic, Aorta, Abdominal, Balloon Occlusion, Wounds, and Injuries. Once these Mesh terms were set, the Boolean operators were used as follows: (((Vena Cava, Superior[Mesh] OR Vena Cava, Inferior[Mesh]) OR (Aorta"[Mesh] OR Aorta, Thoracic[Mesh] OR Aorta, Abdominal[Mesh])) AND Balloon Occlusion[Mesh]) NOT Wounds and Injuries[Mesh]. Duplicate studies were removed using the Rayyan tool.

Study selection

Each author independently reviewed the titles and abstracts of the articles in the database obtained as a result of the search strategy; Articles that were not related to the research question were excluded. Full texts were obtained only from articles considered potentially eligible by at least one reviewer. Subsequently, each author independently reviewed the full texts of the potentially eligible articles, verified the inclusion and exclusion criteria, and established the definitive articles for carrying out the present systematic review. Cases where there was a discrepancy were resolved by consensus in the first instance, and if disagreement persisted, a third reviewer determined whether or not to include the article.

Data extraction process

For data extraction, the artificial intelligence tool SciSpace[10] was used as the first instance, where the articles included in the study

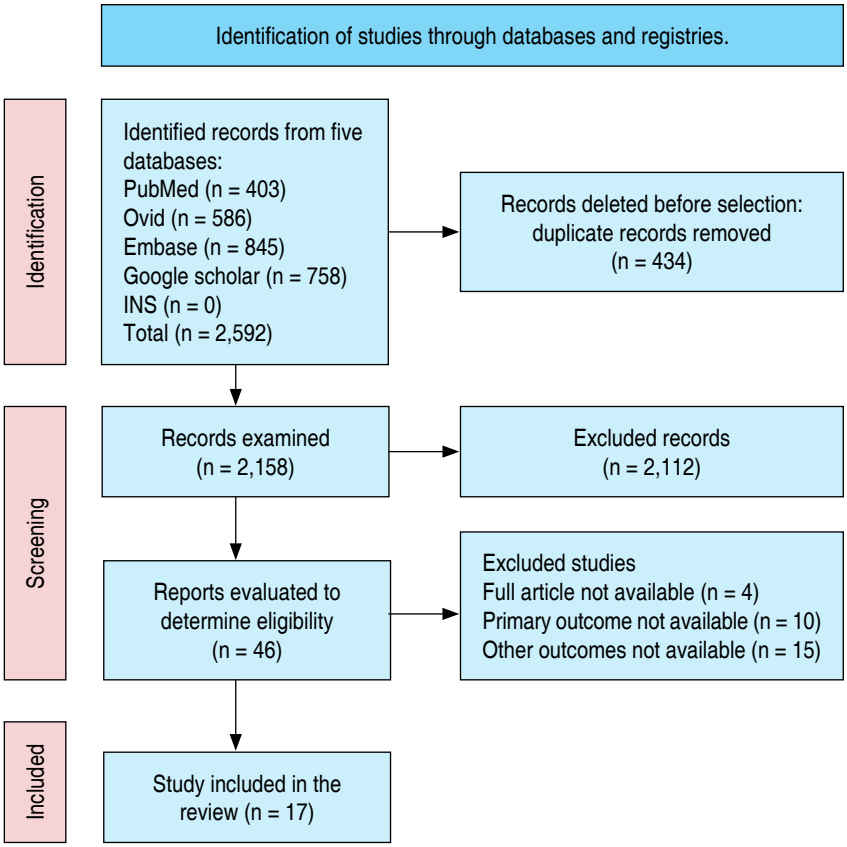

Figure 1:

PRISMA diagram.

were entered and the specific data were screened. The information collected from each article included authors, year of publication, study design, number of participants in the intervention group and control group, indication for intravascular occlusion, site of vascular occlusion, amount of bleeding during the intervention, surgical time, and complications associated with the intervention. Additionally, for some numerical variables, dispersion measures such as the mean and standard deviation were recorded. In cases where automatic extraction of information was not obtained, it was added manually. Subsequently, each author independently corroborated the veracity of the information collected.

The data obtained were tabulated in a standardized Excel spreadsheet (Microsoft). Finally, articles that did not provide the total of the mentioned variables were excluded in order to avoid bias in obtaining results and analyzing them.

Risk of bias and quality of included studies

The Newcastle-Ottawa scale was used to assess the risk of bias, a validated and widely used instrument to evaluate the risk of bias in observational studies.[11] This scale considers three domains: selection of participants, comparability between groups, and evaluation of exposure or results.[12] Methodological quality was classified according to the following criteria: (a) Good: three to four stars in selection, one to two in comparability, and two to three in results/exposition; (b) Fair: two stars in selection, one to two in comparability and two to three in results/exhibition; (c): zero to one star for selection, zero for comparability and zero to one for results/exhibition.[11]

Statistical analysis

Data analysis and management were carried out using STATA statistical software. For the

qualitative variables, the log Odds ratio method was used, with a random effects model to calculate the Odds Ratio (OR) and the 95% confidence interval (95% CI). For numerical variables, the inverse variance method with a random effects model was used to determine the standardized mean difference (SMD) with its 95% CI. The presence of statistical heterogeneity was evaluated using the I^2 test to measure the magnitude of heterogeneity; statistical heterogeneity was considered a value greater than 50%.

RESULTS

After applying the search strategy across all databases, we obtained a total of 2,592 articles, distributed as follows: PubMed (n = 403), EMBASE (n = 845), OVID (n = 585), Google Scholar (n = 758), and INS (n = 0). Ultimately, we included 17 articles in the systematic review, excluding the remaining publications through a rigorous screening process *(Figure 1)*.

Our analysis revealed no randomized controlled trials regarding occlusion balloons in elective surgery. Among the 17 included studies, 10 were retrospective cohorts,[13-22] one was a prospective cohort study,[23] and six were case-control studies.[24-29] We assessed the quality and risk of bias of all studies using the Newcastle-Ottawa Scale for cohorts and case-control studies, focusing on selection, comparability, and outcomes. Two retrospective cohorts exhibited a moderate risk of bias, while the remaining articles demonstrated good quality and low risk of bias *(Table 1)*.

This review included a total of 3,379 patients, comprising 157 men (4.7%) and 3,222 women (95.3%). The average age in the intervention group was 36.4 years (SD: 5.9), compared to 37.0 years (SD: 6.1) in the non-intervention group *(Table 2)*.

The conditions for which intravascular occlusion balloons were utilized in elective surgical treatments included abnormal placentation (placenta accreta) in 2,281

Table 1: Results of quality assessment using the Newcastle-Ottawa scale for all studies.

Study	Type of study	Selection	Comparability	Exposure or results	Methodological quality
Ioscovich A (2023)	Cases and controls	4	2	3	Good
Hao Z (2016)	Cases and controls	4	1	3	Good
Zeng C (2017)	Cases and controls	3	1	1	Regular
Filho S (2019)	Retrospective cohort	4	1	3	Good
Huo F (2021)	Retrospective cohort	4	1	2	Good
Kaneda H (2017)	Cases and controls	4	1	2	Good
Kyozuka H (2023)	Retrospective cohort	4	1	3	Good
Papillon-Smith J (2020)	Retrospective cohort	4	1	3	Good
Ye Y (2023)	Retrospective cohort	4	1	3	Good
Wu Q (2016)	Retrospective cohort	4	1	3	Good
Peng W (2020)	Retrospective cohort	2	1	2	Regular
Zhao X (2016)	Cases and controls	4	2	2	Good
Duan X (2018)	Retrospective cohort	3	1	2	Good
Wang Y (2020)	Retrospective cohort	4	1	3	Good
Peng Y (2020)	Cases and controls	4	2	3	Good
Zhao Z (2020)	Prospective cohort	3	1	2	Good
Zangh Y (2018)	Retrospective cohort	4	1	3	Good

Good: 3 to 4 stars for selection, 1 to 2 for comparability, and 2 to 3 for results/exhibition; Fair: 2 stars in selection, 1 to 2 in comparability and 2 to 3 in results/exhibition; Bad: 0 to 1 on selection, 0 on comparability and 0 to 1 on results/exposure.

Table 2: Comparative outcomes in groups studied with respect to age, indication and site of occlusion.

Study	Intervention group (ball)					Non-intervention group (no ball)					Indication	Occlusion site
	Patients	n	Gender		Age (years) Mean ± SD	n	Gender		Age (years) Mean ± SD			
			H	M			H	M				
Ioscovich A 2023	21	10	0	10	35 ± 5.02	11	0	11	33.8 ± 4.5		Abnormal placentation	Infrarenal abdominal aorta
Hao Z 2016	41	18	11	7	34.2 ± 2.5	23	14	9	34 ± 2.1		Complex acetabular fracture	Infrarenal abdominal aorta
Zeng C 2017	86	48	0	48	32.3 ± 5.27	38	0	38	33.1 ± 5.23		Abnormal placentation	Infrarenal abdominal aorta
Filho S 2019	35	28	0	28	33 (24-43)*	7	-	-	-		Abnormal placentation	Bilateral internal iliac artery
Huo F 2021	33	17	0	17	32.82 ± 4.45	16	0	16	34.44 ± 4.79		Abnormal placentation	Infrarenal abdominal aorta
Kaneda H 2017	518 (Hysterectomy) 305 (Miomectomy)	12	0	12	49.5 (36-62)*	506	0	506	47 (34-69)*		Large uterine cervical fibroid	Bilateral internal iliac artery
		10	0	10	35.5 (28-40)*	295	0	295	38 (23-63)*			
Kyozuka H 2023	37	13	0	13	37.5 (30.8-41)*	24	0	24	35 (32-38)*		Abnormal placentation	Supraceliac Aorta
Papillon-Smith J 2020	79	47	0	47	35 (22-51)*	32	0	32	34 (25-44*)		Abnormal placentation	Internal iliac artery
Ye Y 2023	364	278	0	278	34 (30-37)*	86	0	86	34 (32-36)*		Abnormal placentation	Infrarenal abdominal aorta
Wu Q 2016	268	230	0	230	29.5 ± 3.6	38	0	38	30.4 ± 4		Abnormal placentation	Infrarenal abdominal aorta
Peng W 2020	586	252	0	252	32.69 ± 4.62	296	0	296	32.74 ± 4.84		Abnormal placentation	Infrarenal abdominal aorta
Zhao X 2016	57	23	13	10	44.36 ± 13.34	34	15	19	45.41 ± 15.7		Pelvic or hip tumor resection	Infrarenal abdominal aorta
Duan X 2018	45	22	0	22	32,1 ± 6.9	23	0	23	31.7 ± 8.5		Abnormal placentation	Infrarenal abdominal aorta
Wang Y 2020	623	623	0	623	-	23	0	-	-		Abnormal placentation	Infrarenal abdominal aorta
Peng Y 2020	104	48	0	48	32.08 ± 3.94	56	0	48	33.46 ± 4.53		Abnormal placentation	Bilateral internal iliac artery
Zhao Z 2020	121	57	33	24	48 (18-70)*	64	34	30	45 (18-70)*		Pelvic or hip tumor resection	Infrarenal abdominal aorta
Zangh Y 2018	56	30	20	10	42 ± 18	26	17	9	50 ± 19		Pelvic or hip tumor resection	Infrarenal abdominal aorta

* Median and (range)
SD = Standard deviation.

patients (67.5%), giant cervical uterine fibroids in 823 patients (24.3%), resection of sacrococcygeal tumors in 234 patients (6.9%), and open reduction and internal fixation of complex acetabular fractures in 41 patients (1.2%) *(Table 2)*.

The anatomical sites selected for endovascular balloon occlusion were infrarenal abdominal aorta in 68% (n = 2,301), bilateral internal iliac arteries in 30.8% (n = 1,041), and suprarenal aorta in 1.09% (n = 37).

Regarding intraoperative bleeding, the intervention group (endovascular occlusion balloon use) had an average blood loss of 1,256 mL (SD: 669.9), while the non-intervention group (no balloon use) reported an average blood loss of 2,112 mL (SD: 1,027.8) *(Table 3)*.

Table 4: Intervention group with respect to complications.

Complication	n (%)
Arterial thromboembolism	79 (53.00)
Emergency hysterectomy	45 (30.20)
Skin lesions or local hematoma	12 (8.05)
Vasospasm	5 (3.35)
Femoral pseudoaneurysm	2 (1.34)
Balloon dysfunction	2 (1.34)
Femoral nerve injury	1 (0.67)
Arteriovenous fistula	1 (0.67)
Operative site infection	1 (0.67)
Arterial dissection	1 (0.67)
Total	149 (100.00)

Table 3: Comparative outcomes in groups studied with respect to amount of bleeding.

	Intervention group (ball)				Non-intervention group (no ball)			
	Bleeding (mL)		Time (min)		Bleeding (mL)		Time (min)	
Study	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ioscovich A 2023	1,060	296.64	119	29.41	4,400	2,787	149.81	47.69
Hao Z 2016	1,247.2	67.1	213.3	8.9	1,526.1	69.9	248.30	7.00
Zeng C 2017	1,467.71	1,075.77	92.19	32.5	2,218.42	1,572.2	119.47	59.37
Filho S 2019	1,193	679	332	70	2,273.4	–	–	–
Huo F 2021	3,167.65	3,255.71	–	–	2,831.25	1,906.03	–	–
Kaneda H 2017	510	–	178	116-300*	350	–	165.50	57-686
	727.5	–	157.5	156-218*	390	–	160	52-366*
Kyozuka H 2023	1,110	–	144	112-163*	2,160	–	146	126-164*
Papillon-Smith J 2020	1,713	181	353	14.00	1,874	245	227	13.00
Ye Y 2023	1,370.5	752	96.3	37.6	3,536.8	1,383.2	160.60	45.50
Wu Q 2016	921	199	64.1	5.1	2,790	335	92.10	9.70
Peng W 2020	1,967.66	1,466.64	191.05	59.4	1,338.18	1,286.14	153.02	57.33
Zhao X 2016	437.23	54.32	193.28	63.47	1,846.45	87.56	273.63	73.31
Duan X 2018	597	359	63.8	12.3	2,687	575	118.80	22.40
Wang Y 2020	620	570	65.3	14.5	2,687	575	–	–
Peng Y 2020	1,504.17	1,123.44	158.44	57.32	1,108.04	1,008.32	104.20	46.22
Zhao Z 2020	1,000	–	185	100-500*	1,350	–	260	180-600*
Zangh Y 2018	2,000	–	215	110-430*	2,650	–	225	115-340*

* Range.
SD = Standard deviation.

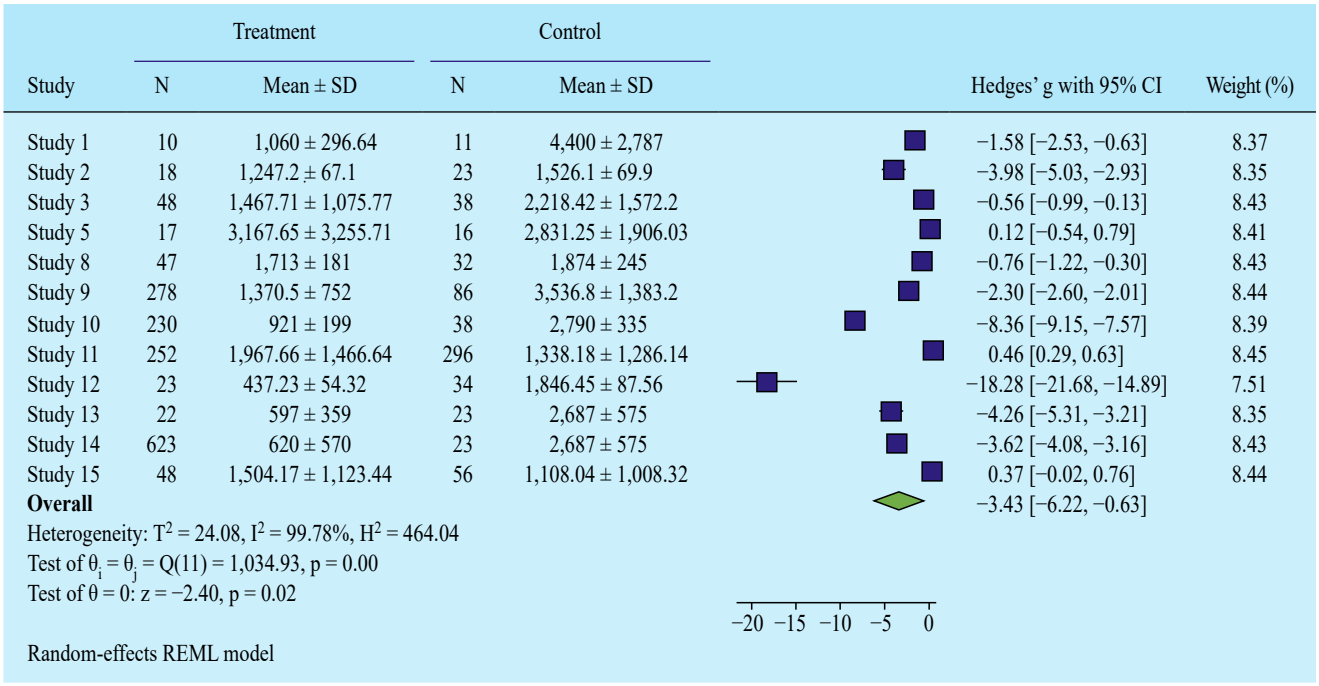

Figure 2: Forest Plot. Statistical analysis of intraoperative bleeding variables.

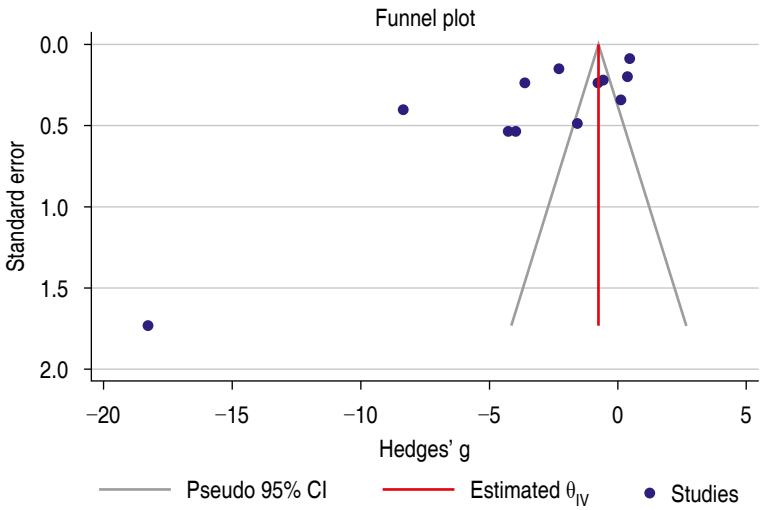

Figure 3: Funnel Plot. Statistical analysis of intraoperative bleeding variables.

Surgical duration also constituted a measured outcome in this study. In the intervention group, the average duration of surgical procedures was 165.9 minutes (SD: 84), while in the non-intervention group, it was 173.5 minutes (SD: 58.6).

A total of 149 participants (4.4% of the total included) experienced complications related to the use of the endovascular occlusion balloon. These included 79 arterial thromboembolic events, 45 emergency hysterectomies due to uncontrolled bleeding, 12 cases of skin and subcutaneous tissue injuries or local hematomas, five cases of vasospasm, two pseudoaneurysms of femoral vessels, and two cases related to balloon issues (migration and rupture). Other less frequent complications included femoral nerve injury, arteriovenous fistula, surgical site infection, and femoral artery dissection (one case each). Five studies reported no complications *(Table 4)*.

Quantitative Analysis

The systematic review (meta-analysis) was performed on 17 studies encompassing a total of 3,379 patients. The following variables were analyzed in the meta-analysis.

Intraoperative Bleeding

In this outcome, only 12 studies were subjected to statistical analysis *(Table 5)*, revealing that the

intervention serves as a protective factor against bleeding, with an odds ratio (OR) of −3.43 (95% CI −6.22; −0.63). The overall analysis exhibited high statistical heterogeneity (I^2 of 99.7%) with a significant p-value *(Figure 2)*.

The general asymmetry of the funnel plot for this variable suggests significant publication bias. However, the dispersion observed in smaller studies may indicate heterogeneity among them *(Figure 3)*.

The lack of alignment of most studies along the regression line suggests general disparity in the meta-analysis results, characterized by marked heterogeneity *(Figure 4)*.

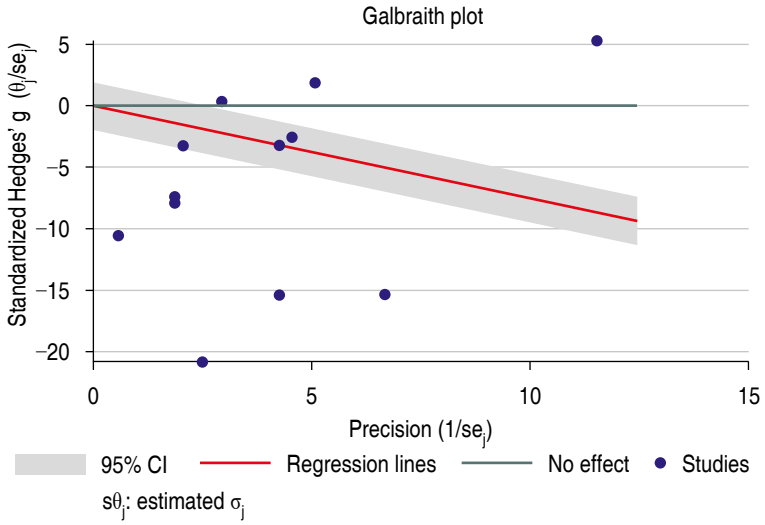

Figure 4: Galbraith Plot. Statistical analysis of intraoperative bleeding variables.

Gender

No significant differences were found, with an OR of 0.19 (95% CI −0.26; 0.64), and no statistical heterogeneity was observed (I^2 of 0%) *(Figure 5)*.

Age

No significant differences were identified with respect to age, with an OR of 0.06 (95% CI −0.15; 0.04), and no statistical heterogeneity

Study	Treatment Yes	Treatment No	Control Yes	Control No	Log odd-ratio with 95% CI	Weight (%)
Study 1	0	10	0	11	0.09 [−3.92, 4.10]	1.26
Study 2	11	7	14	9	0.01 [−1.25, 1.27]	12.62
Study 3	0	48	0	38	−0.23 [−4.17, 3.71]	1.30
Study 5	0	17	0	16	−0.06 [−4.04, 3.92]	1.28
Study 6	0	12	0	506	3.70 [−0.26, 7.66]	1.29
Study 7	0	13	0	24	0.60 [−3.38, 4.57]	1.28
Study 8	0	47	0	32	−0.38 [−4.32, 3.57]	1.30
Study 9	0	278	0	86	−1.17 [−5.10, 2.76]	1.31
Study 10	0	230	0	38	−1.79 [−5.72, 2.15]	1.30
Study 11	0	252	0	296	0.16 [−3.76, 4.08]	1.31
Study 12	13	10	15	19	0.50 [−0.57, 1.57]	17.74
Study 13	0	22	0	23	0.04 [−3.92, 4.01]	1.29
Study 15	0	48	0	48	0.00 [−3.94, 3.94]	1.30
Study 16	33	24	34	30	0.19 [−0.53, 0.91]	39.01
Study 17	20	10	17	9	0.06 [−1.05, 1.17]	16.43
Overall					0.19 [−0.26, 0.64]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$ = Q(14) = 5.10, p = 0.98
Test of $\theta = 0$: z = 0.81, p = 0.42

Random-effects REML model

Figure 5: Forest Plot. Statistical analysis of gender variables. (Yes: men; No: Women).

Study	Treatment N	Treatment Mean ± SD	Control N	Control Mean ± SD	Log odd-ratio with 95% CI	Weight (%)
Study 1	10	35 ± 5.019	11	33.8 ± 4.5	0.24 [−0.58, 1.07]	1.35
Study 2	18	34.2 ± 2.5	23	34 ± 2.1	0.09 [−0.52, 0.69]	2.51
Study 3	48	32.27 ± 5.27	38	33.13 ± 5.23	−0.16 [−0.58, 0.26]	5.16
Study 5	17	32.82 ± 4.45	16	34.44 ± 4.79	−0.34 [−1.01, 0.33]	2.04
Study 6	12	49.5 ± 49	506	47 ± 51.5	0.05 [−0.52, 0.62]	2.82
Study 7	13	37.5 ± 35.45	24	35 ± 35	0.07 [−0.59, 0.73]	2.11
Study 8	47	35 ± 36.5	32	34 ± 34.5	0.03 [−0.42. 0.47]	4.65
Study 9	278	34 ± 33.5	86	34 ± 34	0.00 [−0.24, 0.24]	15.80
Study 10	230	29.5 ± 3.6	38	30.4 ± 4	−0.25 [−0.59, 0.10]	7.83
Study 11	252	32.69 ± 4.62	296	32.74 ± 4.84	−0.01 [−0.18, 0.16]	32.70
Study 12	23	44.36 ± 13.34	34	45.41 ± 15.77	−0.07 [−0.59, 0.45]	3.38
Study 13	22	32.1 ± 6.9	23	31.7 ± 8.5	0.05 [−0.52, 0.62]	2.79
Study 15	48	32.08 ± 3.94	56	33.46 ± 4.53	−0.32 [−0.71, 0.06]	6.20
Study 16	57	48 ± 44	64	45 ± 44	0.07 [−0.29, 0.42]	7.31
Study 17	30	42 ± 18	26	50 ± 19	−0.43 [−0.95, 0.10]	3.35
Overall					−0.06 [−0.15, 0.04]	

Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(14) = 8.06$, $p = 0.89$
Test of $\theta = 0$: $z = -1.20$, $p = 0.23$

Random-effects REML model

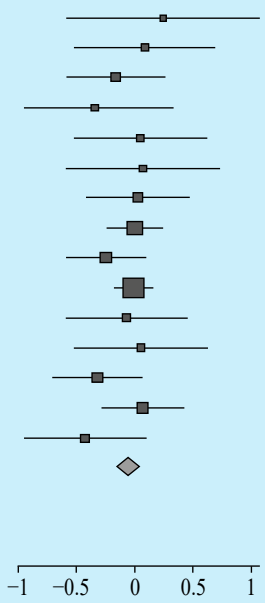

Figure 6: Forest Plot. Statistical analysis of age variables.

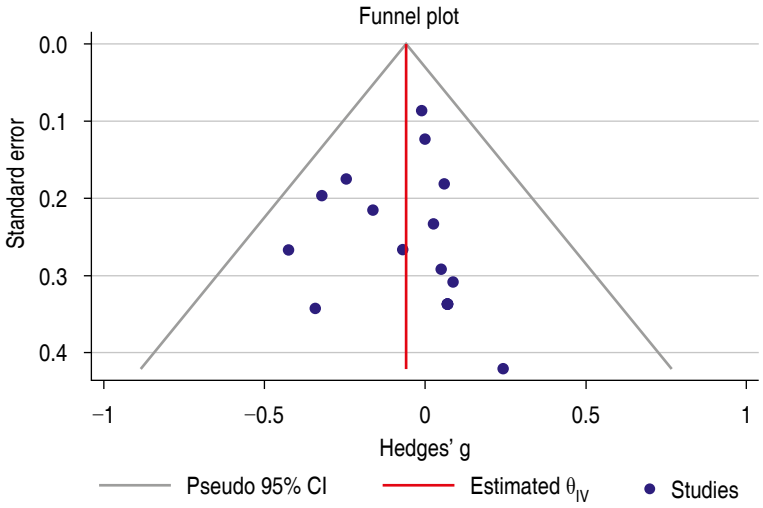

Figure 7: Funnel Plot. Statistical analysis of age variables.

was observed (I^2 of 0%) *(Figure 6)*. The general symmetry of the funnel plot suggests an absence of relevant publication bias. However, the slight dispersion observed in smaller studies may indicate some heterogeneity, warranting further exploration to identify potential differences in study designs or populations *(Figure 7)*. The alignment of most studies along the regression line indicates overall consistency in the meta-analysis results, with limited heterogeneity and no outlier studies contributing to the overall heterogeneity *(Figure 8)*.

Surgical duration

No significant differences were found in terms of duration reduction, with an OR of −0.47 (95% CI −2.13; 1.18), and statistical heterogeneity was observed (I^2 of 99.5%) *(Figure 9)*. The overall asymmetry of the funnel plot for this variable suggests significant publication bias. However, the dispersion in smaller studies may indicate heterogeneity among them *(Figure 10)*. The lack of alignment of most studies along the regression line suggests general disparity in the meta-analysis results, characterized by marked heterogeneity *(Figure 11)*.

DISCUSSION

Our results indicate that certain sociodemographic variables, such as female gender and age, characterize the population in which the intravascular balloon occlusion technique is most frequently applied. These findings align with the observational study by Wang Y,[21] which included approximately 623 female patients, and the study by Peng W[19] with 296 female patients. Both studies were conducted by gynecology groups focusing on abnormal placentation pathologies. Age, as an isolated variable, is supported by studies from Ye Y,[17] Wu Q,[18] Peng W,[19] and Wang Y,[21] which suggest that abnormal placentation is more prevalent among young women of reproductive age, typically under 40 years.

The pathology most frequently addressed using this technique was abnormal placentation, corroborated by studies such as those by Peng W[19] and Ye Y.[17] This was followed by the presence of giant fibroids, as highlighted in Kaneda H's study,[27] which reported the largest patient cohorts and emphasized the technique's role in reducing morbidity and mortality. Notably, the third most common pathology was non-gynecological in nature,

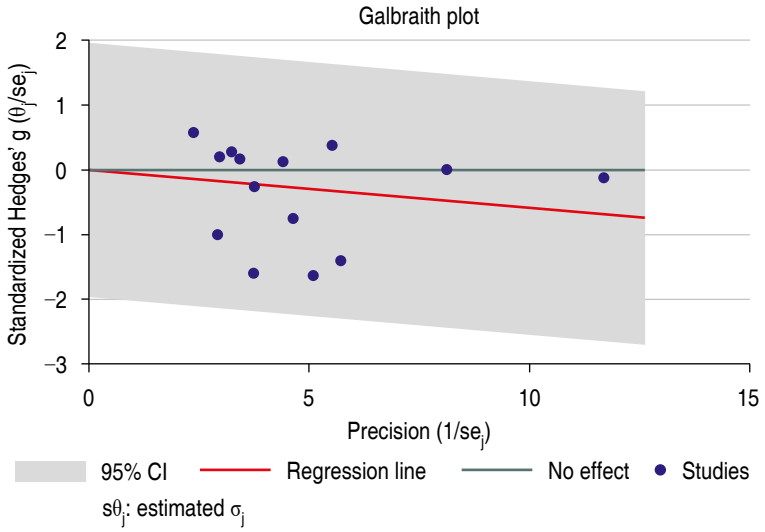

Figure 8: Galbraith Plot. Statistical analysis of age variables.

Study	Treatment N	Treatment Mean ± SD	Control N	Control Mean ± SD	Log odd-ratio with 95% CI	Weight (%)
Study 1	10	119 ± 29.41	11	149.81 ± 47.69	−0.74 [−1.59, 0.11]	7.10
Study 2	18	213.3 ± 8.9	23	248.3 ± 7.0	−4.35 [−5.47, −3.23]	7.01
Study 3	48	92.19 ± 32.5	38	119.47 ± 59.37	−0.58 [−1.01, −0.15]	7.20
Study 6	12	178 ± 46	506	165.5 ± 671.75	0.02 [−0.55, 0.59]	7.18
Study 7	13	144 ± 12.75	24	146 ± 9.5	−0.18 [−0.84, 0.48]	7.15
Study 8	47	353 ± 14	32	227 ± 13	9.17 [7.67, 10.67]	6.83
Study 9	278	96.3 ± 37.6	86	160.6 ± 45.5	−1.62 [−1.89, −1.35]	7.22
Study 10	230	64.1 ± 5.1	38	92.1 ± 9.7	−4.69 [−5.21, −4.16]	7.19
Study 11	252	191.05 ± 59.4	296	153.02 ± 57.33	0.65 [0.48, 0.82]	7.23
Study 12	23	193.28 ± 63.47	34	273.63 ± 73.31	−1.14 [−1.70, −0.58]	7.18
Study 13	22	63.8 ± 12.3	23	118.8 ± 22.4	−2.97 [−3.81, −2.13]	7.10
Study 15	48	158.44 ± 57.32	56	104.2 ± 46.22	1.04 [0.63, 1.45]	7.21
Study 16	57	185 ± 100	64	260 ± 105	−0.73 [−1.09, −0.36]	7.21
Study 17	30	215 ± 80	26	225 ± 56.25	−0.14 [−0.66, 0.38]	7.19
Overall					−0.47 [−2.13, 1.18]	

Heterogeneity: $T^2 = 9.85$, $I^2 = 99.50\%$, $H^2 = 201.55$
Test of $\theta_i = \theta_j$ = Q(13) = 781.65, p = 0.00
Test of $\theta = 0$: z = −0.56, p = 0.58

Random-effects REML model

Figure 9: Forest Plot. Statistical analysis of surgical time variables.

specifically the open reduction of long bone fractures in the lower extremities, as reported by Hao Z.[25] This study also included the highest number of male patients in our review.

Regarding the occlusion sites, all procedures were performed within the arterial system, primarily at the infrarenal aorta. In two studies, Kaneda H[27] and Peng W,[19] occlusions were performed as distally as possible, bilaterally at the internal iliac arteries. These findings correspond with studies that had the largest patient populations and most representative pathologies, specifically abnormal placentation and gynecological-pelvic tumors.

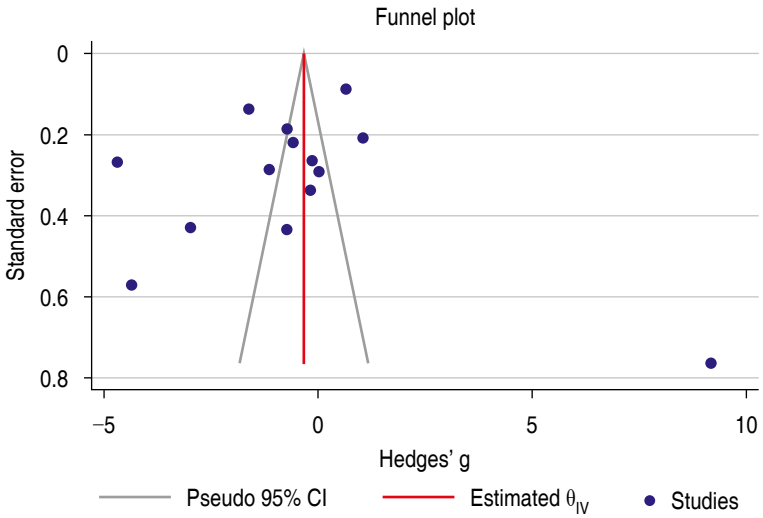

Figure 10: Funnel Plot. Statistical analysis of age variables.

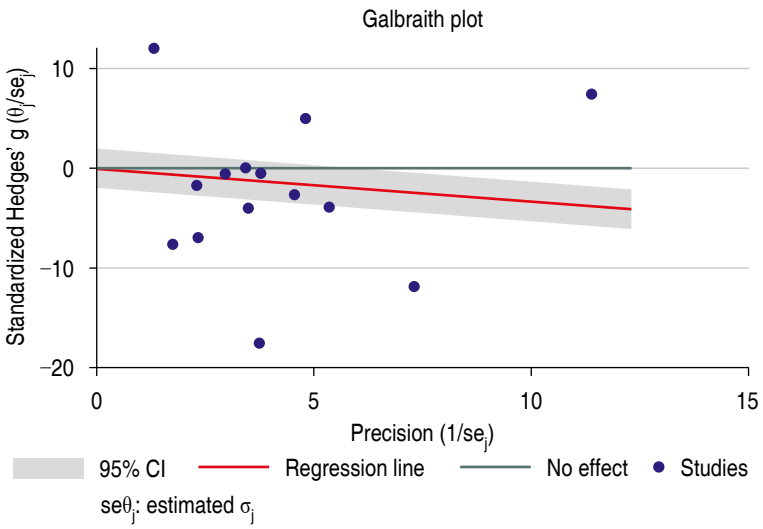

Figure 11: Galbraith Plot. Statistical analysis of age variables.

Concerning bleeding, the primary variable studied, our findings indicate that the application of prophylactic occlusion effectively reduced intraoperative bleeding. This result aligns with studies such as those by Zhao X,[28] Duan X,[20] Zeng C,[26] and Ye Y,[17] demonstrating that this method helps control and prevent intraoperative hemorrhage, thereby improving outcomes.

The most common complication observed was transient arterial thrombotic events, which were resolved with medical management. This was followed by emergency conversions to hysterectomy due to uncontrolled bleeding, predominantly in patients with abnormal placentation. However, this complication rate did not exceed 5% of the included population, suggesting that the risks associated with using this technique in elective surgery are acceptable.

Regarding the limitations of our research, we note the absence of randomized controlled trials specifically addressing the primary outcome of bleeding. Additionally, significant heterogeneity existed among the included studies, which we attempted to address through various stratification methods and statistical analyses.

In summary, our study suggests that the intravascular occlusion technique is effective in reducing intraoperative bleeding and may have significant clinical applications. Nevertheless, further research through controlled clinical trials is necessary to establish clear diagnostic inclusion criteria for participants and to individualize outcomes based on specific interventions within our population, thereby confirming these findings.

CONCLUSIONS

Intravascular balloon occlusion effectively reduces intraoperative blood loss in elective general non-cardiac surgical procedures with a high risk of hemorrhage. The most common complications include transient arterial thrombosis and localized issues at the puncture site.

While various clinical scenarios exist for applying this technique, the strongest evidence

Table 5: GRADE level of evidence and certainty. Intravascular balloon occlusion compared with not using intravascular occlusion balloon to reduce intraoperative bleeding.

Certainty assessment							N of patients		Effect			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravascular occlusion balloon	not intravascular occlusion balloon	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Ioscovich A 2023	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	10 cases –	11 controls 0.0%	**OR −1.58** (−2.53 to −0.63)	– **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	Important
Hao Z 2016	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Very strong association	18 cases –	23 controls 0.0%	**OR −3.98** (−5.03 to −2.93)	– **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	Important
Zeng C 2017	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Very strong association	48 cases –	38 controls 0.0%	**OR −0.56** (−0.99 to −0.13)	– **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	Important
Huo F 2021	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Very strong association	17/33 (51.5%)	16/33 (48.5%)	**OR 0.12** (−0.54 to 0.79)	**383 fewer per 1,000** (from 1,000 fewer to 58 fewer)	⊕⊕⊕⊕ High	Important
Papillon−Smith J 2020	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	47/79 (59.5%)	32/79 (40.5%)	**OR −0.76** (−1.22 to −0.30)	**1,000 fewer per 1,000** (from 1,000 fewer to 662 fewer)	⊕⊕⊕◯ Moderate	No important
Ye Y 2023	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	278/364 (76.4%)	86/364 (23.6%)	**OR −2.30** (−2.60 to −2.01)	**1,000 fewer per 1,000** (from 1,000 fewer to 1,000 fewer)	⊕⊕⊕◯ Moderate	Important

Contents

Continuos Table 5: GRADE level of evidence and certainty. Intravascular balloon occlusion compared with not using intravascular occlusion balloon to reduce intraoperative bleeding.

Certainty assessment							N of patients		Effect			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravascular occlusion balloon	not intravascular occlusion balloon	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Wu Q 2016	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Very strong association	230/268 (85.8%)	38/268 (14.2%)	**OR −8.36** (−9.15 to −7.57)	**1,000 more per 1,000** (from 1,000 more to 1,000 more)	⊕⊕⊕⊕ High	Important
Peng W 2020	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	252/586 (43.0%)	296/586 (50.5%)	**OR 0.46** (0.29 to 0.63)	**186 fewer per 1,000** (from 277 fewer to 114 fewer)	⊕⊕⊕◯ Moderate	Important
Zhao X 2016	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	23 cases 34 controls –	0.0%	**OR −18.28** (−21.68 to −14.89)	– **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	No important
Duan X 2018	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	22/45 (48.9%)	23/45 (51.1%)	**OR −4.26** (−5.31 to −3.21)	**778 more per 1,000** (from 709 more to 913 more)	⊕⊕⊕◯ Moderate	Important
Wang Y 2020	Non-randomised studies	Not serious	Not serious	Not serious	Serious	Strong association	600/623 (96.3%)	23/623 (3.7%)	**OR −3.62** (−4.08 to −3.16)	**198 fewer per 1,000** (from 222 fewer to 175 fewer)	⊕⊕◯◯ Low	No important
Peng Y 2020	Non-randomised studies	Not serious	Not serious	Not serious	Not serious	Strong association	48/104 (46.2%)	56/104 (53.8%)	**OR 0.37** (−0.02 to 0.76)	**237 fewer per 1,000** (from 562 fewer to 68 fewer)	⊕⊕⊕◯ Moderate	Important

focuses on obstetric procedures, particularly those involving abnormal placentation.

Further research is essential, especially controlled clinical studies that establish clear diagnostic inclusion criteria for participants. Additionally, individualizing results based on specific interventions within our population is crucial to validate these findings.

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REVIEW

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Metformin in the management of non-alcoholic fatty liver disease: current evidence and future perspectives

Metformina en el manejo del hígado graso no alcohólico: evidencia actual y perspectivas futuras

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Keywords:
metformin, non-alcoholic fatty liver disease, biomarkers.

Palabras clave:
metformina, hígado graso no alcohólico, biomarcadores.

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), linked to obesity and type 2 diabetes, affects nearly one billion people globally, with rising prevalence due to both improved diagnostics and increasing incidence. In Mexico, NAFLD prevalence may exceed 50%. A particular study was conducted on 505 young adults, where 47% were at risk for non-alcoholic steatohepatitis (NASH), and 67.8% showed abnormal liver stiffness or confirmed NASH. NAFLD management requires a comprehensive approach, from early-stage lifestyle changes to targeted pharmacological treatments for advanced fibrosis or cirrhosis. Metformin, a widely used diabetes medication, shows promise in NAFLD by improving liver damage markers and insulin resistance and potentially reducing hepatocellular carcinoma risk, though evidence of significant liver histological improvements is limited. This article explores metformin's role in NAFLD treatment, focusing on its potential impact in Mexico and beyond.

RESUMEN

La enfermedad por hígado graso no alcohólico (NAFLD, por sus siglas en inglés), asociada con la obesidad y la diabetes tipo 2, afecta a casi mil millones de personas a nivel mundial, con una prevalencia en aumento debido a tanto mejoras en los métodos diagnósticos como al incremento en su incidencia. En México, la prevalencia de la NAFLD podría superar el 50%. Un estudio realizado en 505 adultos jóvenes encontró que el 47% estaba en riesgo de esteatohepatitis no alcohólica (NASH, por sus siglas en inglés) y que 67.8% presentaba rigidez hepática anormal o un diagnóstico confirmado de NASH. El manejo de la NAFLD requiere un enfoque integral, desde cambios en el estilo de vida en las etapas iniciales hasta tratamientos farmacológicos dirigidos para fibrosis o cirrosis avanzadas. La metformina, un medicamento ampliamente utilizado para la diabetes, muestra potencial en la NAFLD al mejorar los marcadores de daño hepático y la resistencia a la insulina, y podría reducir el riesgo de carcinoma hepatocelular, aunque la evidencia sobre mejoras histológicas significativas en el hígado es limitada. Este artículo analiza el papel de la metformina en el tratamiento de la NAFLD, con énfasis en su posible impacto en México y a nivel global.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a growing global concern, with prevalence linked to significant clinical and economic impact. It is estimated that this condition affects almost a third of the population worldwide. It is recognized as the most common liver disease in Western countries. A study based on data from the National Health and Nutrition Examination Survey in the United States showed that NAFLD prevalence was highest amongst Mexican Americans; the estimated prevalence of the disease could surpass 50%

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amongst this population.[1] Although national studies are lacking, the Mexican population is prone to this condition. A study conducted on 505 young Mexican adults showed that 47% were at risk of non-alcoholic steatohepatitis (NASH), and among them, 67.8% presented with abnormal liver stiffness or a confirmed diagnosis of NASH.[2] The burden of NAFLD is not only due to increased awareness and advances in diagnosis but also to a true rise in its occurrence, particularly parallel to rising obesity and type 2 diabetes rates, with estimates suggesting that approximately one billion people worldwide may be affected by NAFLD *(Figure 1)*.[3] Therefore, a simplified approach to prevention, diagnosis, and treatment is needed.[4] Lifestyle interventions, such as dietary changes and exercise, can be effective in the early stages of the disease, but as it progresses, there is a growing demand to develop pharmacological agents targeting advanced stages like fibrosis or cirrhosis.[5]

Exploring metformin as a possible therapeutic option for NAFLD and non-alcoholic steatohepatitis (NASH) is of great relevance. Metformin has been shown to have beneficial effects on NAFLD by protecting against cardiac ischemia-reperfusion injury, atherosclerosis, and pancreatic β-cell dysfunction induced by oxidative stress[6] Moreover, metformin has demonstrated therapeutic effects in NAFLD patients by improving markers such as Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG), and insulin resistance. Furthermore, insulin resistance plays a key role in the development of NAFLD and contributes to its progression from simple fatty liver to more severe conditions such as steatohepatitis, cirrhosis, and hepatocellular carcinoma. It is also recognized as a common feature in individuals with type 2 diabetes and a significant factor in its underlying pathophysiology.[7]

Studies have indicated that metformin could be a promising treatment option for NASH, with potential efficacy demonstrated in pediatric pilot data.[8] Additionally, metformin has been suggested to reduce the risk of hepatocellular carcinoma (HCC) and protect against NASH-related HCC, highlighting its potential to prevent liver cancer.[9] However, it is important to note that while metformin has weight loss and insulin-sensitizing properties, evidence supporting its efficacy in improving liver histology in NAFLD or NASH is still lacking.[10]

The purpose of the review article is to critically examine and consolidate existing knowledge on the use of metformin in the context of NAFLD.

MECHANISM OF ACTION

Metformin is a widely used oral antidiabetic medication known for its effectiveness in managing type 2 diabetes. Its mechanism of action involves several processes that contribute to its effects. Pharmacokinetically, metformin is well absorbed orally, with peak plasma

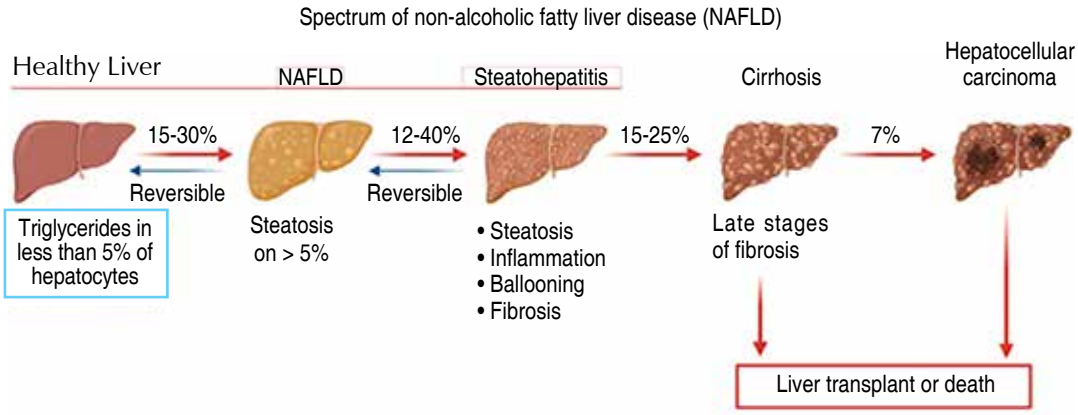

Figure 1: Spectrum of non-alcoholic fatty liver disease in NAFLD. Liver abnormalities progress from steatosis to NASH. NASH is a progressive condition that can further advance to cirrhosis and hepatocellular carcinoma (HCC). HCC = hepatocellular carcinoma. NAFLD = non-alcoholic fatty liver disease. NASH = non-alcoholic steatohepatitis.

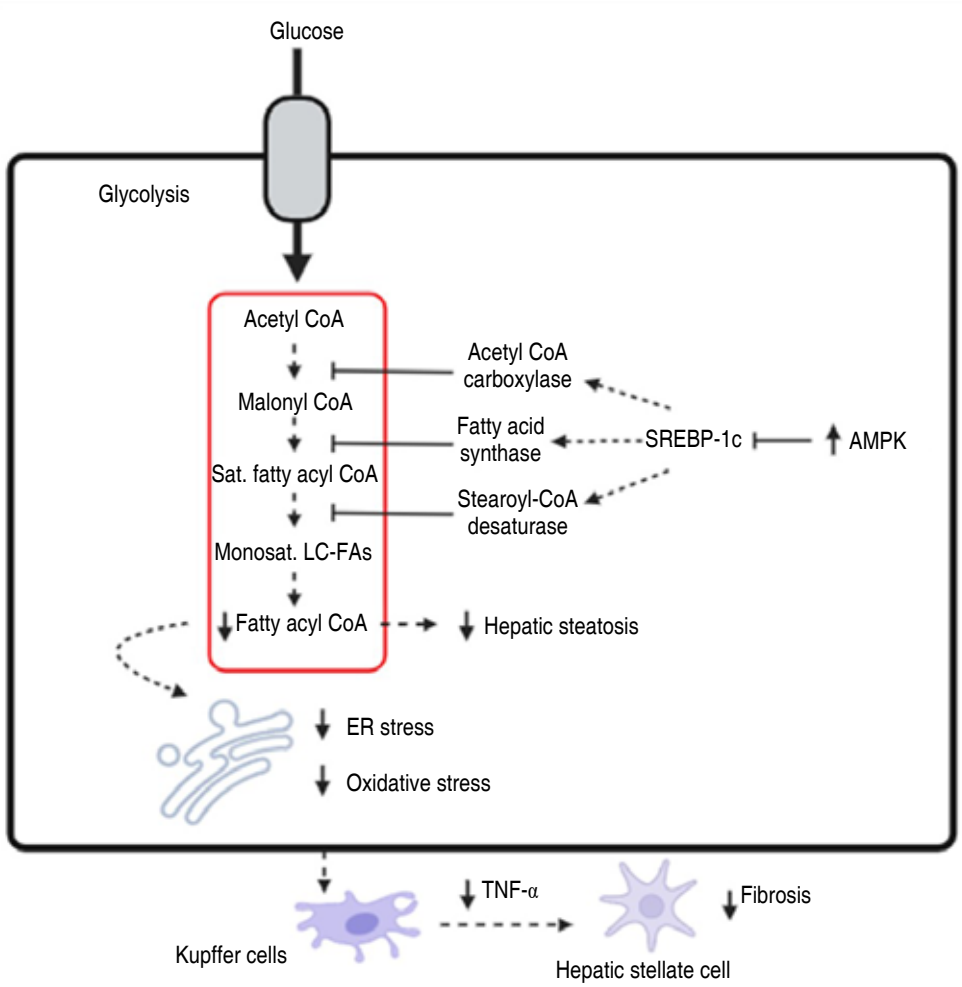

Figure 2: Metformin mechanism of action in NAFLD. Lipogenic gene expression of proteins involved in hepatic lipogenesis, including sterol regulatory element-binding protein 1 (SREBP-1c), acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase, are reduced with metformin treatment. It is speculated that these changes are related to the activation of AMPK. The resulting decrease in monounsaturated long-chain fatty acids (LC-FAs) and fatty acyl CoA also decreases hepatic steatosis by decreasing lipid-induced endoplasmic reticulum (ER) stress and decreasing substrates for fatty acid β-oxidation. Finally, reduction in oxidative stress and endoplasmic reticulum stress reduces alpha tumor necrosis factor produced by Kupffer cells, reducing hepatic stellate cell activation and resulting in a reduction of inflammation and fibrosis.

AMPK = AMP-activated protein kinase. CoA = coenzyme A. ER = endoplasmic reticulum. LC-FAs = long-chain fatty acids. NAFLD = non-alcoholic fatty liver disease. SREBP-1c = sterol regulatory element-binding protein 1. TNF-α = Tumor Necrosis Factor alpha.

concentrations reached 2 to 3 hours after administration.[11,12] It has minimal protein binding and is primarily excreted unchanged in the urine, with a half-life of approximately 6 hours.[13,14] Pharmacodynamically, metformin reduces hepatic glucose production by inhibiting gluconeogenesis, leading to lower blood glucose levels and improved insulin sensitivity.[15-17] Additionally, metformin activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy metabolism, playing a crucial role in mediating its effects on glucose and lipid metabolism.[18,19] Metformin's activation of AMPK reduces lipogenesis by inhibiting acetyl-CoA carboxylase (ACC) and decreases fatty acid oxidation, which helps to reduce the accumulation of hepatic fat, a hallmark of NAFLD progression *(Figure 2)*. By

improving mitochondrial function and reducing oxidative stress, metformin further prevents the development of steatohepatitis.[20]

Finally, by these pathways, metformin can reduce fasting and postprandial blood glucose levels by enhancing insulin sensitivity and decreasing hepatic glucose production. It also influences metabolic pathways related to glucose and lipid metabolism, contributing to its overall therapeutic effects.[21,22] Metformin's impact on glucose metabolism is further enhanced by its modulation of the cellular redox balance, affecting various metabolic pathways and cellular processes.[20]

METFORMIN AND NAFLD: KEY STUDIES

NAFLD is a spectrum of liver disorders characterized by excessive fat accumulation in the liver without significant alcohol consumption. One of the driving forces in NAFLD is insulin resistance, which results in increased lipolysis, leading to an influx of free fatty acids into the liver. This excess fat, combined with impaired mitochondrial function, promotes oxidative stress and inflammation, progressing from simple steatosis (fatty liver) to NASH, where inflammation and liver cell damage occur. Over time, this can lead to fibrosis, cirrhosis, and eventually hepatocellular carcinoma.[6]

Diagnosing NAFLD is challenging due to the absence of specific symptoms in the early stages. It is often identified incidentally during imaging for other conditions or through elevated liver enzymes in blood tests. However, the gold standard remains liver biopsy, which can differentiate between simple steatosis and NASH. Non-invasive diagnostic methods are under development, but current limitations in distinguishing disease stages hinder early intervention.[6,23]

Current treatments for NAFLD primarily revolve around lifestyle modifications, such as weight loss through diet and exercise, which remain the cornerstone of management. No specific pharmacological treatment for NAFLD has been approved yet. The limitations in treating advanced stages of the disease, such as cirrhosis or hepatocellular carcinoma, highlight the urgent need for more targeted therapies.[6,23]

In this context, metformin, a widely used drug for type 2 diabetes, has gained attention for its potential benefits in treating NAFLD. Given its effects on insulin sensitivity and hepatic glucose production, metformin could address some of the underlying drivers of NAFLD progression.

Several key studies have demonstrated the positive effects of metformin in treating NAFLD, showing improvements in liver enzyme levels and metabolic parameters. A study by Zhou et al.[6] demonstrated the therapeutic effect of metformin in treating NASH by reducing hepatic glucose production. Another study by Woo et al.[23] found that metformin had beneficial effects on improving histological parameters such as inflammation, steatosis, and fibrosis in patients with NAFLD. Feng et al.[24] compared the effects of gliclazide, liraglutide, and metformin in patients with type 2 diabetes (T2DM) and NAFLD, showing metformin's positive impact on both diabetes and NAFLD treatment. A study by Zhang et al.[9] highlighted metformin's protective mechanisms in hepatocytes and immune cells against NAFLD-related hepatocellular carcinoma (HCC). Pinyopornpanish et al.[25] found that metformin, in combination with diet, improved insulin resistance in NAFLD patients, indicating positive effects on metabolic parameters. Additionally, Green et al.[26] conducted a meta-analysis and network pharmacology study supporting metformin's efficacy in treating NAFLD, emphasizing its potential benefits on liver enzymes and glucose metabolism. These studies suggest that metformin's benefits in reducing hepatic steatosis are particularly evident in individuals with higher BMIs, potentially due to its pronounced effects on improving insulin sensitivity and reducing liver fat content.

However, while metformin has shown promise in treating NAFLD, there are challenges and limitations to its efficacy. Not all patients experienced the same degree of improvement in liver enzymes, histology, or metabolic parameters in these studies.[6,23] Metformin may be more effective in the early stages of NAFLD and might have limited efficacy in advanced disease stages, particularly in cases of severe fibrosis or cirrhosis.

Adverse effects, especially gastrointestinal side effects like diarrhea, nausea, and abdominal discomfort, are associated with metformin and may affect patient adherence.[9,25] While it showed improvements in liver enzymes and metabolic parameters, its impact on histological changes in the liver, such as fibrosis regression, was unclear.[27,28] Studies used a wide range of doses, indicating that the optimal dose and duration of metformin treatment for NAFLD are still under investigation, and individualized treatment approaches may be necessary for optimal outcomes. However, efficacy in reducing intrahepatic lipids has been demonstrated *in vivo* studies with mice, where a dose of 3 mg/kg/day orally for 5 weeks showed a decrease in hepatic triglycerides and total cholesterol and increased AMPK activity. A dose of 300 mg/kg/day orally for 6 weeks improved liver histology and delayed NAFLD development, as well as reduced NAFLD activity scores.[25]

FUTURE PERSPECTIVES

Conducting long-term studies to evaluate the sustained effects of metformin on liver enzymes, histology, and metabolic parameters in NAFLD patients is essential to determine treatment durability. Comparative studies are crucial to assess metformin's efficacy against other treatment modalities, such as lifestyle interventions, other medications, or combination therapies, to identify the most effective approach for managing NAFLD. Mechanistic studies play a vital role in investigating the underlying mechanisms of metformin action in NAFLD, including its effects on hepatic metabolism, inflammation, fibrosis, and immune response, thus elucidating the pathways involved in its therapeutic effects. Additionally, imaging studies using advanced modalities like MRI or spectroscopy are important for assessing changes in liver fat content, fibrosis, and inflammation in response to metformin treatment.[6,23,24,29]

Emerging biomarkers, such as cytokeratin-18 (CK-18) and Patatin-like phospholipase domain-containing protein 3 (PNPLA3) variants, show promise in providing non-invasive means to assess disease severity and progression in NAFLD patients. These markers may soon play a crucial role in identifying individuals at higher risk for fibrosis or hepatocellular carcinoma.

In patients with NAFLD, elevated levels of CK-18 fragments in the blood correlate with increased hepatocyte apoptosis, which is a hallmark of disease progression from simple steatosis to NASH. The ability of CK-18 to differentiate between these stages is important since NASH is associated with a higher risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma. This provides the potential to replace invasive liver biopsies in diagnosing and monitoring NASH. Elevated CK-18 levels have been validated in multiple studies as a marker of liver inflammation and fibrosis severity, making it a useful tool in both clinical trials and clinical practice for evaluating the efficacy of treatments like metformin. For instance, CK-18 could help identify NAFLD patients who are more likely to benefit from metformin therapy based on the extent of liver cell injury and disease progression.[30]

Meanwhile, PNPLA3 is a gene that encodes a protein involved in lipid metabolism. Variants in the PNPLA3 gene, particularly the I148M polymorphism, have been strongly associated with the development and progression of NAFLD. This variant is associated with an increased accumulation of triglycerides in hepatocytes, which exacerbates liver fat deposition and contributes to the progression of NAFLD. Patients with this variant are at higher risk of developing more severe forms of NAFLD, including NASH, fibrosis, cirrhosis, and hepatocellular carcinoma.[30]

The identification of PNPLA3 variants in patients could serve as a genetic biomarker for assessing disease risk and severity. Screening for PNPLA3 variants might help in stratifying NAFLD patients based on their risk for progression to severe fibrosis or HCC. This could be particularly useful for personalized treatment approaches, as individuals carrying this variant may require more aggressive management, including the consideration of therapies like metformin.[30]

Novel biomarkers hold significant potential for guiding the treatment of NAFLD. For example, elevated CK-18 levels may serve as an indicator for intensifying therapeutic interventions in patients at higher risk of

disease progression. Similarly, identifying the PNPLA3 variant in patients could facilitate early implementation of lifestyle modifications and targeted pharmacological treatments, such as metformin, to mitigate disease progression and reduce the risk of severe complications, including cirrhosis and hepatocellular carcinoma (HCC). These advancements pave the way for more personalized and effective management strategies in NAFLD care.[30]

The treatment landscape of NAFLD is evolving, focusing on identifying effective strategies for managing this condition. We are entering an era of precision medicine, so future studies should explore the potential role of genetic factors in determining individual responses to metformin treatment in NAFLD patients, leading to personalized treatment approaches.

CONCLUSION

Long-term studies are essential to evaluate metformin's effects on liver enzymes, histology, and metabolic parameters in NAFLD. Comparative studies should assess its efficacy against lifestyle interventions, other medications, or combination therapies. Mechanistic studies will further elucidate metformin's impact on hepatic metabolism, inflammation, and fibrosis.

In conclusion, while metformin shows promise for NAFLD treatment, its efficacy is context-dependent, with benefits primarily seen in early-stage disease. It holds potential for integration into a precision medicine framework, particularly when combined with other therapies or targeted interventions. Further research is warranted to establish optimal dosing, duration, and combination strategies, paving the way for personalized treatment approaches that address the complexities of NAFLD management.

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Review

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Leptin: a description of its intriguing biology. A review. Part I

Leptina: descripción de su intrigante biología. Una revisión. Parte I

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Abbreviations:
BMI = Body Mass Index
CRH = Cytokine Receptor Homology
CRP = C Reactive Protein
CVD = CardioVascular Diseases
DM2= Type 2 Diabetes Mellitus
FNIII = FibroNectin III-like domains
IGD = ImmunoGlobulin-like Domain
IL-6 = Interleukin-6
JAK2= Janus tyrosine Kinase 2
LepR or ObR = Leptin Receptor
MAFLD = Metabolic Dysfunction-Associated Fatty Liver Disease
MS = Metabolic Syndrome
O/O = Obesity and overweight
PPRγ = Peroxisome Proliferator-Activated Receptor Gamma Agonists
STAT3= Signal Transducer and Activator of Transcription 3
TNF-α = Tumor Necrosis Factor-α

INTRODUCTION

Obesity and overweight (O/O) are significant public health problems worldwide. Recent estimates from the World Health Organization indicate that around two and a half billion adults are overweight, and 850 million are obese (one in eight adults in the world suffers from O/O).[1] These pathologies are defined as chronic, heterogeneous, and recurrent diseases due to an imbalance between caloric intake and energy expenditure, in which an expansion of white adipose tissue occurs, often associated with abnormal adipocyte function, insulin resistance, and secondary hyperinsulinism, low-intensity systemic inflammation, nitroxidative stress, and endothelial dysfunction, affecting various organs and systems of the economy.[2]

The expanding and deepening knowledge of energy metabolism, adipocyte function, and humoral and endocrine control of weight has modified many paradigms supporting their diagnostic and therapeutic management. However, until this time, more attention is paid to the cardiometabolic consequences of O/O (systemic arterial hypertension, dysglycemia, and dyslipidemia) than to the anthropometric, structural, and pathophysiological disorder milieu that generates them, as the increase and dysfunction of adipocyte mass and one of the more overlooked aspects in its genesis, the abnormalities of the appetite/satiety cycle that motivates animals to search for food. The interoceptive sensation of appetite or hunger is present in numerous species.[3] In animals with a more developed brain, appetite is regulated by a complex system of signals and responses involving the hypothalamus' nuclei, the cerebral cortex, digestive hormones, the pancreas, and fatty tissue, among other structures.[3] In animals with a more developed brain, appetite is regulated by a complex system of signals and responses involving the hypothalamus' nuclei, the cerebral cortex, digestive hormones, the pancreas, and fatty tissue, among other structures. The mechanism of the gastrointestinal system-adipose tissue-pancreas-hypothalamus axis, controlling the appetite/satiety cycle, is disturbed in

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O/O. In this context, among the elements of this physiological axis, leptin plays a fundamental role.[4]

This review is focused on describing leptin, an adipocyte-derived hormone (adipohormone), and its receptors, discussing its varied and complex functions, and reviewing the epidemiological data linking it to disorders, such as O/O, the so-called metabolic syndrome (MS), type 2 diabetes mellitus (DM2), metabolic dysfunction-associated fatty liver disease (MAFLD) and cardiovascular diseases (CVD), among others, as well as the pathophysiological mechanisms that trigger its deregulation. This review is based on a question that still has no clear answer: whether a deeper understanding of leptin and other adipohormones levels can improve the prevention, diagnosis, and preventive and therapeutic management of O/O syndrome.

LEPTIN

This adipohormone is a protein composed of 167 amino acid residues, encoded by the LEP gene located on the long arm of chromosome 7.[5] It is a member of the family of long-chain helical cytokines (such as interleukin 6) found not only in terrestrial and marine mammals but also in non-mammalian vertebrates, such as fish and reptiles.[6] Likewise, crustaceans and insects produce the hormone or analogs that form complex loops intestine-brain that regulate appetite.[6] For example, the fruit fly's brain (genus *Drosophila*) produces a series of satiety peptides, one of them an analog of leptin from the family of unpaired proteins (Upd1).[7] Interestingly, leptin analogs have not been found in worms.[8]

Leptin is produced in humans mainly in the white adipocyte, the principal energy reserve and source and target of numerous substances.[9] To a lesser extent, the hormone is secreted in other tissues and organs such as the mammary gland, placenta, ovary, skeletal muscle, stomach, epithelia, pituitary gland, hepatocytes, and lymphoid tissue.[10]

There is sexual dimorphism in the concentration of leptin. The values in thin women and men are 12-13 and 4-5 mg/L, respectively. The different values relate to a more significant amount of fatty tissue in women, estrogens' stimulating effect, and the androgens' inhibitory role.[11-13] Women have a 50% greater leptin production than men, even before puberty and after menopause. Age also influences the concentration of the hormone. *Table 1* shows leptin concentrations at different ages in both genders.

There are also considerable interethnic differences. Europeans have lower circulating levels than Asians and Latin Americans. Afro-American women have the highest levels of this adipohormone.[14,15] Leptin concentrations are also influenced by glucocorticoids, insulin, peroxisome proliferator-activated receptor gamma agonists (PPRγ), estradiol, follicle-stimulating hormone, various proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (IL-6 and TNF-α), glucose, fructose, and L-glutamate.[16] Conversely, catecholamines, free fatty acids, exposure to cold, testosterone, and thyroid hormones exert an inhibitory action on its secretion.[17,18] Serum concentrations of this adipohormone present a higher concentration in the early morning[17] and decrease rapidly after fasting or with caloric restriction.[19]

Leptin links the individual's nutritional status with other physiological functions, such as reproduction and immune response. In general, the increase in body mass index (BMI) is associated with a proportional increase in leptin concentration in both genders, correlating better with the percentage of body fat than with BMI, which is known to be a marker of corpulence, which is not only associated with obesity but also with skeletal muscle mass.[18,60] Although most obese persons have hyperleptinemia, a small percentage do not, which is one of the paradoxes of this intriguing molecule.[61] One of the possible explanations for this fact is that the use of BMI can be misleading in muscular subjects and does not reflect the accumulation of visceral fat.[62] Another is that the metabolic disorders of obesity, such as insulin resistance/hyperinsulinism syndrome, dysglycemia, dyslipidemia, the increased production of proinflammatory cytokines, and hyperleptinemia, among others, do not occur in all obese people but only in those with ischemic, dysfunctional and inflamed adipose

Table 1: Leptin concentration values according to age and gender.

Age groups	Number of studies	Gender: Men Mean [range], µg/L	Gender: Women Mean [range], µg/L	Differences Δ (%*)
Umbilical cord[20-28]	9	6.26 [1.2-11.5][20,21]	9.78 [1.5-19.6][20,21]	3.52 (56)
Newborns[29,30]	2	1.36 [0.93-1.8][29,31]	1.84 [1.38-2.3][29,31]	0.48 (35)
< 6 months[31-33]	3	2.85 [1.5-4.5][31,32]	3.29 [1.73-4.8][31,32]	0.44 (15)
6-12 months[31-33]	3	2.26 [0.43-5.0][31,32]	2.64 [0.53-5.7][31,32]	0.38 (16)
1-4.9 years old[33,34]	2	1.36 [1.3-1.42][33,34]	2.05 [1.9-2.2][33,34]	0.69 (47)
5-10 years old[34-36]	3	3.08 [1.7-4.38][34,35]	4.34 [2.0-5.57][34,36]	1.26 (40)
10-15 years old[12,35-37]	4	3.88 [1.6-7.61][12,37]	9.66 [5.8-15.4][12,37]	5.78 (149)
15-20 years old[12,36-38]	4	3.27 [1.1-6.7][12,37]	13.9 [7.6-16.7][12,37]	10.63 (325)
20-50 years old[39-51]	13	6.7 [1.37-14.9][39,40]	17.28 [5.91-46.3][39,40]	10.58 (157)
50-65 years old[39,41,42,45,47,51-55]	4 (men) 10 (women)	6.31 [2.12-10.0][39,42]	14.47 [5.21-31.4][39,41]	8.16 (129)
> 65 years old[40,42,47,48,50,51,56-59]	5 (men) 10 (women)	5.8 [2.11-10.0][42,56]	15.69 [6.4-25.1][56,57]	9.89 (170)

* Women compared to men.
Average 3.92 ± 2.01 µg/L in men, and 8.73 ± 6.01 µg/L in women (difference of 4.71 µg/L, p = 0.023).

tissue, which is observed when the growth of fat mass exceeds the possibilities of tissue nutrition that depends on appropriate angiogenesis.[63,64] In this respect, our research group has found that 17.4% of subjects with O/O had normal metabolism (5.4% of obese subjects and 12% of those with overweight).[64] Other studies have shown that a higher leptin concentration is associated with dysmetabolism.[65,66] The inflammatory state favors the production of leptin because proinflammatory cytokines induce the synthesis of the hormone.[67] However, other studies did not show significant differences in leptin concentration between «metabolically healthy» obese subjects and those with dysmetabolism.[68] The causes of this apparent paradox remain to be elucidated.

LEPTIN PHYSIOLOGY

Leptin is a classic multifunctional substance with almost 100 known functions in different tissues, organs, and systems. *Table 2* describes some of these actions in the cardiovascular and nervous systems and energy, lipid, and carbohydrate metabolism. However, the hormone has numerous other effects not considered in this review, for example, milk production, various reproductive and placental processes, the systemic immunoinflammatory reaction, bronchial muscle tone, bone density, carcinogenesis, certain mental states such as depression, absorption, and digestion of nutrients in the intestine, and the production of mucus in the colon, among many others.

THE LEPTIN RECEPTOR

The leptin receptor (LepR or ObR) belongs to the class I cytokine receptors family. Six isoforms of this receptor exist, caused by alternative splicing. They share the binding sites and the same N-terminal region while differing in the C-terminal cytoplasmic region. There is a long-form (LepRb), four short forms: LepRa, LepRc, LepRd, LepRf, and a soluble form (LepRe) *(Figure 1)*.[125,126] Only 10 to 20% of LepRb is expressed in the cell membrane; the rest is found

Table 2: Actions of leptin in various functions and systems.

Cardiovascular system	
Vasodilation	Increases eNOS activity, NO availability, EDHF, and endothelin-1 expression[69-71]
Angiogenesis	Stimulates the production of VEGF and the expression of the VEGF-R2 receptor. It raises COX-2 enzymes and promotes endothelial and smooth muscle cell proliferation[72]
Heart rate and blood pressure	Both increase as a consequence of sympathetic nervous system stimulation[73]
Contractility of cardiac and vascular muscle	Increments in the activity of voltage-gated Ca^{++} channels and GPCRs promote the functioning of proteins such as calreticulin, cAMP-dependent protein kinase type II, and tropomyosin. Furthermore, it stimulates cell growth and proliferation through myotrophin, myoferlin, and fibrin-1 synthesis[74]
Coagulation	Increases factor VIII and IX concentrations[75]
Atherosclerosis	Promotes platelet aggregation, ROS formation, and the expression of endothelin-1, MCP-1, and thrombospondin 1. Increases local and systemic inflammation by increasing the production of TNF-α, IL-6, and IL-1β in mononuclear leukocytes[76-81]
Natriuresis	Activates the Na^{+}-K^{+}-ATPase pump in the renal tubule, promoting the excretion of Na^{+} and water[82]
Vascular fibrosis	Causes increased production of metalloproteinases MMP-2 and MMP-9, collagen types I and IV, fibronectin, TGF-β and CTGF[83-85]
Cardiac hypertrophy	It causes cardiac hypertrophy due to increased actin production.[86,87] Furthermore, hypertrophy is stimulated by an increase in heart rate and blood pressure, secondary to overactivation of the sympathetic nervous system[88]
Heart failure	Leptin concentration is a prognostic factor for heart failure in dilated cardiomyopathy, probably due to the induction of inflammation, fibrosis, and alterations in Ca^{++} homeostasis, and also for the induction of hypertrophy and endothelial dysfunction, among several other factors[89,90]
Cardiac protection	Leptin limits the extension of myocardial infarction by stimulating the enzyme RISK, inhibiting cardiomyocyte apoptosis,[91] reducing cardiac lipotoxicity, preventing the opening of the mPTP pore, and inhibiting death cell caspase 3 induced by TNF- α[86]
Central nervous system	
Effect on appetite	It reduces appetite by inhibiting the orexigenic NPY/AgRP neurons and activating the anorexigenic cells of the proopiomelanocortin/CART system.[92,93] It modulates the solitary tract's function, which includes the transmission of food flavor and the regulation of portion sizes.[94] It intervenes in the reward circuit by inhibiting dopaminergic neurons in the ventral tegmental area,[95.96] decreasing the sensitivity of the olfactory bulb[94,97]
Sympathetic nervous system	It activates the sympathetic system through the MTC4 receptor in the paraventricular nucleus that stimulates the sympathetic preganglionic neurons[98,99]
Cognitive functions	It regulates memory and learning functions in the hippocampus through NMDA receptors,[100] stimulates neuroplasticity in some areas of the cortex and hippocampus. It exerts a neuroprotective effect in neurodegenerative diseases such as Parkinson's and Alzheimer's, mediated by the increase of the BDNF factor[101, 102]
Hypothalamic hormones	Releases the hormones GnRH, ACTH, and TRH[102-105]
Metabolic functions	
Lipolysis	This is due to increased sympathetic activation and activation of ATG and HSL lipases[106,107]
Free fatty acid oxidation	Due to the greater activity of PPARα, PGC1α, CPT1, AMPK, and acyl-CoA oxidase[107-111]
Citric acid cycle	Enhanced by stimulating citrate synthase[112]
Lipogenesis	It is inhibited by reducing the SREBP1, FASN, and ACC1 activity in white adipose tissue[93]
Hepatic gluconeogenesis	Decreases hepatic gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase, glucose 6-phosphate phosphatase, CREB, and PGC1[113,114]
Glycolysis	Incremented by stimulating PFK and hexokinase[115,116]
Cholesterol metabolism	It raises the concentration of LDL by decreasing the density of the hepatic LDL receptor[117] and increasing cholesterol synthesis by stimulating the activity of HMG CoA reductase[118]

Contiuous Table 2: Actions of leptin in various functions and systems.

Relation with insulin	It decreases insulin synthesis by increasing the conductance of K^+ channels in pancreatic cells.[119] Also, it improves insulin sensitivity by sharing the IRS-PI3k signaling pathway with insulin.[120] Finally, it enhances insulin inhibition of gluconeogenesis and hepatic glycogenolysis[121,122]
Glycogen genesis	It is stimulated by increasing insulin sensitivity[120]
Adipose tissue	It induces the expression of the heat-producing protein UCP-1, characteristic of brown and beige adipocytes.[123] It reduces fat mass by activating lipolysis and inhibiting lipogenesis[124]

ACC1 = Acetyl-CoA carboxylase. ACOX1 = Acyl-CoA oxidase 1. ACTH = Adrenocorticotropic hormone. AgRP = Agouti-related peptide. AMPK = AMP-activated protein kinase. ATG = Adipose triglyceride lipase. CART = Cocaine- and amphetamine-regulated transcript. COX-2 = Cyclooxygenase-2. CREB = Cyclic AMP-response element binding protein. CTGF = Connective tissue growth. EDHF = Endothelium-derived hyperpolarizing factor. eNOS = Endothelial nitric oxide synthase- NO, nitric oxide. FASN = Fatty acid synthase. G6PD = Glucose-6-phosphate dehydrogenase. GnRH = Gonadotropin-releasing hormone. GPCRs = G protein-coupled receptors. HD = High-density lipoprotein. HK2 = Hexokinase 2. HMG CoA = β-hidroxi-β-metilglutaril-CoA. HS = Hormone-sensitive lipase. IRS = Insulin receptor substrate. LDL = Low-density lipoprotein. MMP-2 and 9 = Matrix metalloproteinase-2 and -9. NFAT = nuclear factor of activated T cells. NMDA = N-metil-D-aspartate. NPY = neuropeptide Y. PAI-1 = plasminogen activator inhibitor-1. PEPCK = phosphoenolpyruvate carboxykinase. PFK = phosphofructokinase. PGC 1γ = peroxisome proliferator-activated receptor gamma coactivator-1. PGC1α = peroxisome proliferator-activated receptor-gamma coactivator 1-alpha. PI3k = phosphoinositide 3-kinase. POMC = proopiomelanocortin. PPARα = peroxisome proliferator-activated receptor alpha. PT1 = carnitine palmitoyltransferase. ROS = reactive oxygen species. SREBP1 = sterol regulatory element binding protein. TGF-β = transforming growth factor-β. TRH = thyrotropin-releasing hormone. UCP-1 = uncoupling protein-1. VEGF = vascular endothelial growth factor. VEGF-R2 = vascular endothelial growth factor receptor 2.

in the endoplasmic reticulum, the endosomes, and especially in the Golgi apparatus and trans-Golgi system. When internalized, leptin receptors can be transported back to the cell membrane or ubiquitinated (attached to the small protein ubiquitin, which marks them for degradation).[125] The presence of leptin is the primary determinant of modulating the density of LepR in the membrane. It has been shown that when the hormone increases, its receptor is endocytosed by clathrin (a protein that coats some membrane vesicles) dependent pathways. The nutritional status also contributes to the density of the leptin receptor in the membrane; for example, a high-fat diet increases it, while caloric restriction and fasting decrease its density in the membrane.[127]

The primary function of the short receptor isoforms is to transport the hormone into the central nervous system and for renal elimination.[128] The transmembrane isoforms are cleaved by cathepsin L and the metalloproteases ADAM 10 and ADAM 17, forming the soluble receptor LepRe, the central plasma leptin binding protein, thus regulating its availability.[129,130] The long isoform is found mainly in the hypothalamus and other tissues such as the heart, placenta, muscle, liver, pancreas, spleen, prostate, testis, ovary, small intestine, and colon.[131] LepRb has the most extended intracellular portion capable of activating different cell signaling pathways leading to the expression of various proteins, enzymes, and neurotransmitters, in addition to regulating other receptors, hormones, and cytokines, which explain all the complex physiological effects of leptin.[132]

The extracellular region comprises six domains: an N-terminal domain, two cytokine receptor homology (CRH) domains, CRH1 and CRH2, separated by an immunoglobulin-like domain (IGD), and two fibronectin III-like domains (FNIII) *(Figure 1)*. The primary binding sites of the adipohormone to the receptor are CHR2 and FNIII.[132,133]

The Leptin binding to its receptor activates several signaling systems, as shown in *Figure 2*. The Janus tyrosine kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) is a signaling cascade comprising a receptor, a phosphorylating kinase, and a transcription element. Leptin binding to its receptor induces the transphosphorylation of the kinase, which phosphorylates some tyrosine residues that attach to the STAT3 factor. After it is phosphorylated, it is released from the kinase

and translocated through the nuclear pore, inserting itself into several genes' regulatory, non-coding regions and activating them. As a counter-regulatory loop, STAT3 induces, in turn, the expression of the suppressor of cytokine signaling 3 (SOCS3), which inhibits the phosphorylation and activation of STAT and JAK components. Also, the tyrosine-protein phosphatase non-receptor type 1(PTP1B), expressed during endoplasmic reticulum stress, inhibits the JAK phosphorylation. This negative feedback mechanism prevents the overactivity of the leptin receptor activation. Other signaling pathways are the insulin receptor substrates (IRS)/phosphoinositol 3-kinase (PI3K), the protein tyrosine phosphatase Src homology 2 (SHP-2)/mitogen-activated protein kinases (MAPK), and the 5-AMP-activated kinase (AMPK)/acetyl coA carboxylase (ACC).

In humans, the LepRa is the most abundant isoform, expressed mainly in the choroid plexus, regulating the leptin transport to the central nervous system. Being a receptor-mediated transport, it is a saturable system in which there is no further increase in leptin amount in cerebrospinal fluid when the leptin concentration exceeds 25-30 ng/mL.[133,134]

The LepRe generated by the fragmentation of transmembrane receptors is the main protein regulating the availability of adipohormone. The serum concentration of LepR is lower in obese than in lean persons, contrary to what is expected in hyperleptinemia, and the density of the transmembrane receptors decreases due to ligand-induced receptor sensitization. The Free Leptin Index (FLI), the ratio between the hormone and LepRe serum concentrations, reflects the tissue sensitivity to the hormone, which decreases after weight loss.[135,136]

In this regard, hyperleptinemia in patients with O/O is related and probably caused by tissue resistance to the hormone. Patients with O/O have, in general, higher FLI values than lean subjects. Remarkably, in patients with O/O and hyperleptinemia, a paradoxical fact is observed: the hormone does not suppress appetite and does not activate energetic metabolism.[129] This leptin resistance must be interpreted as an adaptive response in some situations. For example, in grazing animals during winter months or in women during the last trimester of pregnancy, it is a mechanism for storing energy.

Some leptin mutations or its receptors commonly cause tissue resistance in humans. On the other hand, even if there is a genetic predisposition, only 3 to 5% of obesity cases are of genetic origin, either by mutation of leptin, the LepRb receptor, or some substances related to its actions (POMC, proconvertase 1,

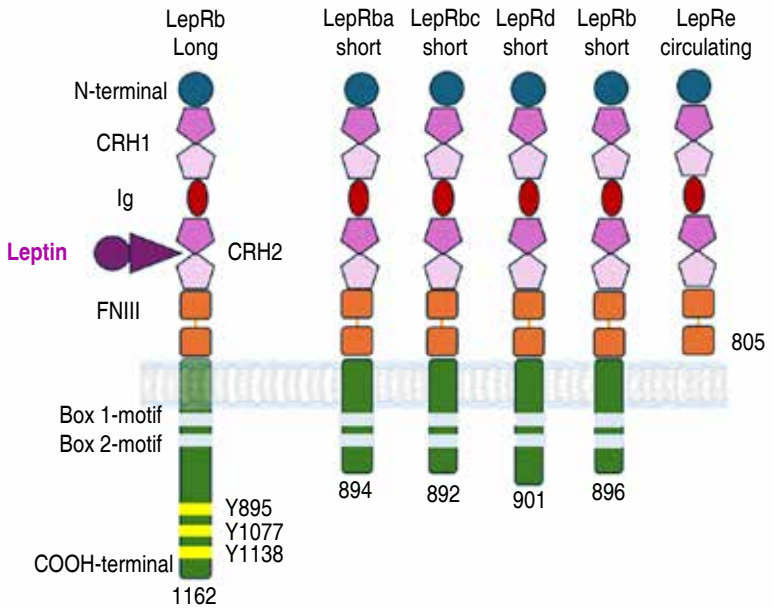

Figure 1:

The leptin receptor isoforms. LepRb (Leptin Receptor b), LepRa (Leptin Receptor a), LepRc (Leptin Receptor c), LepRd (Leptin Receptor d), LepRf ((Leptin Receptor f), LepRe (Leptin Receptor e), CRH1 (cytokine receptor homology 1), CRH2 (cytokine receptor homology 2), IGD (immunoglobulin-like domain), FNIII (fibronectin III-like domain).

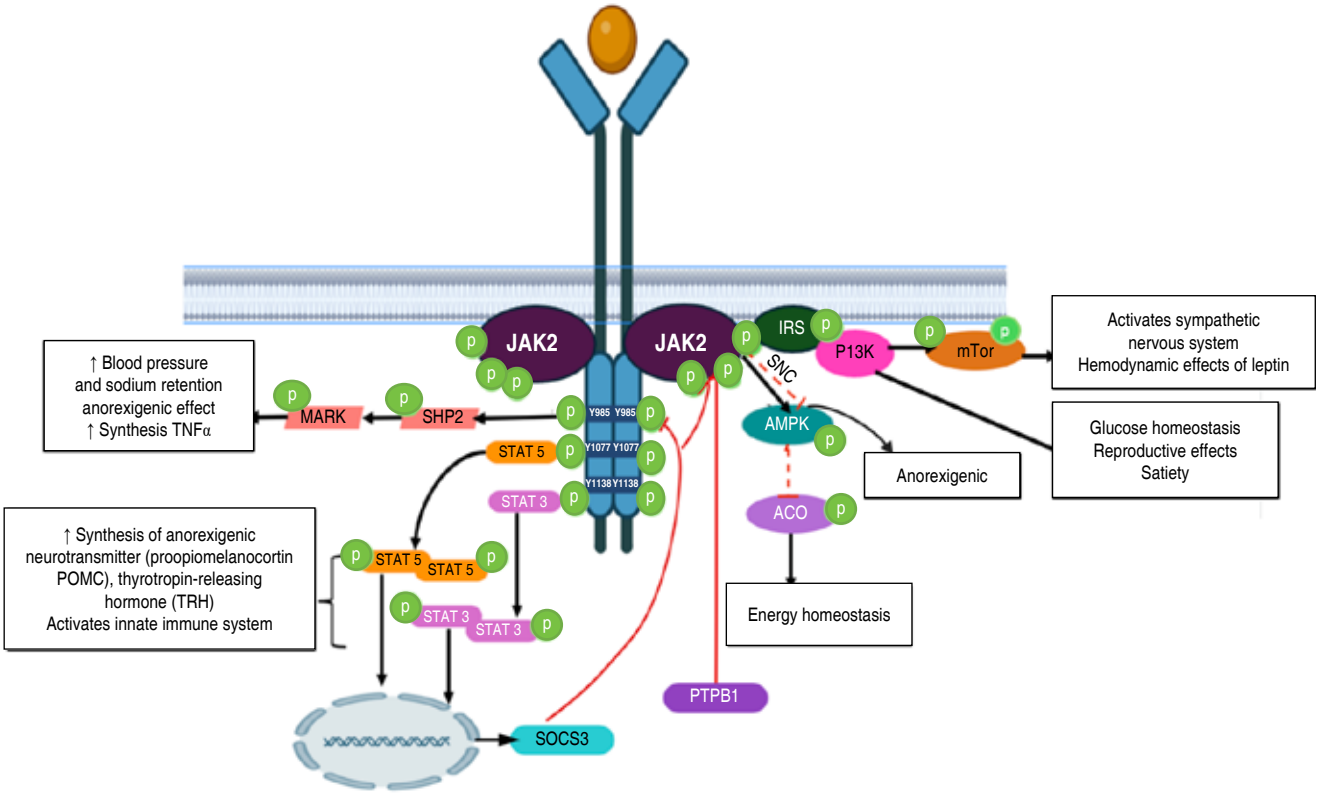

Figure 2: Leptin receptor signaling: Jak2 (Janus tyrosine kinase 2), MAPK, SHP2, STAT 3 (signal transducer and activator of transcription 3), STAT 5 (signal transducer and activator of transcription 5), ACC (acetyl CoA carboxylase), AMPK (5-AMP-activated kinase), IRS (insulin receptor substrates), PI3K (phosphoinositol 3-kinase), mTor (mammalian target of rapamycin), SOCS3 (suppressor of cytokine signaling 3), PTPB1 (protein tyrosine phosphatase 1B).

prohormone convertase 1 (PC1), Sh2b1[137] and MC4R.[138] Congenital leptin deficiency is a rare condition causing hyperphagia and early-onset obesity, accompanied by decreased thyroid-stimulating hormone and hypogonadism.[139] The arrival of leptin to the hypothalamic nuclei is crucial to exert its anorexigenic and metabolic effects. In subjects with hyperleptinemia, there is a decrease in its transport.[140] Despite the exogenous administration of leptin, there is no adequate decrease in appetite and weight.[141] In murine models of obesity, peripheral administration of leptin is not associated with a reduction in appetite and weight.[142] Leptin does not decrease food intake, whereas intrathecal administration does do so. This is because the leptin transport system is receptor-mediated and saturable. A diet high in fat, fructose, and salt decreases the transport to the central nervous system.[143,144]

O/O patients have a condition of chronic low-degree inflammation and substantially higher production of proinflammatory cytokines and markers of inflammation, affecting leptin sensitivity. For example, the concentration of C reactive protein (CRP) is directly proportional to leptinemia.[145] CRP attaches to the hormone, interfering with the leptin-receptor interaction. Also, when incorporated into the receptor's structure (transmembrane and soluble), it is rendered functionally unable. On the other hand, the proinflammatory cytokines causing endoplasmic reticulum stress also activate the NF-κB, a multiple transcription factor, leading to the expression of SOCS3 and PTB1B. These molecules inhibit the functioning of the leptin receptor, as was described before.[146]

The physiology of leptin, a classical multifunctional hormone, exceeds its essential role as a key appetite and energy regulator.

From a biological point of view, nutritional status, depending at large on the sufficient ingestion of food, is a *sine qua non* condition for correct organic performance, immunological competence, and reproductive capacities. The knowledge of this complex, intriguing, and sometimes paradoxical hormone can change the prejudices and false concepts around obesity.

In a forthcoming publication, we will discuss the implications of leptin abnormalities in the clinical settings of obesity, high blood pressure, and diabetes.

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