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Case report

Stem cells and exosomes therapies in mesial temporal sclerosis: a case report.

Terapia de células madre y exosomas en la esclerosis mesial del temporal: a propósito de un caso.

Ciarrochi, Eduardo[1]; Ciarrochi, Juan Bautista[1]; Ugartemendía, Leonardo Adrián[1].

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Abstract

Mesial temporal sclerosis (MTS) is a well-defined form of structural focal epilepsy, characterized by neuronal loss and gliosis in the hippocampus and related structures. It is associated with a neurotoxic microenvironment that disrupts neurogenesis, synaptogenesis and dendritic spines plasticity, leading to cognitive, memory, and emotional dysfunctions. We present the case of a 14 years old patient, clinically and radiologically diagnosed with MTS, who exhibited severe cognitive, affective and behavioral impairments, including working memory deficits, receptive and expressive language disturbances and marked attention deficits. A novel therapeutic strategy was proposed combining autologous stem cells and exosome application, with focus on their immunomodulatory properties aimed at promoting structural and functional regeneration of hippocampal tissue. During follow-up, the patient showed progressive improvement in higher cognitive functions, including restoration of both anterograde and retrograde memory, enhanced attentional capacity, enriched language use, and marked socio-emotional maturation. This case highlights the therapeutic potential of stem cells and exosomes therapies as an innovative strategy for regeneration of structural and functional impairments in MTS.

Keywords: Stem cells, exosomes, mesial temporal sclerosis, Hippocampus, immunomodulation

Introducción

La esclerosis mesial del temporal (EMT) es una entidad bien definida de epilepsia focal estructural caracterizada por gliosis y perdida neuronal a nivel del hipocampo y estructuras aledañas (1). Esta pérdida neuronal, es particularmente significativa a nivel del giro dentado y en las regiones CA1 (área de Sommer) y CA3 del hipocampo, con predilección por las células piramidales (2). Se ha observado una desregulación inmune en los pacientes epilépticos, con elevación de citoquinas tales como IL-1B, IL-18, CCL2, CCL3 y CCL4, mostrando a la inflamación como un componente importante en la epileptogénesis (2). Sus crisis se distinguen por su complejidad y heterogeneidad clínica con participación de manifestaciones sensitivas, sensoriales, psíquicas, de la actividad mnésica y motoras (3). Esta patología, se asocia a un estado de neurotoxicicidad provocando muerte neuronal temprana, destrucción de células gliales y estrés oxidativo (4). Asimismo, la función astrocitaria se ve comprometida, afectando así el desarrollo neuronal, la sinaptogénesis y neurogénesis (5). Todo esto, se acompaña de una alteración en la expresión de los receptores de glucocorticoides y las concentraciones de dicha hormona a nivel del hipocampo, produciendo atrofia y reducción de la densidad en las espinas dendríticas (6). Contribuyendo así a la pérdida de plasticidad de estas estructuras, lo que se relaciona con los déficits mnésicos característicos del cuadro. El hipocampo, es un fuerte regulador de la función del eje hipotálamo-hipófisis- adrenal (7). Dicha cualidad se ve mermada debido a la alteración estructural y funcional del mismo presente en la EMT.

Caso clínico

Paciente de 14 años de edad que presenta epilepsia focal caracterizada clínica e imagenológicamente como EMT. Neurodesarrollo normal en la adquisición de pautas madurativas de motricidad gruesa y fina, marcha, lenguaje y control de esfínteres. Durante toda su niñez presentó episodios de convulsión febril, con diagnóstico de epilepsia en el año 2022. La paciente presenta diversas manifesta-

ciones tanto pre críticas (pródromos y aura) críticas, poscríticas e intercríticas. A los cinco años se notaron dificultades en el equilibrio y motricidad fina. Clínicamente se presenta con graves déficits de atención momentáneos, con fijación de la mirada en un punto y perdida de contacto con el entorno. La paciente, presenta grandes complicaciones en su habilidad cognitiva visuoespacial y su memoria de trabajo. Posee alteraciones tanto en el lenguaje receptivo como expresivo. En cuanto al primer aspecto, presenta dificultades en la ejecución de tareas de imitación verbal o dictado en la escritura, a su vez, presenta dificultad en la lectura y su comprensión. En concordancia con este aspecto, se le deben repetir las indicaciones o preguntas ya que se mantiene en silencio sin responder, mostrando una clara desconexión con el medio. Siguiendo el segundo aspecto del lenguaje, su articulación de la palabra en ocasiones es incomprensible, habla en volumen bajo y le cuesta mantener una conversación adecuada. En octubre de 2024 se describe una internación psiquiátrica debido a un episodio depresivo grave con síntomas psicóticos. La resonancia magnética previa a la terapéutica propuesta, mostró estas características: "dilatación de astas temporales en forma bilateral, acompañada con disminución de volumen de hipocampos predominantemente en el lado derecho". (Figura 1)

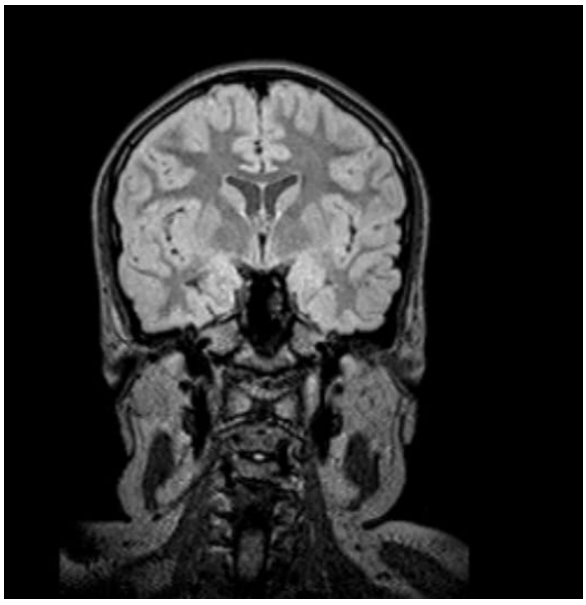

Figura 1: Corte coronal, disminución del tamaño del hipocampo a predominio derecho.

Comentarios

Destacamos el gran interés que ha recibido la fascia superficial como un sustrato relevante en la terapia con células madre para el tratamiento de diversas patologías (8). Este tejido constituye una plataforma biológica activa y una vía de comunicación para el transporte y circulación de las células madre (9). En su estructura, se encuentra una alta densidad de fibroblastos, los cuales secretan múltiples factores bioactivos, entre los que se destaca la familia de Factor de crecimiento de fibroblastos (FGFs) (10). Estas moléculas, tienen una estrecha relación con las células madre, estimulando su diferenciación, proliferación y expansión. Además, tiene acción mitógena, neurotrófica y neuroprotectora (10).

Las células madre son células indiferenciadas con capacidad de autorrenovación y diferenciación hacia diversos tipos de tejidos. Mantienen una estrecha interacción con el sistema inmunológico, pudiendo actuar sobre el microambiente inflamatorio presente en diversas patologías (11). A su vez, secretan una amplia variedad de biomoléculas activas como proteínas, ácidos nucleicos, exosomas y microvesículas que en conjunto se liberan mediante estructuras conocidas como secretomas (12). Este complejo, complementa la capacidad regenerativa y terapéutica de las células madre (12). A través de mecanismos celulares (acción sobre linfocitos Treg, macrófagos) y humorales (exosomas, secretomas), las células madre ejercen una acción inmunomoduladora capaz de regular la inflamación y favorecer la reparación tisular. Esta propiedad las convierte en una estrategia terapéutica para distintos tipos de patologías (13).

Un punto importante en nuestra estrategia propuesta es la terapia libre de células, basada en la aplicación de exosomas. Estos, tienen una importante función terapéutica, actuando como vehículos de moléculas que tienen su sostén en estructuras llamadas "Lipid Rafts", las cuales facilitan la neurogénesis y la migración neuronal (14).

Estas premisas, ayudan a comprender con mayor detalle los avances clínicos y estructurales observados en este caso de EMT. Los mismos, serán presentados cronológicamente a continuación.

Durante el primer encuentro con la paciente, ingresó con mínima intención comunicativa, estableciendo contacto únicamente con su hermana, quien respondía por ella. En el transcurso del procedimiento de extracción de células madre, presentó un episodio de desregularización neurovegetativo caracterizado por sudoración profusa, ruborización cutánea y alteraciones vasotónicas compatibles con una reacción neurovegetativa. El procedimiento continuó con éxito.

En los controles posteriores, los cuales iban acompañados de la aplicación de células madre autólogas y exosomas, se constató una progresiva mejoría en habilidades cognitivas superiores, destacándose: la atención, memoria y lenguaje. La paciente fue disminuyendo progresivamente los episodios de interrupción del pensamiento y fijación de la mirada en un punto, aumentando su atención hacia su entorno como así también la capacidad de entender y realizar las tareas que se le piden, tanto físicas como mentales. El correlato de la regeneración hipocampal se ve reflejado en una recuperación de la memoria anterógrada pudiendo realizar tareas y retener información de corto plazo con éxito, lo cual le facilitó por ejemplo, la realización de rutinas de ejercicios y actividades de coordinación fina. A su vez, su memoria retrógrada se vio favorecida, pudiendo evocar recuerdos y relatar experiencias vividas en las sucesivas visitas, algo anteriormente impensado. La paciente comenzó a expresar intereses personales, mantiene diálogos coherentes y acordes a su edad, su lenguaje se vio enriquecido con mayor variedad de palabras y descripciones detalladas.

En conjunto, se observa una maduración cognitiva, emocional y social progresiva; manifestando un perfil evolu-

tivo notablemente más adaptado y funcional. Todos estos avances encuentran su correlato en la resonancia magnética del 27/6/25 en donde se objetiva el comienzo dela regeneración a nivel de la región hipocampal, dicha imagen fue informada como normal (Figuras 2 y 3).

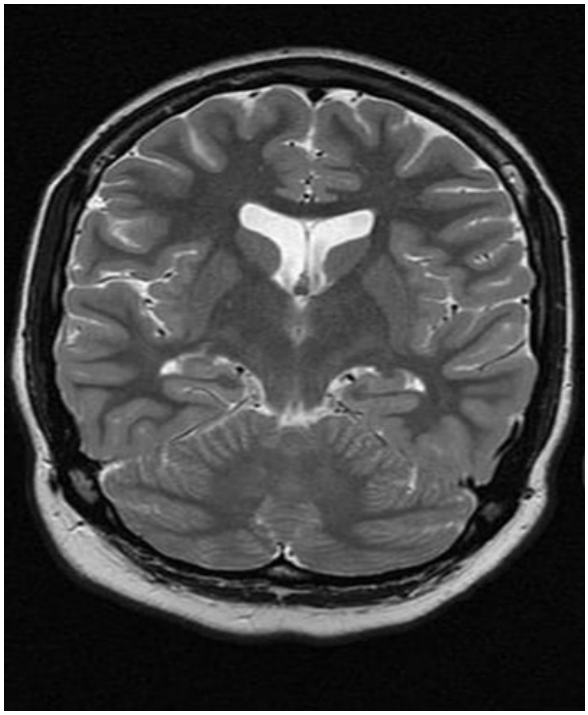

Figura 2: Corte coronal, región hipocampal con señal, tamaño y morfología conservada.

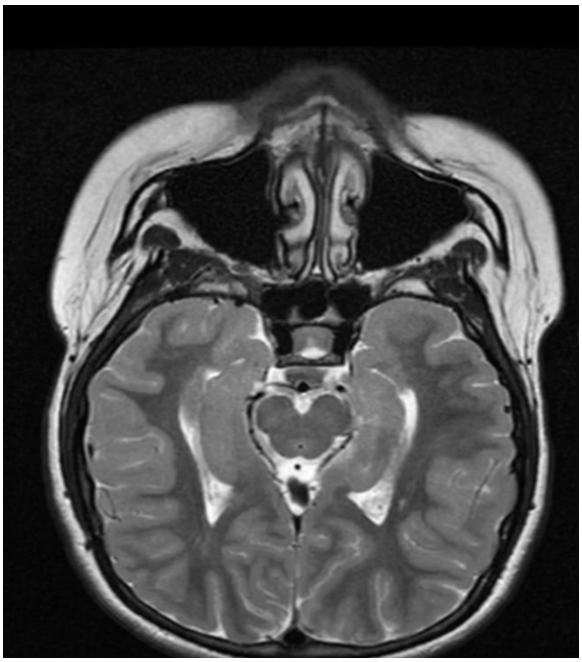

Figura 3: Corte axial, hipocampos de morfología normal, astas temporales sin dilatación.

Conclusión

La EMT es una entidad compleja caracterizada por alteraciones estructurales acompañadas de una manifestación clínica heterogénea. Esto se orquesta, en un microambiente de neurotoxicidad en donde funciones esenciales del tejido nervioso tales como la neurogéne sis, sinaptogénesis y plasticidad, se ven comprometidas. Las células madre poseen propiedades inmunomodulatorias, pudiendo promover un perfil antiinflamatorio tanto a nivel celular como humoral, favoreciendo la regeneración a nivel del tejido afectado. La terapia combinada con células madre y exosomas representa una terapia novedosa para la esclerosis mesial del temporal. Los avances clínicos e imagenológicos objetivados en este caso, la posicionan como una terapia prometedora para esta compleja patología.

Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Resumen
La esclerosis mesial del temporal (EMT) es una entidad bien definida de epilepsia focal estructural, caracterizada por gliosis y perdida neuronal a nivel del hipocampo y estructuras aledañas. Esta patología, se asocia a un microambiente neurotóxico que interfiere con la neurogénesis, sinaptogénesis y plasticidad de las espinas dendríticas, llevando a disfunciones cognitivas, mnésicas y emocionales.Presentamos el caso de una paciente de 14 años de edad, diagnosticada clínica e imagenológicamente como EMT, quien evidenciaba un compromiso cognitivo, afectivo y conductual significativo, incluyendo déficits en la memoria de trabajo, alteraciones del lenguaje receptivo como expresivo y marcados trastornos de la atención. Se propuso una estrategia terapéutica basada en la aplicación de células madre autólogas y exosomas, con un enfoque centrado en su función inmunomoduladora, orientado a favorecer la regeneración estructural y funcional del hipocampo. Durante su evolución, la paciente presentó una progresiva mejoría en funciones cognitivas superiores tales como la memoria anterógrada y retrógrada, atención sostenida, el uso enriquecido del lenguaje y la maduración socio-emocional. Este caso, resalta el potencial terapéutico de la terapia combinada con células madre autólogas y exosomas como una estrategia innovadora para la regeneración estructural y funcional en la EMT.

Palabras clave: Células madre, exosoma, esclerosis mesial del temporal, hipocampo, inmunomodulación

Case report

Pseudopapilar solid tumor of the pancreas (Franz tumor), a case report.

Tumor sólido pseudopapilar de páncreas (tumor de Franz), reporte de un caso.

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Abstract

Introduction: This paper presents a comprehensive review of Pseudopapillary Cystic Solid Tumor (PPST), a rare pancreatic neoplasm, and reports a clinical case of a patient diagnosed with this disease. The aim is to better understand the characteristics, diagnosis, and treatment of this type of tumor. Clinical Case: A young woman with no relevant medical history presented recurrent abdominal pain. Imaging studies revealed a solid-cystic lesion in the pancreas, compatible with a PPST. A splenopancreatectomy was performed and histopathological analysis confirmed the diagnosis. The patient had a favorable postoperative evolution. Results: Histopathological analysis of the surgical specimen confirmed the presence of typical PPST features, such as pseudopapillae and uniform neoplastic cells. The patient had a successful recovery after surgery. Discussion: PPST is a neoplasm that mainly affects young women and usually presents as an abdominal mass. Histologically, it is characterized by the presence of pseudo papillae and neoplastic cells with a low mitotic index. The treatment of choice is surgery, and the prognosis is generally good. Conclusions: The clinical case presented illustrates the importance of early diagnosis and timely surgical management of TSPP. Despite being a rare neoplasia, it is essential that health professionals are familiar with its characteristics to ensure an accurate diagnosis and adequate treatment. The need to continue researching this disease to improve our knowledge and optimize clinical management is highlighted.

Keywords: pancreatectomy; Pancreatic neoplasms; pancreatic disease , Pancreatic Cancers, Preneoplastic.

Introducción

El tumor sólido quístico pseudopapilar (TSPP) es una neoplasia pancreática poco frecuente, caracterizada por su histología distintiva y su comportamiento clínico variable. A pesar de su baja incidencia, representa un desafío diagnóstico y terapéutico debido a su potencial maligno (1-7). En las últimas décadas, se han realizado numerosos estudios que han descrito las características moleculares, inmunohistoquímicas y clínicas de esta entidad. El presente trabajo tiene como objetivo realizar una revisión exhaustiva de la literatura científica disponible y reportar un caso de TSPP cuya sospecha diagnóstica concluyó en un adecuado manejo terapéutico. Se analizarán los hallazgos histopatológicos, inmunohistoquímicos y genéticos más relevantes, así como los datos disponibles sobre su comportamiento biológico y pronóstico. Además, se discutirán las estrategias terapéuticas actuales y las perspectivas futuras en el tratamiento de esta neoplasia.

Caso clínico

Paciente femenina sin antecedentes patológicos ni alérgicos, en tratamiento con anticonceptivos orales y un episodio de interrupción voluntaria del embarazo. Consultó en varias oportunidades por guardia por dolor abdominal epigástrico a repetición. Se le realizaron estudios de imágenes en el cual la RMN concluye imagen focal de aspecto sólido-quística unilocular y contornos lobulados de 47 por 43mm a nivel de la unión corporo-caudal del páncreas con crecimiento exofítico anterior. Hallazgos que pueden corresponder a tumor pseudopapilar del páncreas. (Figura

1).
Se solicitó Ca 19-9 y laboratorio de rutina, todo dentro de parámetros normales.

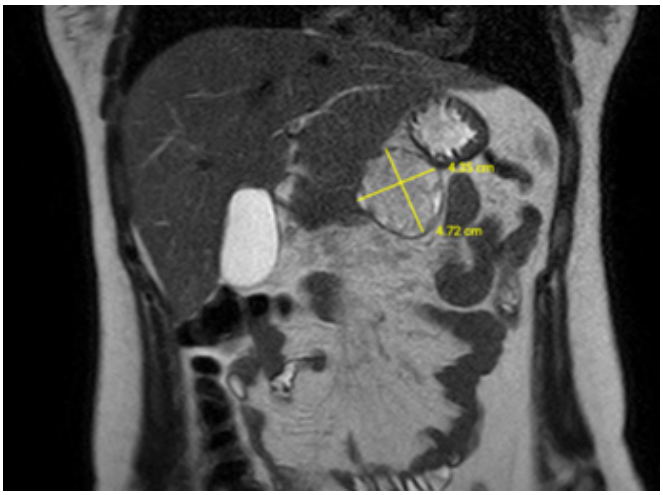

Figura 1. Resonancia magnética nuclear de abdomen. Lesión tumoral en cuerpo y cola de páncreas. Fuente: Elaboración propia.

Se propone tratamiento quirúrgico. Se realiza esplenopancreatectomia abierta. Se envía pieza quirúrgica (Figura 2) a anatomía patológica que confirma el diagnóstico de tumor sólido pseudopapilar. (Figura 3 A-B). Paciente evoluciona sin eventualidades hasta la actualidad.

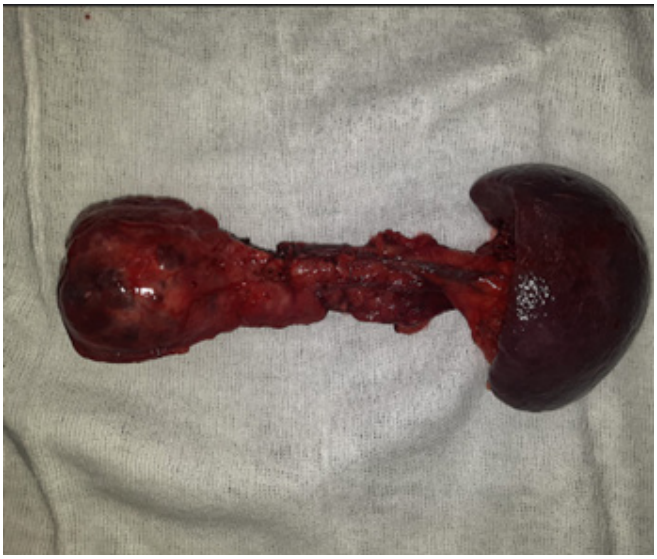

Figura 2. Pieza quirúrgica de pancreatectomía corporo caudal con esplenectomía. Tumor de 4x5cm que compromete cuerpo y cola del páncreas. Fuente: Elaboración propia.

El tumor sólido quístico pseudopapilar también conocido como tumor de Frantz es un tipo raro de neoplasia, representa aproximadamente un 1-2% de los tumores pancreáticos. Fue descrito por primera vez en 1959 por el patólogo Volker K Frantz. Durante mucho tiempo se lo consideró un tumor benigno, actualmente se conoce que puede tener un comportamiento maligno. (1)
Este tipo de lesión se presenta más comúnmente en mujeres en una relación 2:1, incluso mayor. (1,2) Su incidencia es rara, el rango de edad más comúnmente afectado es entre 20 a 30 años, siendo aún mucho más infrecuentes en la infancia. (3 - 4).

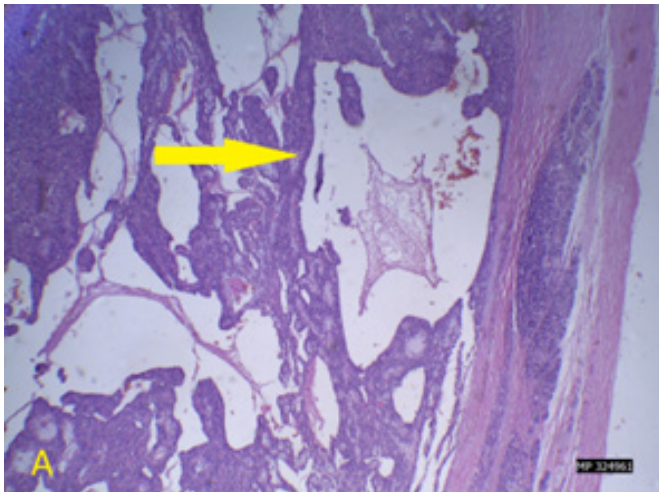

Figura 3A: Tinción hematoxilina-eosina. Microscopio LEICA ICC50. Aumento 40x. Imagen de porción quística del tumor (flecha amarilla).

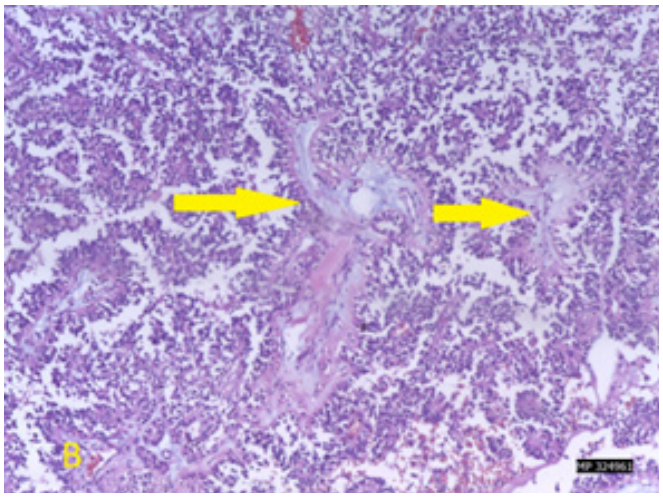

Figura 3B: Aumento 100x. Se observan pseudopapilas con eje fibroconectivo (flechas amarillas). Fuente: Elaboración propia.

El origen de los tumores sólidos pseudopapilares no es bien conocido. Se ha sugerido que estas neoplasias pueden tener un desarrollo a partir de células primordiales pluripotenciales, neuroendocrinas, epiteliales ductales o incluso extra pancreáticas. (1,2). También se ha sugerido que la preferencia al sexo femenino puede estar relacionada con factores hormonales.
Histológicamente se caracteriza por células uniformes, grandes y redondeadas, con escaso índice mitótico, conformando pseudopapilas sobre un eje fibroconectivo vascular. Presenta además áreas estructurales sólidas. Las principales proteínas tumorales expresadas fueron β-catenina, ciclina D-1, CTNNB1 y vimentina. Un artículo desestima en gran medida la utilidad diagnóstica de la inmunohistoquímica. (5)
Es importante determinar las características macroscópicas y microscópicas para el diagnóstico preciso y diferen-

cial con otros tumores. Una correcta correlación inmunofenotípica permitirá el diagnóstico diferencial con otras entidades pancreáticas.
Un estudio de Gurevich y colaboradores, (6) realizado en 60 casos, expresa que este tipo de tumores presenta un inmunofenotipo único, marcado por la presencia de claudina a nivel nuclear como citoplasmático, siendo una de sus características particulares.
Aunque la mayoría de las veces los pacientes pueden ser asintomáticos, algunos presentan dolor abdominal difuso o localizado en hemiabdomen superior, pérdida de peso, náuseas y vómitos. La ictericia es menos frecuente, pero puede deberse a obstrucción al flujo normal de la vía biliar en caso de afectación a nivel de la cabeza del páncreas o por metástasis hepáticas.
En general, las metástasis pueden encontrarse en el 10 a 15% de los casos según sugieren la mayoría de los autores, (1,2) además del hígado también afecta a ganglios linfáticos, bazo, colon y mesocolon.
El diagnóstico puede basarse en estudios de imágenes como tomografía de abdomen con contraste o resonancia magnética nuclear, en los cuales se observan grandes lesiones sólidas quísticas, encapsuladas, que pueden superar los 10 cm. Otras herramientas para el estudio son la ecografía de abdomen y la ecoendoscopia, que permite, además, la toma de biopsias para un análisis histológico previo a cualquier tipo de tratamiento.
El abordaje terapéutico es quirúrgico por ser el más efectivo. Dentro de las opciones se puede ofrecer, dependiendo el caso, pancreatectomía cefálica, pancreatectomía corporo caudal con o sin preservación de bazo o solo la enucleación con conservación de tejidos. El tamaño del tumor no debe considerarse como factor de irresecabilidad. La quimioterapia y la radioterapia pueden ser útiles en casos avanzados. Este abordaje se ha propuesto en tumores irresecables o metastásicos, pero no se ha estandarizado un esquema aún.
El pronóstico del tumor de Frantz es generalmente favorable tras una resección quirúrgica. Según la mayoría de los artículos y estudios, se reporta una tasa de supervivencia a 5 años del 90-95%. La probabilidad de recurrencia loco-regional es baja. (1)

Conclusiones

El tumor de Frantz requiere un abordaje multidisciplinario. El mismo debe ser realizado principalmente por especialistas en oncología y cirugía de páncreas. Es necesario continuar con la investigación de esta patología rara para mejorar nuestro conocimiento y optimizar el manejo clínico quirúrgico.

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Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Resumen

Introducción: El presente estudio documenta el reporte de caso de una paciente que fue identificada con un Tumor Sólido Pseudopapilar (TSPP), una neoplasia pancreática poco frecuente. El objetivo es profundizar en el conocimiento de su fenotipo, protocolo diagnóstico y manejo terapéutico. Caso Clínico: Una mujer joven, sin antecedentes patológicos relevantes, presentó dolor abdominal recurrente. Los estudios de imagen revelaron una lesión sólida-quística en el páncreas, compatible con un TSPP. Se realizó una esplenopancreatectomía y el análisis histopatológico confirmó el diagnóstico. La paciente evolucionó favorablemente postoperatorio. Resultados: El análisis histopatológico de la pieza quirúrgica confirmó la presencia de las características típicas del TSPP, como pseudopapilas y células neoplásicas uniformes. La paciente presentó una recuperación exitosa tras la cirugía. Conclusiones: El caso clínico presentado ilustra la importancia de un diagnóstico precoz y un manejo quirúrgico oportuno del TSPP. A pesar de ser una neoplasia poco frecuente, es esencial que los profesionales de la salud estén familiarizados con sus características para garantizar un diagnóstico preciso y un tratamiento adecuado. Se destaca la necesidad de continuar investigando sobre esta enfermedad para mejorar nuestro conocimiento y optimizar el manejo clínico.

Palabras Clave: Pancreatectomía; Neoplasias pancreáticas; Enfermedad pancreática; Cánceres pancreáticos, Preneoplásico.

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Evaluation and advantage of posteriorly sited curved stent tube, in congenital bilateral choanal atresia.

Evaluación y ventaja del tubo de stent curvado situado posteriormente, en la atresia de coanas bilateral congénita.

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Abstract

Background: Choanal atresia is a congenital disorder in which the posterior nares are close by unresolved membrane or bony partition. This disease is treated surgically. Aims of the study: To evaluate the outcome and complications of different methods of stenting in bilateral congenital choanal atresia and to identify the most suitable method in our practice. Methods: A prospective study carried out at Departments of Otolaryngology. Sixteen neonates with congenital bilateral choanal atresia underwent operation via convention transnasal approach with stenting. The neonates were submitting to full history taking, examination, investigations including imaging in form of computed tomography (CT) scan of nose and paranasal sinuses. Portex endotracheal tubes were fashioned preoperatively, then use for stenting the posterior choanae after removing the obstructing element for 12 weeks. Patients were arranging into two groups: group A (10 patients) with the curved part of the stent tube was sited posterior to the choanae and, group B (6 patients) curved part of the stent tube was sited anterior to columella. Complications of stenting are compared, including stent dislodgement, early extraction, erosion of nares, obstruction, granulation and nose bleeding were assessed, and the outcomes are evaluated for the two groups. Results: Sixteen neonates (11 female and 5 male). Their age was between 2 and 7 days. After removal of the stent tubes, the outcome and complication of stent for the two groups are compared after follow up (mean duration of follow up 6.5 months). Choanae assessed by endoscopic examination in outpatient, one of (group A) needed a second operation while five patients in (group B) needed it. Two patients from group B need a third operation while none of (group A) are needed. The patients had patent posterior choanae at last follow up. Conclusion: Stenting after correction of congenital bilateral choanal atresia is desirable to prevent restenosis. The stability of stenting better obtained by using posteriorly placed curve of a single portex tube as stent (arch), (group A). While the stability of stenting by two separate tubes or anteriorly placed curved end is unobtainable because of the cheese wire effect of securing silk suture on the posterior end of septum (group B). Several complications were significantly less frequent with posteriorly placed curve of single portex tube stent method. Therefore, it is recommended applying posteriorly placed curve of a single portex tube method in practice.

Keywords: Choanal atresia, Sited curved stent tube, Newborns, Bucconasal membrane

Introduction

Choanal atresia is an obliteration, in newborns, of the airway at the level of posterior nasal aperture resulting in absence of connection between the nasal cavity and the erodigestive tract. It was first described in 1755 by Johan Roderer.

Congenital Choanal atresia is a rare condition (incidence 1 in 5000 - 8000 births live births) [1].

There are four popular theories regarding congenital choanal atresia development: (i) Persistence of the bucconasal membrane of Hochstetler, (ii) Misdirection of mesodermal flow secondary to local genetic factors, (iii) Persistence of a buccopharyngeal membrane from the foregut, and

(iv) The abnormal persistence or location of mesodermal adhesions in the choanal region [2]. The blockage had thought to be either bony or membranous in origin. In reality, a mixed picture is usually seen (70% of cases) with the remainder being purely bony. Choanal atresia involving the right side is more common than in the left side. The newborn infant is an obligatory nose breather for the first few days after birth and has no ability to breathe through the mouth. Unilateral choanal atresia may go undiagnosed until childhood or even adulthood. Bilateral choanal atresia, on the other hand, poses a medical emergency immediately at birth causing respiratory distress and demanding immediate intervention. Unrecognized bilateral choanal atresia will almost certainly lead to death due to neonatal asphyxia. Choanal atresia is being two times more prevalent in females (2:1). And unilateral atresia is more common than bilateral atresia. This disorder can be transmitted as an autosomal recessive trait. Most cases of choanal atresia are isolated malformations, but the association with other congenital deformities is not exceptional [2, 3]. Boundaries of the atretic plates are the sphenoid bone superiorly, medial pterygoid lamina laterally, vomer medially, and horizontal portion of the palate inferiorly [3-5]. This anatomical knowledge of atrophic plates is highly valuable while performing surgery on these patients [2]. The diagnosis of the choanal atresia is done by the high suspension of clinical presentation then by doing physical exam, plain films and tomograms of the skull with radiopaque dye, CT scan [6]. Which is the single radiographic study of choice. The CT scan has proven valuable in the accurate assessment of both the normal and abnormal anatomy of the nasal cavity, posterior nasal choanae and nasopharynx [7, 8]. CT scan also helps exclude most if not all of the other diseases that could cause nasal obstruction of the newborn [9].

Establishing a secure airway is paramount, in many circumstances, this done prior to any investigative procedures. If the child has no underlying lung disease or laryngotracheal abnormalities, placement of an oral airway may be sufficient. An alternative to the conventional oral airway may be a feeding nipple cut at the end. Either of these should be secure by taping or tracheotomy ties placed around the head. Oxygen saturation monitoring can determine the efficacy of this maneuver and, if the child does not maintain adequate saturation levels, supplemental oxygen may be required. Alternatively, Oro-tracheal intubation with possible ventilator support may be required [5]. Feeding, usually gavages feeding is required until the child has learned to mouth breath. Then once the child learns the mouth breath, then he will swallow air and need frequent 'breathing/burping breaks' [6].

The technique for surgical repair of choanal atresia has evolved over the past 150 years. Through the transpalatal approach, To the currently favored endoscopic transnasal approach [1]. The ideal surgical procedure should provide adequate functional Choanal patencies, low rate of restenosis, avoid harm to any structure in development, enable shorter surgery and hospitalization time, and minimize morbidity and mortality. Many approaches have been used in the repair of choanal atresia, including transnasal approach, transpalatal approach and transseptal approaches nowadays, in unilateral atresia the endoscopic approach combining transnasal and posterior trans-septal technique considered as the gold standard [10].

Once the atresia is surgically corrected, the surgeon is often faced with the problem of restenosis. The rates of restenosis vary widely and range from 0 - 85% [5]. Many authors report on the use of postoperative stenting for variable periods [11].

Methods

Study design and setting

This was a prospective study and carried out at Department of Otolaryngology/Hospital of Specialized Surgeries – Medical City Teaching Complex, India.

Patients' selection

This study involved sixteen neonates with congenital bilateral choanal atresia, age ranged from 2 days - 7 days, during a period from April 2012 - October 2013. The patients planned for surgical treatment and followed up for three months after removal of the stent.

Inclusion criteria

Neonates with bilateral choanal atresia.

Exclusion criteria

Neonates are free from other congenital disorders, such as:

1. Unilateral choanal atresia.
2. Associated pyriform aperture stenosis.
3. CHARGE with sever associated malformation.
4. Infants with bad general condition.
5. Sever neurological deficits are either congenital or acquired.

According to the above criteria 3 neonate excluded 2 because of sever cardiorespiratory problems and one neonate pyriform aperture stenosis. The patients were submitted to:

1. Appropriate pre and postnatal history was taken. This includes age at diagnosis, gender of patient, family history of choanal atresia, medical history of birth and early infancy, maternal disease, history of any associated anomalies, symptoms, age at time of surgery.
2. General physical examination and otolaryngology examination.
3. Radiological imaging including chest X-ray, and CT scan (Figure 1).
4. General blood investigation and cardiac evaluation, ECG, and Echo.

Bilateral choanal atresia is a medical urgency, but not a surgical emergency. The immediate management of neonates presenting with intermittent cyanosis was insertion

of an oral airway and feeding via orogastric tube. This provides adequate airways to the infant and helps to buy time till the child has gained adequate weight to withstand corrective surgery and for evaluation of potential associated features. Due to the limitations of the surgical field the removal of obstructing plate of choanal of atresia in our study, was carried out transnasal by (Cold steel approach), puncture, dilation and stenting. The operations are carried out by transnasal approach using conventional headlights with or without endoscope. Under general anesthesia with cuffed Oro endotracheal tube. Tilley Lichtwitz antral trocar or straight urethral sound used to perforate the thin central component of atresia. Then the opening dilated gradually by removing bone from medial pterygoid and sometime vomer crest by fine cupped forceps and sometime gentle tap by gauge hummer, or by transnasal drilling with small electric burrs, or by uses the microdebriders.

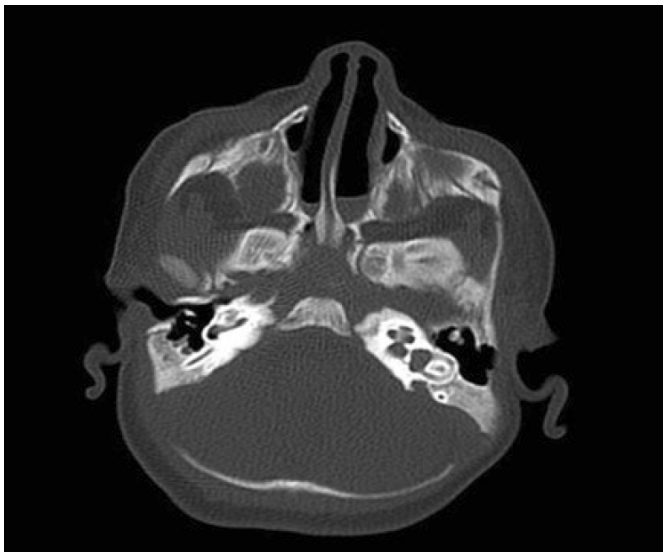

Figure 1: CT scan axial view shows bilateral choanal atresia.

Then small portex endotracheal tube stent (usually number 3.5 mm) fashioned by folding from the middle making two exactly equal lengths. The posterior fenestration (outer curved side) of the tube at the midpoint created with a No. 11 blade for the air to pass from the nose to the nasopharynx, while the anterior part of the tube (inner curved end) remains in continuity. Smaller vents or holes are made in a different site for the drainage of nasal secretions. Our patients divided into two groups according to surgeon preference each stent was use for them but one group the curved end of single modified endotracheal tube was behind the posterior choanae (nasopharyngeal end), and the other group uses two separate tubes or using single portex tube with anteriorly placed curved end anterior to columella. To place the stent correctly in place, two small suction tubes were introduced into both nostrils and pulled out through the mouth. Each limb of the modified portex tube tied to one suction tube. The suction tubes pulled out and the tube stent passed out through the nose, then suction tubes removed from the tube stent. The two limbs of the stent then tied together with silk suture either anterior to columella or behind the vomer. With a small bridge placed between the two ends of nasal stents anteriorly. A circumferential one zero silk suture is then placed through stent #1 behind the septum through stent #2 and then passed through the bridge back to stent #1 and tied or through stent and tied in front columella. One must use an attachable needle to penetrate the endotracheal tube. Easy passage of a suction catheter through the stent confirmed satisfactory stent position and alignment. Stenting performed in all patients generally for a period of about three months. The stent removed and examination of choanae done by endoscope examination to reassess the stenosis and looking for granulation tissue formation.

Postoperative care

The nurses and parents instructed to irrigate the child's nose and stent with warm normal saline by fine suction catheter at home, several times a day. The hospital stay is 48 h, after discharge, the patients are seen by their otolaryngologist and all patients have been followed regularly after: weekly, for the first month then every two weeks for the next three to six months. The length of the stents should be clearly recorded to facilitate accurate position. Oral antibiotics are generally prescribed. After stent removal, a 2 week course of local nasal steroids prescribed. The follow up period was at least six months.

Ethical consideration

Consent of all patients' family were obtained prior to operation and participation in this study.

Results

A total of 16 neonates with congenital bilateral choanal atresia were recruited in this study. Out of the 16 patients, females were 11 (68.57%) and males were 5 (31.57%), with a female to male ratio of 2.2:1, indicating a higher incidence among females (Table 1). The mean age at diagnosis of the patients was 4.25 ± 1.4 days. The range was 2 - 7 days.

Furthermore, one patient (6.25%) was aged 2 days, 5 patients (31.25%) were aged 3 days, 4 patients (25%) were aged 4 days, 2 patients (12.5%) were aged 5 days, 3 patients (18.75%) were aged 6 days, and one patient (6.25%) was aged 7 days. The mean age at operation of the neonate was 18.4 ± 2.7 days ranging between 10 - 32 days (Table 2).

Full term neonate represented the majority of patients; 14 out of the 16 patients (87.5%) and the remaining two patients (12.5%) were preterm. On the other hand, the mean gestational age was 38.4 ± 2.3 weeks (Table 3). The mean body weight of studied neonates was 2.9 ± 1.1 kg with a range of 2.3 - 3.9 kg (Table 3). 13 patients (81.25%) had mixed type, 3 patients (18.75%) had bony type, but none had membranous type (Table 4). All the patients presented with cyclical cyanosis, 13 patients (81.25%) presented with feeding difficulty, 10 patients (62.5%) presented with nasal obstruction and 9 patients (62.25%) presented with nasal discharge (Table 5).

The mean duration of follow up after removal of stent was 6.5 months and ranged 3 - 12 months. There were 7 types

Gender	No.	Percentage
Female	11	68.77
Male	5	31.57
Total	16	100.0

Table 1: Gender distribution of 16 neonates with choanal atresia.

Age (days)		No.	Percentage
At diagnosis days	5	1	6.25
	3	5	31.25
	4	4	25.0
	5	2	12.5
	6	3	18.75
	7	1	6.25
	Total	16	100
	Mean ± SD	4.25 ± 1.4	-
	Range	2 - 7	-
At operation days	Mean ± SD	18.4 ± 2.7	-
	Range	10 - 37	-

Table 2: Age distribution of patients.

Variable		No.	Percentage
Maturity	Term	14	87.5
	Preterm	2	12.5
	Total	16	100
Gestational age at delivery (week)	Mean ± SD	38.4 ± 2.3	-
	Range	27 - 42	-
Body weight (kg)	Mean ± SD	2.9 ± 1.1	-
	Range	2.3 – 3.9	-

Table 3: Perinatal characteristics of the patients.

of complications developed in our studied group, by comparing the incidence of complications in between groups A (10 patients) and B (6 patients), it had been significantly found that the incidence of 6 complications was lower in group A than group B. The stability of stenting by two separate tubes or anteriorly placed curved end is unobtainable because of the cheese wire effect of securing silk suture on the posterior end of septum.

This was developed in four patients (40%) in group A vs all patients (100%) in group B (p = 0.031). This has occurred in 5 patients (83.3%) in group B vs none in group A (p = 0.002). This has occurred in one patient (10%), and in 5 patients (83.3%) in group A and B respectively (p =0.008). This was not found in group A but was found in four patients (66.7%) in group B (p = 0.009). This has developed in three patients (30%) of group A, and in all patients (100%) in group B. This was in 1 patient (10%) in group A, and 5 patients (83.3%) in group B, (p = 0.008). This has occurred in one patient (10%) in group A, and in two patients (33.3%) in group B. This difference was significant clinically, but it was statistically not significant (p > 0.05). All these findings were summarized in table 6. One patient in group A and 5 patients in group B needed a second operation, and two patients in group B but none in group A needed a third operation, while none of the patients in both groups needed a fourth operation (Table 7).

Discussion

Management of choanal atresia still faces the problem of restenosis.

Several studies in the literature describe different methods

Type of atresia	No.	Percentage
Mixed	13	81.25
Bony	3	18.75
Membranous	0	0.0
Total	16	100

Table 4: Distribution of types of atresia.

Presenting symptom	No.	Percentage
Cyclical cyanosis	16	100.0
Feeding difficulty	13	81.25
Nasal obstruction	10	62.50
Nasal discharge	9	56.25

Table 5: Presenting symptoms of studied group.

& tools to improve the outcome of its surgical treatment. Most case series studies are small and often represent the collective experience of several surgeons in one or multiple institutions using different surgical approaches to the use of adjuvant tools or medications.

Stenting began as a way to prevent the inevitable restenosis after simple transnasal puncture. Currently advocates of stenting reason that the stenting aid in the support and healing of mucosal flaps around the neochoanae and allow for nasal patency until scarring has occurred. By reviewing our data, we tried to evaluate the congenital bilateral choanal atresia and the effect of posteriorly curved end of portex stent tube on the outcome of choanal atresia repair and restenosis. Out of the 16 patients, the females were 11 (68.57%) and the males were 5 (31.57%), with a female to male ratio of 2.2:1. This not in agreement with Singh [12], who found the ratio about 5:1. But Kim et al. [13] have found the number of males and females was similar in bilateral congenital choanal atresia, Uzomefuna et al. [14], say that 75% of all bilateral cases in his study occurred in females. However, others reported no difference in sex ratio. Also, Sharma et al. [15] noted that Al-Ammar [16] found female to male ratio is 2:1. The mean age at diagnosis was 4.25 ± 1.4 days with a range of 2 - 7 days.

Complication	Group A (n = 10)		Group B (n = 6)		p value
	No.	Percentage	No.	Percentage	
Stent obstruction	4	40.0	6	100	0.031
Stent dislodgment	0	0.0	5	83.3	0.002
Early extraction	1	10.0	5	83.3	0.008
Erosion of nares	0	0.0	4	66.7	0.009
Granulation	3	30.0	6	100	0.013
Restenosis	1	10.0	5	83.3	0.008
Nose bleeding	1	10.0	2	33.3	0.31

Table 6: Comparison of complications developed during follow up period distributed by groups of patients.

Further operation	Group A (n = 10)		Group B (n = 6)		p value
	No.	Percentage	No.	Percentage	
Second operation	1	10	5	83.3	0.0035
Third operation	0	0.0	2	33.3	0.24
Fourth operation	0	0.0	0	0.0	-

Table 7: Further operations needed in both groups of patients.

This finding was not in agreement with Kim et al. [13], who found the mean age of presentation to be 4.5 months. Also, in disagreement with Velegrakis et al. [17] who found age at diagnosis 1 day, nor with Al-Ammar [18] who found age at presentation 3 months.

The mean age at operation of the 16 neonate was 18.4 ± 3.7 days ranging from 10 - 32 days. This result is disagreed with Al-Ammar [18] who has mentioned that the age at operation was below one month in (73%) of neonate. Velegrakis et al. [17] said that; age at operation was 4 days. Uzomefuna et al. [14], said that the time of surgery varied from 1 day - 15 years, with a mean age of 23.4 months. Zuckerman et al. [19] found that the mean age at the time of surgery was 8 days ranged between 5 - 15 days.

Full term neonates represented the majority of patients; 14 out of the 16 patients (87.5%) and two patients (12.5%) were preterm, Samedi et al. [20], said there is association between prematurity and congenital bilateral atresia. On the other hand, the mean gestational age was (38.4 ± 2.3 weeks). The mean body weight of studied neonates was 2.9 ± 1.1 kg with a range of 2.7 – 3.9 kg. This agree with Velegrakis et al. [17] who found Mean birth weight was 2,740 g (range 980 – 4,150 g). Friedman et al. [21] had shown that re-stenosis occurred more frequently in low weight infants at the time of surgery than in (normal) higher-weight children.

13 patients (81.25%) had mixed type of atresia, and three patients (18.75%) had bony type, and none had membranous type. This disagrees with the finding of Velegrakis et al. [17] in which most atretic plates were bony (87%) and none had mixed type. While Sharma et al. [15] found that six patients had bilateral congenital atresia. Three of these had mixed (50%), two had bony type (33%) and one had membranous type (16%) types. The stents were maintained in position for 3 months, this in agreement with Mantovani et al. [22], who have suggested stenting for at least 4 - 12 weeks. And in agreement with Sharma et al. [15] who have suggested stenting for at least 8 - 12 weeks, and agree with Friedman et al. [21], who also suggest stenting for 12 weeks [21].

All the patients presented with cyclical cyanosis. This agrees with Almmar [16] who found that congenital bilateral choanal atresia alwayspresented with respiratory distress and cyclical cyanosis at birth. Which also agrees with Velegrakis et al. [17].

The development of granulation tissue is frequently a possible cause of choanal restenosis. Occurred in 3 patients (30%) in group A and occurred in all patients (100%) in group B. Schoem [23] found that (78%) of his patients who underwent re-examination under general anesthesia 3 to 4 weeks after initial surgery had varying amounts of emerging granulation tissue or minor synechiae that were resolved with microdebrider re-excision.

Erosion of anterior nares has not occurred in group A, but has occurred in four patients (66.7%) in group B. We found that this technique for stenting is more comfortable for the infant, avoids any complications affecting the columella of the nose. This has occurred in 5 patients (83.3%) in group

B vs none in group A. The vomer tightly held the wide widths of curved end of U-shape portex tube, and the infants tolerate them well. So, we avoid cheese wire effect on the posterior end of septum (vomer). This had occurred in one patient (10%) of group A and 5 patients (83.3%) of group B, (p = 0.008). The rate of re-stenosis varies in the literature from 9% to 36%, with an average of four to six reoperations per patient [10]. Goettmann et al. [24] said that the surgical correction of choanal atresia has a primary success rate of 55% - 75%. Wyatt [7] found the success rates was between 68% and 80% percent for bilateral choanal atresia. Al-Ammar [18] in his series of 11 cases with bilateral CA, reported success rate of 60% with the use of nasal stents compared to 33% success rate in cases where nasal stent is not used. Also, the successful rate with Friedman et al. [21] was 64%.

Accurate blood loss from the nose is always difficult to determine precisely due to the amount of saline irrigation during nasal cleaning.

The parents report bleeding from nose in one patient (10%) in group A, and two patients (33.3%) in group B. The bleeding was simple and stopped spontaneously without any medical or surgical intervention. Schoem [23] reports in his study that the estimated blood loss ranged from 10 - 125 cc in all initial operations, in revision operations the blood loss of less than 10 cc, and the initial postoperative bleeding during the first 24 h was minimal in all cases. One in group A and 5 in group B needed a second operation. Two patients in group B and none in group A needed a third operation), while none of the patients in both groups needed a fourth operation. In Assanasen and Metheetrairut [10] study, eight neonatal cases with bilateral congenital bony choanal atresia treated by endonasal puncture with modified stenting technique by utilizing endotracheal tubes, seven did not require further operation, and one required unilateral dilatation [10]. Friedman [21] reporting procedure revision rates ranging between 4.6 and 4.9 to achieve patent choanae.

Conclusion

Stenting after correction of congenital bilateral choanal atresia is better to prevent restenosis. The stability of stenting is better obtained by using posteriorly placed curve of a single portex tube as stent (arch). Clinical finding and CT scan imaging are useful to provide the definitive diagnosis of type of atresia and evaluate other congenital anomalies.

Several complications: like restenosis, granulation tissue formation, erosion of nares, premature extraction, dislodgement and stent obstruction have occurred more frequently with two separate tubes stents or anteriorly placed curved end methods. These complications were significantly less frequent with posteriorly placed curve of single portex tube stent (arch) method. When the curved end of tube placed behind the choanae (posteriorly), the rate of postoperative complication and dislodgment were significantly less frequent than in the two tubes or anteriorly placed curved end methods. Therefore, it is recommended to apply posteriorly placed curve of a single portex tube method in practice.

Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Resumen

Antecedentes: La atresia de coanas es un trastorno congénito en el que las fosas nasales posteriores están cerca por una membrana no resuelta o un tabique óseo. Esta enfermedad se trata quirúrgicamente. Objetivos del estudio: Evaluar el resultado y las complicaciones de diferentes métodos de colocación de stents en la atresia de coanas congénita bilateral e identificar el método más adecuado en nuestra práctica. Métodos: Estudio prospectivo realizado en Departamentos de Otorrinolaringología. Dieciséis neonatos con atresia de coanas congénita bilateral se sometieron a operación mediante abordaje transnasal convencional con colocación de stents. Los neonatos se sometieron a una historia clínica completa, examen e investigaciones que incluyeron imágenes en forma de tomografía computarizada (TC) de nariz y senos paranasales. Los tubos endotraqueales Portex se confeccionaron preoperatoriamente, y luego se utilizaron para la colocación de stents en las coanas posteriores después de retirar el elemento obstructivo durante 12 semanas. Los pacientes se organizaron en dos grupos: grupo A (10 pacientes) con la parte curva del tubo del stent ubicada posterior a las coanas y, grupo B (6 pacientes) parte curva del tubo del stent ubicada anterior a la columela. Se compararon las complicaciones de la colocación de stents, incluido el desprendimiento del stent, la extracción temprana, la erosión de las fosas nasales, la obstrucción, la granulación y el sangrado nasal, y se evaluaron los resultados para los dos grupos. Resultados: Dieciséis neonatos (11 mujeres y 5 hombres). Su edad estaba entre 2 y 7 días. Después de la extracción de los tubos del stent, se compararon el resultado y la complicación del stent para los dos grupos después del seguimiento (duración media del seguimiento de 6,5 meses). Las coanas evaluadas mediante examen endoscópico en pacientes ambulatorios, uno del (grupo A) necesitó una segunda operación, mientras que cinco pacientes del (grupo B) la necesitaron. Dos pacientes del grupo B necesitan una tercera operación, mientras que ninguno del (grupo A) la necesita. Los pacientes tenían coanas posteriores permeables en el último seguimiento. Conclusión: La colocación de stents tras la corrección de la atresia coanal bilateral congénita es recomendable para prevenir la reestenosis. La estabilidad de la colocación se obtiene mejor utilizando un tubo de pórtex único curvado colocado posteriormente como stent (arco) (grupo A). Sin embargo, la estabilidad de la colocación de stents con dos tubos separados o un extremo curvo colocado anteriormente no se logra debido al efecto de alambre de queso al asegurar la sutura de seda en el extremo posterior del tabique (grupo B). Varias complicaciones fueron significativamente menos frecuentes con el método de stent de pórtex único curvado colocado posteriormente. Por lo tanto, se recomienda aplicar el método de stent de pórtex único curvado colocado posteriormente en la práctica.

Palabras clave: Atresia coanal, Tubo de stent curvo ubicado, Recién nacidos, Membrana buconasal

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From skin care to surgical solutions: an overview on advances in cosmetology and plastic surgery in personal transformation.

Del cuidado de la piel a las soluciones quirúrgicas: un panorama sobre los avances en cosmetología y cirugía plástica en la transformación personal.

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Abstract

Cosmetology and plastic surgery have significantly advanced over the past few decades, driven by innovations in non-invasive techniques, surgical methodologies, and regenerative medicine. These fields now offer a wide range of procedures, from botox and dermal fillers to complex reconstructive surgeries, enabling professionals to address both aesthetic desires and functional restoration. The integration of new technologies such as lasers, robotics, and artificial intelligence (AI) has made these procedures safer, more precise, and personalized, providing patients with improved outcomes and faster recovery times. Clinical trials and ongoing research continue to validate these advancements, ensuring that treatments are both effective and scientifically grounded. Despite these advancements, challenges such as safety concerns, variability in treatment results, and the potential for adverse effects remain. However, the future of cosmetology and plastic surgery is promising, with emerging areas like stem cell therapies, bioengineered materials, and AI-driven personalized care poised to address these limitations. As these technologies evolve, they offer the potential for more natural, lasting, and patient-specific outcomes, setting new standards in both cosmetic enhancement and reconstructive procedures. The continued collaboration between clinicians, researchers, and patients will be key to shaping the future of these dynamic fields.

Keywords: Cosmetology, Plastic surgery, Non-invasive treatments, Regenerative medicine, Clinical trials, Artificial intelligence, Injectable therapies, Personalized care

Introduction

Cosmetology and plastic surgery are two interrelated fields that focus on enhancing physical appearance and, in many cases, improving overall well-being [1]. Cosmetology encompasses non-invasive beauty practices such as skincare, hairstyling, and makeup, while plastic surgery involves medical procedures that repair, reconstruct, or alter body structures for aesthetic or functional purposes [2, 3]. According to the American Society of Plastic Surgeons (ASPS), over 1.5 million cosmetic procedures were performed in the United States (US) in 2022, demonstrating the increasing popularity of appearance-enhancing practices (Figure 1) [4]. Both fields serve not only to meet aesthetic desires but also to address psychological and medical needs, improving confidence and quality of life for millions of individuals globally [5].

The economic growth of these industries reflects their significance in modern society. The global beauty and personal care market, which includes cosmetology services, was valued at $112.08 billion in 2022 and is expected to grow at a compound annual growth rate of 14.7% from 2023 - 2030 [6]. Similarly, the plastic surgery market has experienced steady expansion, with reconstructive surgeries increasing annually (Figure 2) [7]. The rise of non-surgical cosmetic treatments, such as botox (over 8.8 million) and dermal fillers, has been particularly noteworthy, accounting for 77% of all aesthetic procedures worldwide [8]. Advances in minimally invasive techniques have made beauty

enhancements more accessible, affordable, and customizable, further fueling demand.

Scientific advancements in both cosmetology and plastic surgery have revolutionized the fields, improving outcomes and patient satisfaction. Innovations in laser technology have transformed skin resurfacing, hair removal, and scar treatments, delivering precise results with minimal downtime [9]. In plastic surgery, breakthroughs in microsurgery and fat grafting have enabled surgeons to achieve more natural, long-lasting outcomes [10]. ASPS reported that over 90% of patients undergoing reconstructive procedures, such as breast reconstruction following mastectomy, expressed high satisfaction with their results, underscoring the transformative impact of these interventions on both physical and emotional health [11].

However, the increasing popularity of cosmetology and plastic surgery also raises critical ethical and psychological concerns. A study found a 40% rise in body dysmorphic disorder among individuals seeking aesthetic treatments, suggesting that societal pressures and unrealistic beauty standards may contribute to a distorted self-image [12]. This highlights the importance of responsible practices within both fields, emphasizing informed decision-making, realistic expectations, and mental health support. By balancing innovation with ethical considerations, cosmetology and plastic surgery can continue to empower individuals while promoting healthy perspectives on beauty and self-worth.

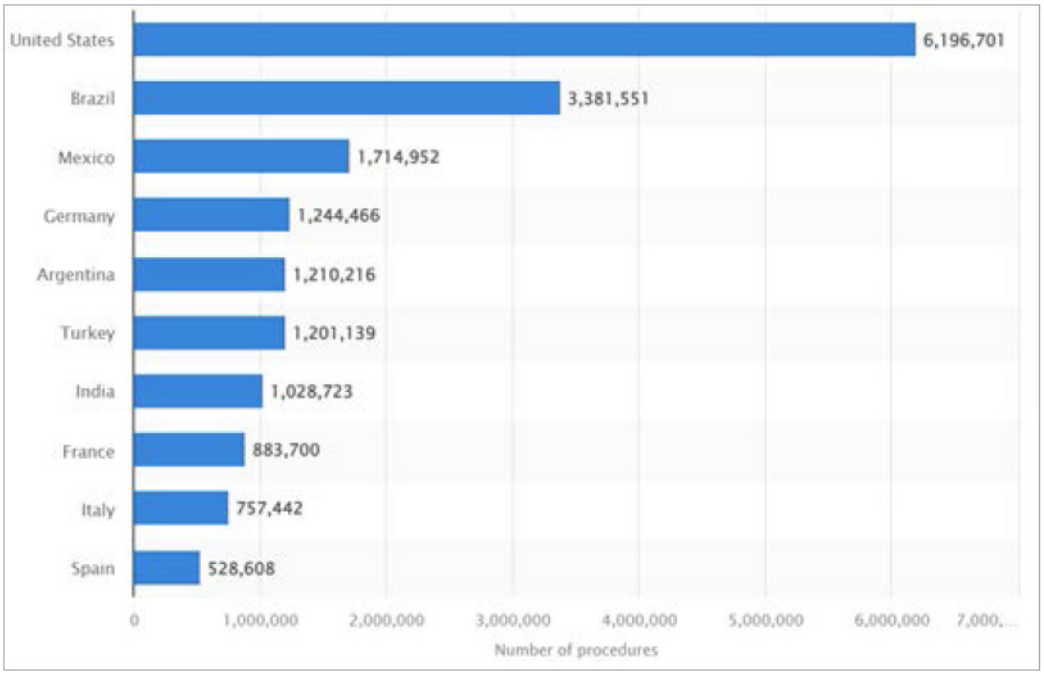

Figure 1: Top countries with most procedures [5].

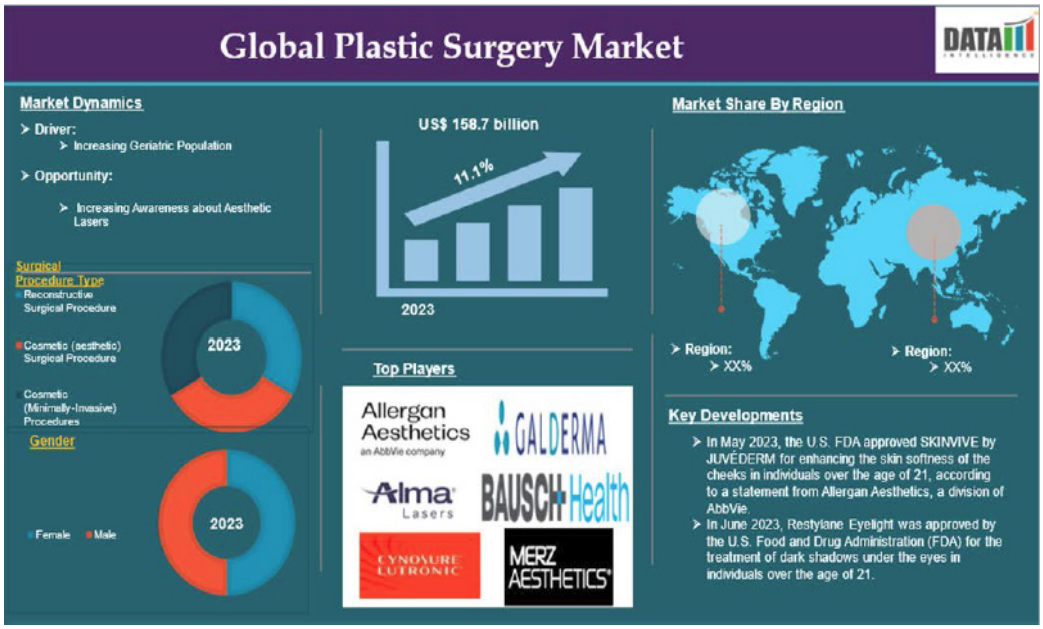

Figure 2: Global plastic surgery market [7].

Most Commonly Done Procedures

Cosmetology and plastic surgery encompass a wide array of procedures aimed at improving appearance, restoring function, and boosting confidence [13]. From minimally invasive cosmetic treatments like botox to surgical procedures such as rhinoplasty, each intervention caters to different needs and expectations (Table 1). These procedures combine artistry with science, relying on advances in dermatology, tissue engineering, and surgical techniques. Below are the few most popular procedures.

Botox injections (Cosmetology)

Botox, derived from the botulinum toxin, is the most widely performed non-surgical procedure globally. According to the ASPS, 8.8 million botox procedures were performed in 2023 [8]. Botox temporarily paralyzes targeted facial muscles, smoothing dynamic wrinkles such as crow's feet, forehead lines, and frown lines. Botox inhibits acetylcholine release at neuromuscular junctions, preventing muscle contraction. Clinically, it is a quick, minimally invasive procedure requiring no downtime, with results lasting 3 - 6 months. Beyond aesthetics, botox is also used for medical conditions like migraines and excessive sweating (hyperhidrosis), showcasing its versatility and safety profile [14, 15].

Dermal fillers (Cosmetology)

Dermal fillers, made of hyaluronic acid or similar biocompatible substances, are the second most common non-surgical cosmetic procedure [16]. Over 3.4 million filler procedures were performed in 2020 in the US alone, targeting facial volume loss, nasolabial folds, and lip augmentation [17]. Hyaluronic acid fillers work by attracting and retaining water, adding volume and hydration to treated areas. Clinically, they provide immediate results with minimal downtime, asting anywhere from 6 months - 2 years depending on the filler type [18]. Ad-

Procedure	Category	Description	Purpose
Botox (Botulinum toxin)	Non-invasive aesthetic	Injectable treatment that temporarily relaxes facial muscles to reduce wrinkles	Reduces fine lines and wrinkles, such as crow's feet and forehead lines
Dermal fillers	Non-invasive aesthetic	Injectable substances that restore volume to the face, reducing wrinkles and folds	Adds volume to cheeks, lips, and under-eye areas, reduces nasolabial folds
Chemical peels	Non-invasive aesthetic	Application of chemical solutions to exfoliate and renew the skin's surface	Treats acne, pigmentation issues, and fine lines
Laser hair removal	Non-invasive aesthetic	Uses laser energy to remove unwanted hair by targeting hair follicles	Permanent hair reduction
CoolSculpting (Cryolipolysis)	Non-invasive aesthetic	Uses controlled cooling to freeze and eliminate fat cells	Reduces localized fat deposits in areas like the abdomen, thighs, and chin
Ultherapy	Non-invasive aesthetic	Uses ultrasound technology to lift and tighten skin	Tightens and lifts skin, commonly on the face, neck, and chin
Microneedling (Collagen induction therapy)	Non-invasive aesthetic	Tiny needles are used to create micro-injuries in the skin to stimulate collagen production	Improves skin texture, reduces scars, and treats acne scars and wrinkles
Thread lift	Non-invasive aesthetic	Involves inserting threads under the skin to lift and tighten tissue	Provides a non-surgical facelift, lifting sagging skin and improving facial contours
RF skin tightening	Non-invasive aesthetic	Uses RF energy to heat the skin and stimulate collagen production	Tightens skin, reduces wrinkles, and improves texture
PRP therapy	Non-invasive aesthetic	Uses the patient's own blood to extract platelets, which are then injected into areas of concern	Improves skin texture, promotes hair growth, and enhances healing in scars
Rhinoplasty	Surgical	Surgical procedure to reshape or reconstruct the nose	Enhances appearance or corrects functional issues (e.g., breathing)
Breast augmentation (Implants or fat grafting)	Surgical	Surgical procedure to enlarge or reshape breasts using implants or fat transfer	Enhances breast size and shape or reconstructs after mastectomy
Facelift (Rhytidectomy)	Surgical	Surgical procedure to remove excess skin and tighten underlying tissues	Reduces sagging, wrinkles, and restores a youthful facial appearance
Liposuction	Surgical	Removal of excess fat from specific areas of the body using suction	Contours the body by removing stubborn fat deposits
Abdominoplasty (Tummy tuck)	Surgical	Removal of excess skin and fat from the abdomen and tightening of abdominal muscles	Improves abdominal contour and removes loose skin, often after pregnancy or weight loss
Blepharoplasty	Surgical	Surgical procedure to remove excess skin, fat, or muscle from the eyelids	Corrects drooping eyelids or puffiness around the eyes
Hair transplant	Surgical	Surgical technique to move hair follicles from one area of the body to another	Treats hair loss or baldness, typically on the scalp
Fat grafting (Autologous fat transfer)	Surgical	Transfer of fat from one part of the body to another for volume restoration	Restores facial volume, enhances breast or buttock shape, and corrects deformities
Tissue expansion	Reconstructive	A technique to stretch skin for reconstructive purposes, often after trauma	Used for reconstructive purposes, such as breast or skin reconstruction post-surgery
Otoplasty (Ear surgery)	Surgical	Surgical procedure to reshape or reposition the ears	Corrects protruding ears or restores natural shape
Gynecomastia surgery	Surgical	Removal of excess male breast tissue	Corrects enlarged male breasts (gynecomastia) for a more masculine chest contour
Abdominal liposuction with tummy tuck	Surgical	Combination of liposuction and abdominoplasty for comprehensive body contouring	Provides overall body contouring while tightening the abdomen
Arm lift (Brachioplasty)	Surgical	Removal of excess skin and fat from the upper arms to create a firmer appearance	Tightens and reshapes sagging skin on the upper arms, often after weight loss
Thigh lift	Surgical	Removal of excess skin and fat from the thighs to improve contour	Enhances thigh shape and firmness, typically after significant weight loss
Body lift (Circumferential lift)	Surgical	A procedure to remove excess skin from the abdomen, thighs, and buttocks	Improves overall body contour, particularly after weight loss

Table 1: Common cosmetology and plastic surgery procedures.

vances in filler technology have improved safety and longevity, making them a popular choice for non-invasive rejuvenation.

Rhinoplasty (Plastic surgery)

Rhinoplasty, or a "nose job," is one of the most sought-after plastic surgeries, with over 352,000 procedures performed annually in the US, according to the ASPS [19]. It addresses both aesthetic concerns, such as reshaping the nose, and functional issues, like correcting nasal obstructions. Rhinoplasty often involves restructuring cartilage and bone, using techniques such as grafting or reshaping nasal tissues. Advances like ultrasonic rhinoplasty reduce trauma and improve precision. Clinically, rhinoplasty demands careful planning, with outcomes tailored to enhance facial harmony and function while maintaining natural results [19].

Liposuction (Plastic surgery)

Liposuction is the most common body contouring procedure, with nearly 395,000 procedures performed in 2023 in the US [20]. It involves the surgical removal of localized fat deposits in areas such as the abdomen, thighs, and arms, creating a slimmer silhouette. Liposuction uses techniques like tumescent liposuction, where saline, lidocaine, and epinephrine are injected into the fat before removal, minimizing bleeding and discomfort. Scientific innovations, including laser-assisted liposuction, enhance fat emulsification for smoother results. While not a weight-loss solution, liposuction effectively targets stubborn fat, improving body contour and proportions [21-23].

Chemical peels (Cosmetology)

Chemical peels rank among the top non-surgical skin rejuvenation treatments, with over 1.3 million procedures performed annually [24, 25]. They involve applying acid-based solutions, such as glycolic
or salicylic acid, to exfoliate damaged skin layers and stimulate regeneration. Chemical peels promote collagen synthesis and improve cellular turnover, addressing concerns like acne scars, pigmentation, and fine lines. Clinically, peels are categorized into superficial, medium, and deep types based on their penetration depth, offering customizable solutions for diverse skin concerns with minimal downtime [26].

Breast augmentation (Plastic surgery)

Breast augmentation remains the most performed cosmetic surgical procedure, with over 300,000 surgeries in 2022 in the US [27]. It involves inserting implants or using fat transfer to enhance breast size, shape, or symmetry. Modern implants, made of silicone or saline, are designed to mimic natural breast tissue. Fat grafting techniques, which transfer fat from other body areas, provide a more natural alternative. Clinically, breast augmentation offers customizable options tailored to patient preferences and body proportions, with advances in surgical techniques ensuring safer, longer-lasting results [28, 29].

Hair restoration treatments (Cosmetology)

Hair restoration, including treatments like platelet-rich plasma (PRP) therapy and hair transplantation, is increasingly popular, addressing androgenetic alopecia and other forms of hair loss [30]. The global hair restoration market was valued at over $6.46 billion in 2023 and continues to grow rapidly [31]. PRP therapy involves injecting growth-factor-rich plasma from the patient's blood into the scalp, promoting follicular health and hair regrowth. Hair transplantation techniques, like follicular unit extraction, transplant hair follicles from donor areas to balding regions, delivering natural-looking results.
These treatments harness regenerative principles, offering hope for individuals struggling with hair loss [32, 33].

Tummy tuck (Plastic surgery)

Also known as abdominoplasty, a tummy tuck addresses loose skin and weakened abdominal muscles, often following pregnancy or significant weight loss [34]. Over 130,000 tummy tuck procedures are performed annually in the US, according to ASPS statistics [35]. Abdominoplasty involves removing excess skin and fat while tightening abdominal muscles, restoring a firmer, flatter abdomen. Advances in surgical techniques, such as drainless tummy tucks, reduce recovery time and complications. For many patients, the procedure not only enhances appearance but also improves posture and core stability [36].
In summary, these procedures highlight the diversity and sophistication of cosmetology and plastic surgery, driven by scientific advancements and clinical precision. Each procedure serves unique needs, whether enhancing natural beauty, addressing medical concerns, or restoring confidence and self-esteem.

Advances in Cosmetology and Plastic Surgery

The fields of cosmetology and plastic surgery have progressed significantly due to continuous innovation and research, bridging the gap between appearance enhancement and medical necessity [37].
These disciplines cater to a wide spectrum of needs, from correcting congenital deformities and trauma-related injuries to meeting the growing demand for youthful, radiant looks. The integration of science, technology, and artistic precision has redefined the way practitioners approach aesthetic and reconstructive challenges.
This growth reflects a societal shift in attitudes toward beauty and self-improvement. Today, people are more open to exploring treatments that enhance their physical appearance and psychological well-being. Clinicians now have access to a broad toolkit of techniques and technologies, enabling them to deliver results tailored to the individual needs of each patient. This personalized care has become a cornerstone of both cosmetology and plastic surgery, setting new benchmarks for patient satisfaction and safety.

Non-invasive skin tightening and rejuvenation

Skin-tightening treatments such as radiofrequency (RF) and ultrasound-based therapies have evolved with greater precision and efficacy [38]. Devices like thermage FLX and ultherapy utilize advanced algorithms to distribute energy evenly,

ensuring consistent results [39].
Additionally, combination treatments that pair RF with microneedling, such as Morpheus8, are gaining traction for their ability to target deeper skin layers while promoting collagen production [40]. These technologies are ideal for patients with mild to moderate skin laxity, offering a preventive approach to aging without the risks of surgery.
These treatments represent a shift toward non-invasive, low-downtime options for skin rejuvenation. Studies have shown that RF and ultrasound therapies stimulate neocollagenesis (new collagen formation), which enhances skin elasticity over time [41]. Patients typically report gradual improvements over several months, making these treatments a valuable addition to the practitioner's toolkit.
Furthermore, advancements in safety protocols and real-time monitoring during sessions have minimized complications, ensuring better outcomes for diverse skin types.

Laser-based therapies

Laser-based therapies have expanded far beyond their original applications, with cutting-edge devices addressing a wide array of dermatological concerns. Picosecond lasers, such as PicoSure and PicoWay, have introduced faster and more effective solutions for pigment removal, including tattoos and melasma [42]. These lasers deliver ultra-short pulses of energy, minimizing thermal damage to surrounding tissues while targeting pigmentation with precision.
Additionally, advancements in vascular lasers like the Vbeam Perfecta have made it easier to treat spider veins, rosacea, and port-wine stains [43].
The versatility of lasers has allowed practitioners to customize treatment plans based on a patient's specific needs and skin type. For example, fractional lasers like fraxel dual combine two wavelengths to treat fine lines and pigmentation simultaneously [44]. Research has also demonstrated that fractional lasers stimulate fibroblast activity, accelerating wound healing and boosting collagen production [45].
As a result, patients experience faster recovery times and fewer complications, making lasers an indispensable tool in modern cosmetology and dermatology.

Injectable innovations: botox and fillers

Beyond traditional botox applications, new uses for botulinum toxin have emerged, including the treatment of "gummy smiles," platysmal banding (neck lines), and even depression, as highlighted in recent clinical studies [46]. New delivery systems, such as micro-botox, involve injecting diluted amounts of the toxin into the superficial dermis to address fine lines and improve skin texture. This method has proven effective for patients seeking subtle, natural results without a frozen appearance [47].
Similarly, dermal fillers have advanced with the introduction of specialized products for different areas of the face, such as Restylane Lyft for cheeks and Juvederm Volbella for lips [48]. The development of bio-stimulatory fillers, like radiesse and sculptra, has further expanded treatment options by promoting collagen synthesis rather than merely filling volume. Clinicians now have greater control over outcomes, and advanced injection techniques, such as the use of cannulas, have enhanced safety by reducing the risk of vascular complications.

PRP therapy

PRP therapy has seen significant advancements, particularly in its application for hair restoration and skin rejuvenation. In the realm of hair loss, PRP is often combined with low-level laser therapy and microneedling to boost its efficacy [49]. Recent studies have demonstrated that PRP injections can prolong the anagen (growth) phase of the hair cycle, resulting in thicker, fuller hair [50].
For skin rejuvenation, PRP is increasingly being used in combination with treatments like fractional lasers and chemical peels.
This synergistic approach enhances healing and optimizes results, particularly for acne scars and hyperpigmentation [51]. Clinically, PRP is a safe, minimally invasive option with little risk of allergic reactions since it uses the patient's own blood. As research continues to explore the role of growth factors and cytokines in PRP, its applications are expected to expand further in both cosmetology and reconstructive medicine.

Fat grafting and fat transfer techniques

Advances in fat grafting have focused on improving fat survival rates, a critical factor in achieving long-lasting results. Techniques such as liposuction with water-jet-assisted systems (e.g., body-jet) and the use of centrifugation or filtration systems to purify fat have significantly improved graft viability [52]. These methods ensure that the transferred fat retains its volume and integrates seamlessly into the surrounding tissues.
Fat transfer has become a popular alternative to synthetic implants for procedures like breast and buttock augmentation. It is also used in reconstructive surgery to address deformities caused by trauma or cancer treatment. The development of nanofat and microfat grafting techniques allows surgeons to target fine wrinkles, scars, and areas of volume loss with unparalleled precision [53]. These innovations demonstrate the growing importance of autologous (patient-derived) materials in achieving natural, biocompatible outcomes.

Minimally invasive body contouring

In addition to cryolipolysis (CoolSculpting) and laser-assisted fat reduction (SculpSure), new technologies like high-intensity focused electromagnetic (HIFEM) energy are redefining body contouring [54]. Devices such as Emsculpt and Emsculpt Neo not only reduce fat but also build muscle, making them unique among non-invasive treatments [55]. These procedures are especially popular for abdominal and gluteal sculpting, as they combine fat loss with muscle toning.
Clinical studies have shown that HIFEM treatments increase muscle thickness by up to 16% while reducing fat by an average of 19% [56]. The procedures are painless and require no downtime, appealing to patients who want visible results without surgery. As these technologies continue to evolve, practitioners can offer a wider range of options for individuals seeking to enhance their physique without undergoing invasive procedures.

Robotic-assisted surgery

Robotic-assisted systems are increasingly being used in complex reconstructive surgeries, such as facial reanimation and breast reconstruction [57]. These systems provide unparalleled precision, allowing surgeons to operate in confined spaces with minimal disruption to surrounding tissues. Additionally, robotic platforms are being integrated with augmented reality (AR) tools, enabling surgeons to visualize anatomy in real time during procedures.
The clinical relevance of robotics extends to improved outcomes and reduced recovery times for patients. For example, in flapbased breast reconstructions, robotic-assisted techniques have minimized donor site morbidity and improved the aesthetic results of microsurgical procedures [58]. As robotic technology becomes more accessible, it is expected to play a larger role in both reconstructive and cosmetic surgery.

Advances in breast surgery

The introduction of hybrid techniques, combining implants with fat grafting, has allowed surgeons to achieve more natural-looking breast augmentation results [59]. This approach addresses issues such as implant rippling and insufficient upper pole fullness, blending the benefits of synthetic and autologous materials. Advances in surgical planning, including the use of 3D-printed custom implants, have further improved precision and patient satisfaction.
On the reconstructive side, innovations like acellular dermal matrices and tissue expanders have simplified procedures for breast cancer survivors [60]. These materials provide a scaffold for tissue growth, reducing complications and expediting recovery. Clinically, these advancements underscore the importance of tailoring procedures to the unique needs of each patient, ensuring optimal aesthetic and functional outcomes.

Skin substitutes and regenerative medicine

Bioengineered skin substitutes, such as MatriStem and Apligraf, are increasingly used in the management of complex wounds, including diabetic ulcers and burns [61]. These products mimic the extracellular matrix, promoting tissue regeneration and reducing scarring. Stem cellbased therapies are also being explored for their ability to regenerate skin and subcutaneous tissue, with promising results in early clinical trials [62].
The integration of regenerative medicine into plastic surgery offers new hope for patients with extensive tissue loss. These approaches not only enhance aesthetic outcomes but also improve functionality, particularly in cases of severe trauma or chronic wounds. As research progresses, the potential applications of regenerative technologies are expected to expand, reshaping the future of reconstructive surgery.

AI and AR

AI-powered platforms are revolutionizing patient consultations by analyzing facial features and recommending personalized treatment plans [63]. These systems consider factors such as skin type, facial symmetry, and aging patterns, offering tailored solutions for each patient. AR tools, like MirrorMe and Crisalix, allow patients to visualize potential outcomes in real time, improving communication and setting realistic expectations [64].
These technologies enhance the decision-making process for both patients and practitioners. By providing a clearer understanding of potential results, AI and AR reduce the likelihood of dissatisfaction and ensure more predictable outcomes. As these tools become more sophisticated, they are expected to play an increasingly central role in the practice of aesthetic medicine.

Rise of combined treatments

Combination therapies are becoming the gold standard in aesthetic medicine, offering synergistic results that address multiple concerns simultaneously. For example, pairing botox with dermal fillers not only reduces wrinkles but also restores facial volume, achieving a more youthful appearance [65]. In body contouring, treatments like CoolSculpting followed by skin-tightening procedures optimize fat reduction and skin elasticity [66].
Combined approaches minimize the need for multiple sessions and reduce overall recovery time, making them highly appealing to patients. The growing trend of holistic, multi-faceted treatments reflects a deeper understanding of the interplay between different aging factors.
By addressing these concerns in tandem, practitioners can deliver comprehensive, natural-looking results that align with patient goals. In summary, the advancements in cosmetology and plastic surgery are not only enhancing aesthetic outcomes but also expanding the therapeutic possibilities of these fields. From regenerative medicine to AI-powered tools, these innovations prioritize patient safety, precision, and satisfaction. Clinically, the integration of these technologies has ushered in a new era of personalized care, allowing practitioners to meet the evolving needs of their patients with unparalleled precision and effectiveness.

Clinical Trials in Cosmetology and Plastic Surgery

Importance of clinical trials

Clinical trials play a pivotal role in advancing cosmetology and plastic surgery by providing scientific validation for new procedures, devices, and treatments (Table 2). These studies assess safety, efficacy, and long-term outcomes, ensuring that innovations meet rigorous medical standards before becoming widely available. For example, trials have been instrumental in the development of new-generation dermal fillers and botulinum toxins, such as Daxxify, which was approved based on clinical evidence demonstrating its extended duration of effect [69]. In the context of plastic surgery, trials have evaluated breast implant safety, leading to innovations such as highly cohesive silicone gel implants that reduce rupture risks.

Minimally invasive technologies under evaluation

Minimally invasive and non-invasive treatments are at the forefront of clinical research due to their growing popularity. Trials are examining the efficacy of novel devices such as high-intensity focused ultrasound and cryolipolysis systems for fat reduction and skin tightening. For instance, clinical studies on Emsculpt Neo, which combines RF and electromagnetic energy, have shown significant improvements in fat loss and-

muscle toning, validated through randomized, placebocontrolled trials [70]. These studies provide clinicians with evidencebased guidelines, ensuring optimal results and minimizing adverse events in patients.

Regenerative medicine and emerging therapies

Regenerative medicine is another key area of clinical trial focus, especially in treatments involving stem cells and PRP. Trials are investigating the use of adipose-derived stem cells for soft tissue regeneration in reconstructive surgery and skin rejuvenation, with promising early results showing improved wound healing and scar reduction [71]. Similarly, PRP therapy has undergone extensive trials to confirm its benefits in hair restoration and acne scar treatment, providing data on optimal protocols, such as injection depth and concentration [72]. These studies are shaping the future of personalized, biologically driven therapies in both fields.

Long-term safety and ethical considerations

Clinical trials also address long-term safety and ethical concerns, particularly for permanent procedures like breast augmentation, fat grafting, and facial implants. For instance, post-market surveillance studies on breast implants monitor complications such as capsular contracture and the rare but serious association with breast implantassociated anaplastic large cell lymphoma [73]. Ethical considerations in trials ensure informed consent and equitable participation, emphasizing patient safety and transparency. As cosmetology and plastic surgery continue to evolve, rigorous clinical research remains essential to advancing these fields while maintaining the highest ethical and scientific standards.

Advanced wound healing and scar management

Clinical trials are integral to developing advanced treatments for wound healing and scar management, areas that overlap significantly with reconstructive plastic surgery. Research focuses on technologies such as bioengineered skin substitutes, stem cell therapies, and growth factor-based treatments to accelerate healing and minimize scarring. For instance, clinical trials of products like Integra (a dermal regeneration template) and epidermal growth factor formulations have demonstrated their ability to improve outcomes in burn and surgical wound management [74]. These studies provide critical insights into the efficacy, safety, and application techniques for such innovations.

NCT ID	Type	Phase	Study
-	Observational	-	Analysis of outcomes in sarcoma reconstruction using intraoperative fluorescence angiography
-	Observational	-	A study to compare the cosmetic outcome of superomedial and inferior pedicle breast reduction
-	Observational	-	A study to evaluate the effectiveness of a healthy living weight loss program in obese patients undergoing bariatric endoscopy on weight loss outcomes
-	Observational	-	A study to evaluate novel nipple reconstruction technique using nipple sharing of a half-split nipple in female-to-male transgender chest-wall contouring
-	Observational	-	A study to evaluate nutritional status in patients presenting for plastic surgery
NCT05457491	Observational	-	Aesthetic study: a new regenerative skin care regimen containing human platelet extract
NCT04533373	Interventional	III	Effect of DIEP flap neurotization on sensory restoration after breast reconstruction
NCT01889381	Interventional	II	Human craniomaxillofacial allotransplantation
NCT02395497	Interventional	II/III	Human penile allotransplantation
NCT04368117	Interventional	-	STAT: standard therapy plus active therapy to improve mobility, long-term activity, and quality of life for severely burn injured patients after skin graft surgery
NCT03544632	Interventional	II	Acellular adipose tissue (AAT) for soft tissue reconstruction

Table 2: Clinical trials [67, 68].

Furthermore, scar treatments like fractional laser therapy and microneedling combined with PRP are undergoing clinical evaluation to standardize protocols and optimize outcomes [75]. Trials assessing drug-eluting patches or silicone-based therapies for hypertrophic scars and keloids are also providing evidence to refine treatment options. This research ensures that both cosmetic and functional aspects of wound healing are prioritized, improving the quality of life for patients.

Emerging fat reduction and body contouring techniques

Non-surgical fat reduction and body contouring are among the fastest-growing areas in cosmetology, with numerous clinical trials focusing on their safety and efficacy. For example, studies on cryolipolysis (CoolSculpting) and high-intensity focused ultrasound consistently validate their ability to reduce localized fat deposits with minimal downtime [76]. More recently, combination devices like Emsculpt Neo, which integrates HIFEM technology with RF, have been evaluated through randomized trials [77]. These studies report improvements in muscle toning and fat reduction, with results backed by imaging technologies like magnetic resonance imaging and ultrasound.

Additionally, clinical trials are exploring injectable fat-reduction agents such as deoxycholic acid (Kybella). These treatments have shown promising results in reducing submental (chin) fat and other small areas of localized fat accumulation [78]. Ongoing research evaluates optimal dosing, safety profiles, and patient selection criteria, ensuring that clinicians can deliver consistent and reliable results.

Neurotoxins and next-generation injectable therapies

Botulinum toxins remain one of the most studied and frequently performed cosmetic procedures, with ongoing clinical trials paving the way for next-generation formulations. Longer-lasting botulinum toxins, such as daxibotulinumtoxinA-lanm (Daxxify), have undergone extensive testing to confirm their extended duration of action compared to traditional botox [79]. Clinical trials are also investigating new therapeu-

tic uses for neurotoxins, such as in the treatment of masseter-hypertrophy, facial asymmetry, and hyperhidrosis (excessive sweating) [80].
In the realm of dermal fillers, novel biostimulatory products like Sculptra and Radiesse are being tested for their collagen-stimulating properties, providing long-term volume restoration [81]. Clinical trials also examine combination approaches, such as pairing fillers with energy-based devices like lasers or ultrasound, to enhance outcomes. These studies not only validate the efficacy and safety of these treatments but also guide best practices for injection techniques, ensuring optimal and natural-looking results for patients.
In summary, clinical trials in cosmetology and plastic surgery are essential for validating the safety and efficacy of emerging treatments, such as advanced wound healing therapies, non-surgical body contouring techniques, and next-generation injectables. These studies enable the development of innovative procedures like stem cell-based regenerative therapies, combination fat reduction technologies, and longer-lasting botulinum toxins, ensuring evidence-based practices for clinicians. By addressing both aesthetic and functional concerns, clinical trials uphold the highest standards of patient safety and pave the way for personalized, cutting-edge solutions in these fields.

Limitations and Future Remarks

While cosmetology and plastic surgery continue to advance, safety remains a significant limitation, particularly with emerging treatments.
Non-invasive procedures such as laser therapies and injectables, though generally safe, can still lead to complications like burns, hyperpigmentation, or vascular occlusion when performed improperly or on unsuitable candidates [82]. For instance, the overuse of dermal fillers has been associated with facial asymmetry or migration, particularly when administered by untrained practitioners [83]. This highlights the need for stringent training, standardized protocols, and improved patient education to mitigate risks.
Another challenge is the variability in results across patients, often due to differences in skin type, age, genetic factors, and healing responses. For example, fat grafting procedures can yield inconsistent outcomes, as the survival rate of transferred fat depends on factors such as harvesting technique and patient health [84]. Similarly, the efficacy of non-surgical body contouring devices like cryolipolysis or HIFEM can vary based on individual metabolic rates and lifestyle [85].
Addressing these limitations requires more personalized treatment planning, incorporating genetic and biological markers to predict outcomes more accurately.
The future of cosmetology and plastic surgery lies in leveraging AI and predictive analytics to enhance treatment precision and patient satisfaction. AI-based tools can analyze facial symmetry, skin conditions, and aging patterns to create personalized treatment plans, reducing variability in outcomes. For example, platforms like Crisalix use 3D imaging to simulate post-surgery results, enabling patients to make informed decisions [86]. As AI evolves, it could further refine techniques, such as optimizing filler placement or laser parameters based on real-time data, to ensure better safety and efficacy.
Regenerative medicine is expected to play a transformative role in overcoming current limitations. Innovations like stem cell therapy and 3D-printed scaffolds offer promising solutions for reconstructive surgery, providing more natural and durable outcomes. For example, clinical trials on adipose-derived stem cells for facial volume restoration and scar revision have shown encouraging results, with fewer complications compared to synthetic implants [71]. Additionally, the development of biocompatible materials, such as bioresorbable implants and nanotechnology-based delivery systems, could reduce complications and enhance healing, ushering in a new era of safer, more effective treatments.
In summary, by addressing these challenges and embracing future opportunities, cosmetology and plastic surgery can continue to evolve, offering safer, more personalized, and scientifically validated solutions for patients.

Conclusions

Cosmetology and plastic surgery have made remarkable strides, blending scientific innovation with clinical artistry to meet both aesthetic and reconstructive needs. From non-invasive procedures like laser treatments and injectables to advanced regenerative therapies and robotics-assisted surgeries, these fields are reshaping the way practitioners' approach physical enhancement and restoration. Despite limitations such as safety concerns, variability in outcomes, and ethical considerations, continuous research and technological advancements have improved the precision, safety, and personalization of treatments, enhancing patient satisfaction and overall quality of care.
Looking ahead, the integration of AI, predictive analytics, and regenerative medicine will further revolutionize these disciplines, offering solutions that are not only more effective but also biologically compatible and sustainable. As these technologies mature, they promise to address current challenges while expanding the possibilities for individualized care. By fostering collaboration between researchers, clinicians, and industry stakeholders, cosmetology and plastic surgery will continue to push the boundaries of innovation, helping patients achieve their goals with confidence and safety.

Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus

instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/ de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Resumen

La cosmetología y la cirugía plástica han avanzado significativamente en las últimas décadas, impulsadas por innovaciones en técnicas no invasivas, metodologías quirúrgicas y medicina regenerativa. Estos campos ofrecen ahora una amplia

gama de procedimientos, desde bótox y rellenos dérmicos hasta complejas cirugías reconstructivas, lo que permite a los profesionales abordar tanto los deseos estéticos como la restauración funcional. La integración de nuevas tecnologías como el láser, la robótica y la inteligencia artificial (IA) ha hecho que estos procedimientos sean más seguros, precisos y personalizados, ofreciendo a los pacientes mejores resultados y tiempos de recuperación más rápidos. Los ensayos clínicos y la investigación continua siguen validando estos avances, garantizando que los tratamientos sean eficaces y tengan una base científica. A pesar de estos avances, persisten desafíos como las preocupaciones sobre la seguridad, la variabilidad en los resultados del tratamiento y la posibilidad de efectos adversos. Sin embargo, el futuro de la cosmetología y la cirugía plástica es prometedor, con áreas emergentes como las terapias con células madre, los materiales de bioingeniería y la atención personalizada basada en IA, preparadas para abordar estas limitaciones. A medida que estas tecnologías evolucionan, ofrecen el potencial de resultados más naturales, duraderos y específicos para cada paciente, estableciendo nuevos estándares tanto en la mejora estética como en los procedimientos reconstructivos. La colaboración continua entre médicos, investigadores y pacientes será clave para forjar el futuro de estos campos dinámicos.

Palabras clave: Cosmetología, Cirugía plástica, Tratamientos no invasivos, Medicina regenerativa, Ensayos clínicos, Inteligencia artificial, Terapias inyectables, Atención personalizada

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Cardiovascular Endocrinology: An Overview on Interplay of Hormones, Developmental Programming and Cardiovascular Diseases.

Endocrinología cardiovascular: Una visión general de la interacción entre hormonas, programación del desarrollo y enfermedades cardiovasculares.

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Abstract

Cardiovascular endocrinology is a rapidly evolving field that investigates the complex interplay between the endocrine and cardiovascular systems. This multidisciplinary area of study is essential for understanding how hormonal imbalances can influence cardiovascular health and disease. The endocrine system, through the secretion of hormones, plays a critical role in regulating cardiovascular functions such as blood pressure, heart rate (HR), and vascular tone. Conversely, cardiovascular events can impact hormone production and release, highlighting the bidirectional communication between these systems. This review explores the physiological interactions and pathophysiological consequences of disruptions in this delicate balance, with a focus on key hormones such as vitamin D, growth hormone, and thyroid hormones, and their implications for cardiovascular health. The review also delves into the role of developmental programming in shaping cardiovascular health, emphasizing the impact of early life factors such as maternal nutrition, stress, and environmental exposures on long-term cardiovascular outcomes. Additionally, it examines the influence of sex hormones, lipoprotein metabolism, and emerging research areas such as the gut microbiome and novel biomarkers on cardiovascular disease (CVD) risk. Clinical studies, including landmark trials like the Framingham heart study (FHS) and the Women's Health Initiative, are discussed to highlight the translation of research findings into clinical practice. The review concludes by addressing the challenges and future directions in cardiovascular endocrinology, underscoring the need for ongoing research to develop effective interventions and improve patient outcomes.

Keywords: Cardiovascular endocrinology, Developmental programming, Hormonal regulation, Lipoprotein metabolism

Introduction

Cardiovascular endocrinology is a multidisciplinary field that explores the intricate interactions between the endocrine and cardiovascular systems. This area of study is crucial for understanding how hormonal imbalances can influence cardiovascular health and disease [1, 2]. The research in this field spans various topics, including the role of hormones like vitamin D, growth hormone, and thyroid hormones in cardiovascular health, as well as the development of pharmaceutical strategies to address cardiovascular and endocrinological disorders [3, 4]. The endocrine and cardiovascular systems are intricately linked, with bidirectional communicationinfluencing numerous physiological processes. The endocrine system, through the secretion of hormones, profoundly impacts cardiovascular function, regulating blood pressure, HR, and vascular tone [5, 6]. Conversely, cardiovascular events can affect hormone production and release, further highlighting the complex interplay between these two essential systems [7].

This article will explore this relations hip, examining both normal physiological interactions and the pathophysiological consequences of disruptions in this delicate balance.
Vitamin D is increasingly recognized as a hormone with potential implications for cardiovascular and metabolic diseases. A study highlighted the association between low vitamin D levels and an unfavorable cardiometabolic profile in obese women with metabolic syndrome, suggesting a need for further research in diverse populations like those in Egypt [8]. Despite the observed associations, randomized controlled trials have shown conflicting results regarding the benefits of vitamin D supplementation for cardiovascular health, indicating that routine screening for deficiency is not universally recommended [9].

Interplay Between the Endocrine and Cardiovascular Systems

Cardiovascular endocrinology explores the intricate relationship between the endocrine system and the cardiovascular system [10-12]. (Table 1).

It extends beyond the well-established connections like diabetes mellitus and its cardiovascular complications [11], delving into novel mechanisms linking the cardiovascular system with a multitude of blood-borne bioactive substances and their cellular targets [11]. This field investigates how hormones influence various aspects
of cardiovascular health, impacting processes like blood pressure regulation, lipid metabolism, and the development of atherosclerosis [13-15]. Natriuretic peptides, for example, play a crucial role in the cardiovascular system's homeostatic mechanisms [16].
Growth hormone plays a crucial role in heart development and function. Growth hormone deficiency can lead to metabolic issues that increase the risk of atherosclerosis, while growth hormone excess, as seen in acromegaly, is linked to CVD and heart failure.
Early detection and treatment of growth hormone-related disorders can prevent these complications [9]. Thyroid hormones are vital for cardiovascular regulation (Figure 1). Both hypothyroidism and hyperthyroidism can lead to various cardiac issues.

Hormone	Source	Cardiovascular effects	Clinical relevance
Angiotensin II	RAAS (Kidneys)	Vasoconstriction, increases blood pressure, promotes aldosterone release	Hypertension, heart failure, atherosclerosis
Aldosterone	Adrenal cortex	Sodium retention, increases blood volume and pressure	Primary aldosteronism, hypertension, heart failure
Epinephrine and norepinephrine	Adrenal medulla	Increases heart rate, cardiac output, vasoconstriction	Stress response, hypertension, arrhythmias
Insulin	Pancreas	Regulates glucose metabolism, endothelial function	Insulin resistance leads to atherosclerosis, diabetes, hypertension
Glucagon	Pancreas	Increases blood glucose, minor cardiac effects	Glucagonoma syndrome (rare), hypoglycemia-related tachycardia
Thyroid hormones (T3 and T4)	Thyroid gland	Regulate heart rate, contractility, vascular resistance	Hypothyroidism: bradycardia, hypertension; hyperthyroidism: tachycardia, atrial fibrillation
Cortisol	Adrenal cortex	Increases blood pressure, alters metabolism	Cushing's syndrome, metabolic syndrome, hypertension
Estrogen	Ovaries	Vasodilation reduces atherosclerosis risk	Cardioprotective; menopause increases cardiovascular risk
Testosterone	Testes, adrenal cortex	Increasing vascular tone may contribute to hypertension	Excess linked to hypertension, polycythemia, and cardiovascular risk
Atrial natriuretic peptide	Heart (Atria)	Promotes sodium excretion, lowers blood pressure	Protective in heart failure, but levels rise in disease states

Table 1: Key endocrine hormones and their cardiovascular effects.

Hypothyroidism may cause hypertension and hyperlipidemia, which can be managed with hormone replacement therapy (HRT). Hyperthyroidism can affect heart structure, function, and rhythm, potentially leading to heart failure if untreated. The use of medications like amiodarone, which can affect thyroid function, underscores the importance of monitoring thyroid health in patients with cardiovascular conditions [9].
Specific endocrine disorders can directly impact the cardiovascular system. Hyperthyroidism, for instance, can lead to thyrotoxic cardiomyopathy, a rare but serious condition [18]. This highlights the potential for endocrine imbalances to induce significant cardiovascular consequences. Conversely, adipose tissue, a key endocrine organ, secretes adipokines that exert endocrine effects on the vascular wall, influencing endothelial function and contributing to cardiovascular risk [19, 20]. The Renin-Angiotensin-Aldosterone System (RAAS) plays a central role in regulating blood pressure and fluid balance, and its dysregulation is implicated in both cardiovascular and endocrine diseases.
The interplay between RAAS and other endocrine systems, such as the parathyroid hormone system, is complex and warrants further investigation [21].
Chronic liver disease significantly impacts both endocrine and cardiovascular homeostasis. The liver's crucial role in metabolic regulation and immune function means that its dysfunction can trigger a cascade of events affecting the cardiovascular system. This can manifest as arrhythmias, cardiomyopathy, and circulatory complications, ultimately leading to conditions like portal hypertension, pulmonary hypertension, and cardiac failure. The interplay between inflammation, oxidative stress, and imbalanced vasoactive mediators, further contributes to the development of these complications. Age, sex, the gut microbiome, and organ transplantation also influence this complex interaction [22].
The interaction between the endocrine and cardiovascular systems extends beyond the examples discussed above. The gut microbiota influences the endocrine system, affecting hormone production and potentially impacting cardiovascular health [23]. The respiratory and cardiovascular systems are also closely linked, with pathologies in one system often affecting the other [24]. Furthermore, social

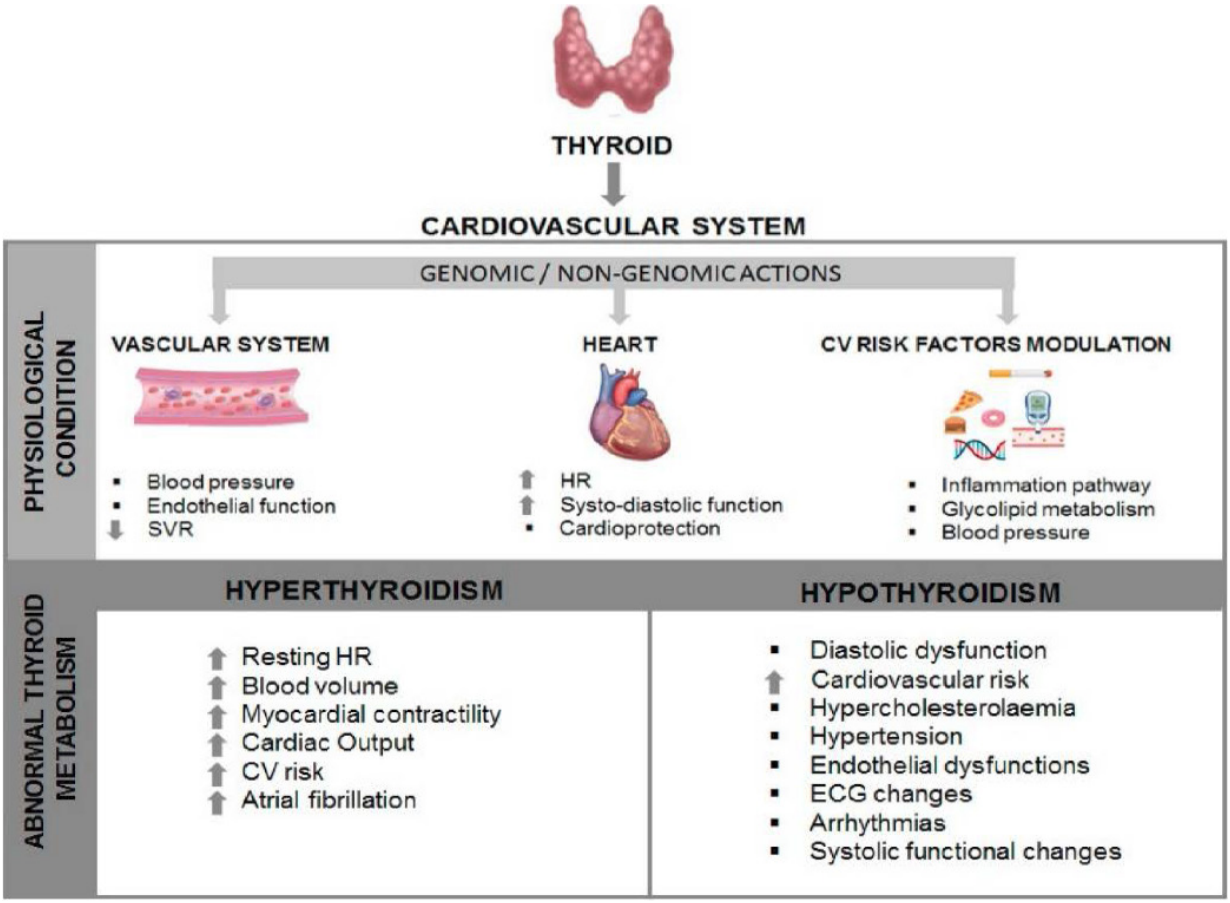

Figure 1: Interaction of the thyroid and the cardiovascular system. SVR: systemic vascular resistance and ECG: electrocardiogram [17].

support has been shown to influence cardiovascular, endocrine, and immune system function [25], underscoring the broader interconnectedness of physiological systems. Finally, the circadian system interacts with the endocrine system influencing hormonal rhythms and impacting cardiovascular function [26]. The interplay between the immune system and endocrine also plays a crucial role especially in organs like the lungs, impacting both immune response and cardiovascular health [27].

Insulin resistance, a hallmark of type 2 diabetes, is a significant risk factor for CVD. It affects glucose metabolism and promotes arteriosclerosis through mechanisms involving oxidative stress and inflammation. Managing insulin resistance is crucial in preventing cardiovascular complications associated with diabetes [28]. The paraventricular nucleus in the brain plays a central role in neuroendocrine regulation of cardiovascular function. It modulates blood pressure and cardiovascular responses through hormones like vasopressin and oxytocin, which have both endocrine and neuromodulatory effects. Dysregulation of paraventricular nucleus activity can lead to hypertension and heart failure [29]. Sex hormones, including estrogen and testosterone, influence cardiovascular health differently in men and women. Abnormal levels of these hormones can

Factor	Mechanism	Long-term cardiovascular impact	Examples/clinical relevance
Maternal undernutrition	Fetal adaptations lead to altered organ development	Increased risk of hypertension, endothelial dysfunction	Dutch famine study: higher rates of CVD in adulthood
Maternal overnutrition and obesity	Fetal exposure to excess nutrients alters metabolism	Increased risk of metabolic syndrome, hypertension, diabetes	Childhood obesity, early-onset hypertension
Gestational diabetes	Fetal hyperinsulinemia, endothelial dysfunction	Higher risk of insulin resistance, vascular dysfunction	Increased CVD risk in offspring
Intrauterine growth restriction	Reduced fetal nutrient supply leads to vascular remodeling	Increased arterial stiffness, hypertension	Barker Hypothesis: low birth weight linked to CVD
Preterm birth	Immature cardiovascular and renal systems	Higher risk of hypertension, heart failure	Preterm individuals show early arterial aging
Placental insufficiency	Poor placental function alters fetal programming	Impaired endothelial function, increased blood pressure	Preeclampsia linked to later maternal and offspring CVD
Prenatal stress and glucocorticoid exposure	Increased fetal cortisol exposure	Altered autonomic regulation, hypertension	Maternal stress, corticosteroid treatment in pregnancy
Environmental toxins (e.g., smoking, pollution, alcohol)	Epigenetic modifications affect vascular development	Increased risk of atherosclerosis, endothelial dysfunction	Fetal alcohol syndrome, smoking-induced fetal growth restriction
Early postnatal nutrition	Overfeeding or underfeeding affects metabolism	Increased risk of obesity, hypertension, metabolic syndrome	Formula feeding vs. breastfeeding impacts cardiovascular risk

Table 2: Impact of early life factors on cardiovascular health.

increase the risk of CVD, as seen in conditions like menopause and Klinefelter syndrome. The effects of sex hormone-based therapies on cardiovascular health remain an area of ongoing research [30].

Developmental Programming and the Cardiovascular System

Early development is a critical period for establishing the lifelong relationship between the endocrine and cardiovascular systems [31].
The interplay between genetic, environmental, and nutritional factors during this time can program the cardiovascular and endocrine systems, influencing disease risk later in life (Table 2) [31]. The perinatal period, in particular, is highly sensitive to various environmental stressors, including nutritional deficiencies, hypoxia, and maternal illness. This programming can be affected by various factors, including maternal health, environmental exposures, and genetic predispositions, which can lead to chronic conditions such as CVD and metabolic disorders [32].Adhesion G protein-coupled receptors play a crucial role in cardiovascular development. Mutations in adhesion G protein-coupled receptors, such as adgrl2, can lead to congenital heart defects, which are the most common congenital birth defects affecting millions of newborns annually. These defects can predispose individuals to further cardiovascular issues later in life, highlighting the importance of genetic factors in early cardiovascular development [33]. Environmental exposures during early development can lead to epigenetic changes that affect cardiovascular health across generations.

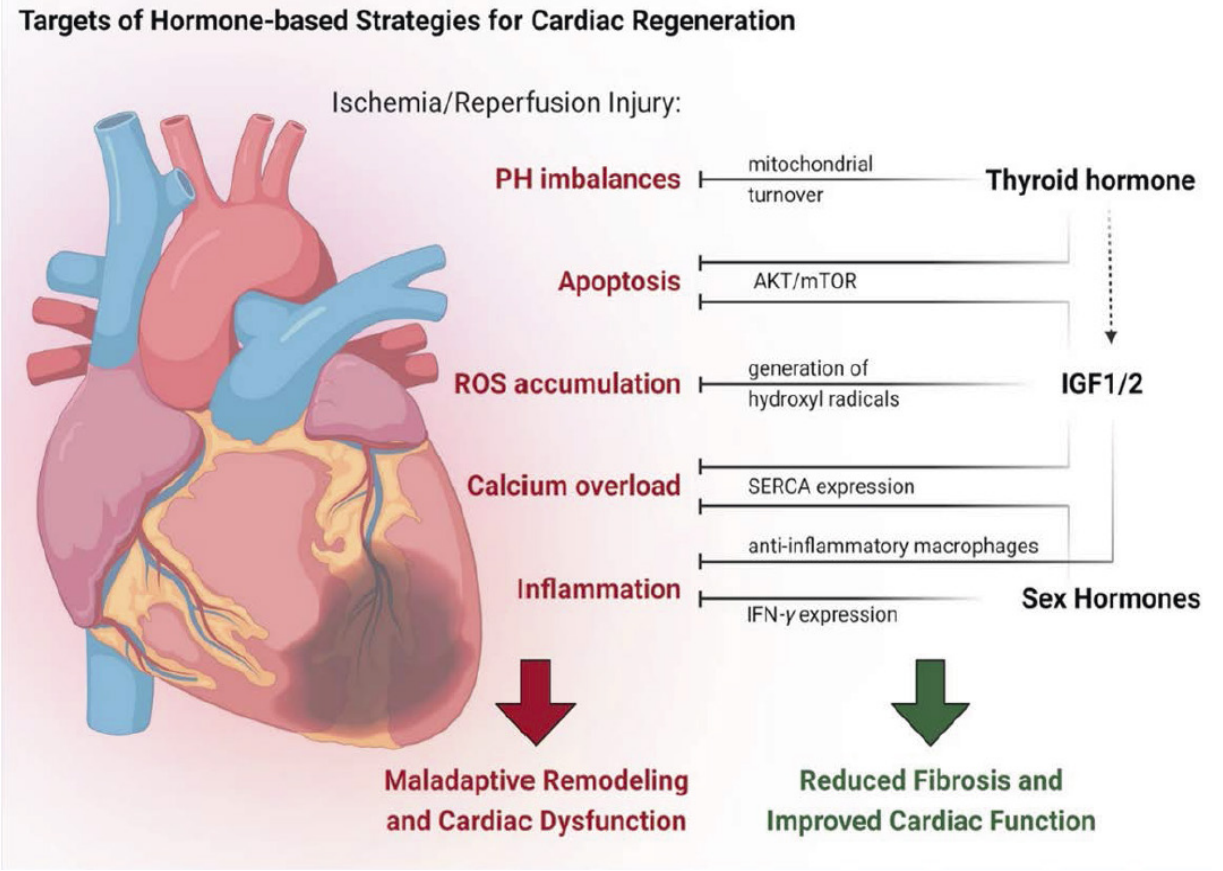

Figure 2: The combined effects of hormones on the structural and functional development of cardiomyocytes and their potential implications for heart regeneration [41].

For instance, exposure to toxicants like lead and phthalates can have sex-specific effects on cardiovascular outcomes, emphasizing the role of epigenetic programming in disease risk [34].
The maternal environment, including nutrition and stress levels, significantly influences fetal development. Nutritional deficiencies or excesses can lead to developmental programming that predisposes offspring to cardiovascular and metabolic diseases. Stressors such as hypoxia and maternal malnutrition can alter fetal cardiovascular and endocrine systems, leading to long-term health consequences [35]. The concept of fetal programming suggests that adverse conditions during fetal development, such as maternal obesity or gestational diabetes, can lead to structural and functional changes in the offspring's cardiovascular system. These changes can increase the risk of diseases like hypertension and coronary heart disease in adulthood [36, 37].
These stressors can perturb the maternal and fetal cardiovascular and endocrine systems, leading to long-term health consequences, a concept known as the "Developmental Origins of Adult Disease."
Research has demonstrated that in utero stress can predispose individuals to cardiovascular and metabolic diseases later in life, such as hypertension, type 2 diabetes, and increased adiposity. The concept of "Predictive Adaptive

Responses" suggests the fetus adapts to its anticipated environment, but mismatches between predicted and actual environments can lead to disease. Animal models, including rats, sheep, and guinea pigs, have been instrumental in studying these developmental programming effects, investigating the impact of various gestational perturbations on cardiovascular development.

These studies highlight the crucial role of utero conditions in shaping cardiovascular health throughout life [35].

While early development is a critical period for establishing the relationship between the endocrine and cardiovascular systems, it is also important to consider the role of postnatal factors. Childhood and adolescence are additional critical periods where environmental influences, such as diet and physical activity, can further shape cardiovascular health. Understanding the interplay between early programming and later life exposures is crucial for developing comprehensive strategies to prevent CVD.

Key Hormonal Influences on Cardiovascular Health Several hormones significantly affect cardiovascular function and disease risk. Hormonal influences play a significant role in cardiovascular health, with sex hormones such as estrogen, progesterone, and testosterone being key determinants [38]. These hormones impact cardiovascular physiology and pathology through various mechanisms, including modulation of vascular function, inflammation, and metabolic processes [39]. The effects of these hormones are particularly evident in the differences observed between men and women in terms of CVD risk and progression [40].

Understanding these hormonal influences is crucial for developing gender-specific strategies for CVD prevention and treatment.

The thyroid hormone's role in atherosclerosis is increasingly recognized [13]. Similarly, growth hormone, insulin-like growth factors I (IGF-I), and IGF-binding proteins are implicated in atherogenesis, particularly through their effects on postprandial lipoprotein metabolism [13]. Disturbances in the growth hormone axis/IGF system are linked to premature atherosclerosis and increased cardiovascular mortality (Figure 2), suggesting a U-shaped relationship between growth hormone axis/IGF system function and cardiovascular morbidity/mortality [13]. Furthermore, vitamin D, now recognized as a multifaceted hormone, potentially modifies the risk of cardiovascular and metabolic diseases [8]. Its deficiency is associated with an unfavorable cardiometabolic profile, particularly in populations with high prevalence of obesity and metabolic syndrome [8]. Finally, the role of PCSK9 in regulating low-density lipoprotein (LDL)-cholesterol levels is emerging as a crucial therapeutic target [42]. Inhibition of PCSK9 dramatically reduces LDL-cholesterol, potentially enhancing the efficacy of statin therapy [42].

Combined oral contraceptives are linked to a heightened risk of cardiovascular events, such as venous thromboembolism and ischemic stroke, with risk levels influenced by estrogen dose and progestogen type. The variability in risk underscores the importance of personalized contraceptive counseling and prescribing practices [43]. Estrogen enhances vasodilation by increasing the release of vasodilators like nitric oxide and prostacyclin, which are more pronounced in women than men [44, 45]. Estrogen acts as a powerful anti-inflammatory agent, contributing to its protective effects against CVD and chronic renal disease [44]. The decline in estrogen levels of post-menopauses is associated with increased risk of atherosclerosis and other cardiovascular disorders, highlighting the protective role of strogen before menopause [45, 46].

Women generally experience CVD at a later age than men, with a delay of about 10 years, attributed to the protective effects of endogenous estrogens [44]. Hormonal fluctuations during events like menarche, pregnancy, and menopause can promote a pro-inflammatory state, increasing CVD risk in women [47]. Hormone therapy, particularly with bioidentical hormones, may extend the cardiovascular protection conferred by endogenous estrogens if initiated early after menopause [44]. The impact of hormone therapy varies based on factors such as timing, administration route, and formulation, necessitating careful consideration in clinical practice [46]. Testosterone and progesterone hormones also contribute to cardiovascular health, with complex interactions affecting heart and blood vessel function differently in men and women [44, 48]. Although not a traditional sex hormone, vitamin D acts as a steroid hormone and its cardiovascular effects are controversial, with both low and high levels associated with increased risk [49].

While the protective role of estrogen in cardiovascular health is well-documented, the influence of other hormones like progesterone and testosterone, as well as the impact of hormonal contraceptives, adds complexity to the understanding of hormonal effects on cardiovascular health. Additionally, the role of vitamin D as a steroid hormone in cardiovascular health remains a topic of debate, highlighting the need for further research to clarify its effects.

Lipoprotein Metabolism and CVD

The diverse lipoprotein subfractions (very low-LDL, LDL, and high-LDL (HDL)) have distinct metabolic properties and varying relationships with coronary heart disease [50]. Sub fractionation of lipoproteins holds potential for improved risk prediction beyond classical lipid risk factors [50]. Understanding the intricate regulation of these lipoproteins and their influence on atherogenesis is critical in cardiovascular endocrinology.

Lipoprotein metabolism plays a crucial role in the development and progression of CVDs and is significantly influenced by endocrine disorders [51]. The intricate relationship between lipoprotein metabolism, endocrine function, and cardiovascular health is underscored by various studies that explore the causal associations, genetic factors, and potential therapeutic interventions [52, 53]. This section will explore the key aspects of this relationship, focusing on the impact of lipoprotein metabolism on cardiovascular health, the influence of endocrine disorders, and potential treatment strategies.

Disorders of lipoprotein metabolism have been causally linked to several CVD, including coronary artery disease, aortic aneurysm, heart failure, hypertension, and stroke. These associations are supported by Mendelian randomization studies, which highlight the significant risk posed by dysregulated li-

poprotein metabolism on cardiovascular health [54]. Lipoproteins such as HDL, LDL, and lipoprotein(a) are critical in lipid transport and metabolism. Dyslipidemia, characterized by abnormal levels of these lipoproteins, is a major risk factor for atherosclerosis and other cardiovascular conditions [55]. Elevated levels of lipoprotein(a) are particularly associated with an increased risk of atherosclerotic CVD and calcific aortic valve disease. Novel therapeutics targeting lipoprotein(a) are under development, aiming to reduce cardiovascular risk [56].
Endocrine disorders such as hypothyroidism, Cushing's syndrome, and polycystic ovary syndrome can lead to dyslipidemia, thereby increasing the risk of atherosclerotic CVD. These conditions often result in elevated LDL-C and triglycerides, contributing to cardiovascular risk [57, 58]. Treatment of the underlying endocrine disorder can improve lipid profiles and potentially reduce cardiovascular risk. For instance, managing hypothyroidism or testosterone deficiency can lead to reductions in LDL-C levels [57]. The interplay between endocrine disorders and lipoprotein metabolism necessitates a comprehensive approach to managing dyslipidemia, often requiring both endocrine treatment and lipid-lowering therapies [58].
Genetic factors play a significant role in lipoprotein metabolism, with variations in genes affecting LDL, HDL, and triglyceride levels.
These genetic predispositions can lead to disorders such as familial hypercholesterolemia and familial hypertriglyceridemia, which are associated with increased cardiovascular risk [59]. Peroxisome proliferator-activated receptor α (PPARα) is a key regulator of lipid metabolism, influencing the functionality of lipoproteins.
PPARα agonists, such as fibric acid derivatives, are used to treat hypertriglyceridemia and low HDL cholesterol levels, although their efficacy in reducing cardiovascular events remains debated [60].
While the relationship between lipoprotein metabolism, endocrine disorders, and CVD is well-established, ongoing research continues to explore the underlying mechanisms and potential therapeutic targets. The development of novel treatments, particularly those targeting specific lipoproteins like lipoprotein(a), holds promise for reducing cardiovascular risk in affected populations. However, the complexity of these interactions necessitates a multifaceted approach to treatment, integrating genetic, metabolic, and lifestyle factors.

Clinical Studies

Cardiovascular endocrinology has been extensively studied through numerous clinical trials, shedding light on the intricate relationship between hormonal regulation and CVD. One of the most influential studies in this field is the FHS, an ongoing cohort study that has tracked over 15,000 participants across multiple generations.
This study identified key CVD risk factors, including hypertension, diabetes, and obesity, and established the role of insulin resistance and thyroid dysfunction in heart disease. The long-term data from FHS has been instrumental in shaping modern preventive cardiology and risk assessment models [61].
The diabetes control and complications trial (NCT00360815) and its follow-up, the epidemiology of diabetes interventions and complications (EDIC) study (NCT00360893), provided groundbreaking evidence on the impact of glucose control in diabetes management. Enrolling 1,441 individuals with type 1 diabetes, the study found that intensive glucose control reduced cardiovascular events by 42% (hazard ratio (HR) 0.58; 95% confidence interval (CI): 0.31 - 1.07; p = 0.08). This effect was confirmed in the long-term EDIC follow-up, emphasizing the importance of early and sustained glucose control in preventing cardiovascular complications. These findings have had a significant influence on diabetes treatment guidelines worldwide [62].
Another pivotal study, the women's health initiative (WHI) (NCT00000611), examined the cardiovascular effects of HRT in postmenopausal women. With a large cohort of 27,347 participants, WHI demonstrated that estrogen-progestin therapy increased the risk of coronary heart disease (HR 1.18; 95% CI: 0.95 - 1.45) and stroke (HR 0.94; 95% CI: 0.78 - 1.14), leading to a major shift in clinical recommendations regarding HRT use. While estrogen-alone therapy showed a neutral or slightly beneficial effect in younger women, the overall findings raised concerns about the widespread use of HRT for cardiovascular protection [63].
The heart outcomes prevention evaluation trial further underscored the importance of the angiotensin-converting enzyme (ACE) inhibition or vitamin E in cardiovascular health. In a study of 9,297 high-risk patients, the ACE inhibitor ramipril significantly reduced myocardial infarction by 20% (relative risk (RR) 0.80; 95% CI: 0.70 - 0.90; p < 0.001), stroke by 32% (RR 0.68; 95% CI: 0.56 - 0.84; p < 0.001), and cardiovascular mortality by 26% (RR 0.74; 95% CI: 0.64 - 0.87; p < 0.001). These findings reinforced the role of ACE inhibitors in reducing cardiovascular risk and improving survival in patients with hypertension and diabetes [64].
The UK prospective diabetes study (UKPDS) provided critical insights into the management of type 2 diabetes and its cardiovascular complications. With 5,102 participants, UKPDS demonstrated that intensive glucose control reduced microvascular complications by 25% (p = 0.0099), while metformin therapy specifically lowered diabetesrelated mortality by 42% (p = 0.017). This study played a crucial role in defining treatment targets for blood glucose levels and emphasizing the benefits of early intervention in diabetes management [65].
Finally, the systolic blood pressure intervention trial (NCT01206062) provided strong evidence supporting aggressive blood pressure management. Among 9,361 participants at high cardiovascular risk but without diabetes, lowering systolic blood pressure to <120 mmHg resulted in a 25% reduction in cardiovascular events (HR 0.75; 95% CI: 0.64 - 0.89; p < 0.001) and a 27% reduction in all-cause mortality (HR 0.73; 95% CI: 0.60 - 0.90; p = 0.003). These findings led to a paradigm shift in hypertension treatment guidelines, advocating for more intensive blood pressure control in high-risk patients [66].
Together, these landmark studies have significantly influenced clinical practice in cardiovascular endocrinology, highlighting the critical role of hormones in regulating blood pressure, glucose metabolism, and vascular function. Their findings continue to shape guidelines for diabetes management, hormone therapy, and hypertension treatment, ultimately improving patient outcomes in car-

Research area	Focus	Potential impact	Advantages	Limitations
Gut microbiome and cardiovascular health	Investigating how gut bacteria influence metabolic and hormonal pathways affecting CVD risk	May lead to microbiome-targeted therapies for hypertension, diabetes, and atherosclerosis	Potential for novel, non-invasive therapeutic approaches and personalized treatments	Complex interactions and limited understanding of how specific microbiota influence CVD
Adipokines and cardiovascular risk	Studying hormones secreted by adipose tissue, such as leptin, adiponectin, and resistin, and their role in heart disease	Could provide new targets for obesity-related cardiovascular disorders	Identification of novel biomarkers and therapies for obesity-induced heart disease	Adipokines' roles are multifaceted, making it difficult to develop targeted therapies without side effects
Sex hormones and CVD	Examining how estrogen, testosterone, and progesterone influence cardiovascular health in men and women	May lead to gender-specific treatment approaches for CVD prevention	Tailored treatments for men and women based on hormonal influences, improving efficacy	Variability in hormonal effects based on age, menopause status, and other factors complicates generalization
Thyroid dysfunction and heart failure	Exploring how hypothyroidism and hyperthyroidism contribute to arrhythmia, heart failure, and vascular dysfunction	Could refine screening and treatment strategies for thyroid-related heart conditions	Improved diagnosis and early intervention for thyroid-related cardiovascular complications	Requires larger studies to clarify thyroid-heart interactions in diverse populations
Endocrine disruptors and cardiovascular health	Investigating environmental chemicals (e.g., BPA, phthalates) that interfere with hormonal regulation and contribute to CVD	May lead to policy changes and preventive measures to reduce exposure	Potential for public health interventions to reduce exposure to harmful chemicals	Limited long-term studies on specific chemicals and their direct cardiovascular effects
Glucocorticoids and cardiometabolic risk	Studying the long-term effects of stress hormones on blood pressure, insulin resistance, and CVD	Could improve management of chronic stress and metabolic syndrome	Could provide new targets for chronic stress-related CVD prevention	Variability in glucocorticoid responses and lack of consensus on treatment guidelines
Chronobiology and cardiovascular health	Exploring how circadian rhythms affect hormone secretion and cardiovascular function	May lead to time-based (chronotherapy) interventions for better treatment outcomes	Innovative approach to treatment that could optimize drug delivery and lifestyle changes	Complexities in circadian biology and the need for more research on clinical applications
Novel biomarkers for CVD risk assessment	Identifying new endocrine markers, such as fibroblast growth factors and irisin, for early detection of CVD	Could enhance personalized risk stratification and early intervention	Potential for more accurate and early detection of cardiovascular risks	Need for validation of biomarkers in large-scale clinical studies
Metabolic syndrome and CVD	Understanding the interplay between insulin resistance, dyslipidemia, hypertension, and hormonal regulation	May refine treatment strategies to prevent cardiovascular complications in metabolic syndrome	Integrated approach could address multiple cardiovascular risk factors simultaneously	Interactions between metabolic components are complex, making it difficult to design targeted therapies
Gene therapy and hormonal regulation	Investigating gene-editing approaches to modulate hormonal pathways linked to CVD	Holds potential for personalized and long-term solutions to endocrine-related heart diseases	Innovative potential for curing genetic conditions that predispose individuals to CVD	Ethical concerns, regulatory challenges, and long-term safety risks associated with gene-editing technologies

Table 3: Emerging research areas in cardiovascular endocrinology.

diovascular health.

Emerging Research Areas in Cardiovascular Endocrinology

Emerging research in cardiovascular endocrinology is advancing rapidly, focusing on the complex interplay between hormones and cardiovascular health (Table 3). This interdisciplinary field is gaining momentum as researchers explore the complex interactions between cardiovascular and endocrine systems, aiming to improve patient outcomes through innovative treatments and a deeper understanding of underlying mechanisms. This section highlights key emerging areas in this field.

GLP1RAs have emerged as a significant area of research due to their dual role in managing type 2 diabetes and providing cardiovascular benefits. Studies have shown that these agents can improve cardiovascular outcomes, making them a focal point in cardiovascular endocrinology research. Research hotspots include the effects of GLP1RAs on cardiovascular outcomes, their efficacy, and protective mechanisms against metabolic abnormalities. Semaglutide, a specific GLP1RA, is a prominent subject of study, particularly in placebo-controlled trials [67].

The cardiovascular implications of various endocrine disorders, such as subclinical hypothyroidism and testosterone deficiency, are under investigation. These conditions have been linked to cardiovascular events, but the benefits of replacement therapies remain controversial due to insufficient evidence from randomized controlled trials.

Growth hormone deficiency is another area of interest, with studies suggesting that replacement therapy may reverse detrimental cardiovascular effects, although more research is needed to confirm these findings [68].

Recent advances in molecular biology have led to the development of new therapeutic strategies targeting the remodeling of cardiac tissue and the role of paracrine and autocrine growth factors in heart disease.

These approaches aim to address chronic cardiovascular conditions such as heart failure [69]. The use of specific receptor antagonists, such as those targeting endothelin, is being explored for their potential to regulate hemodynamic homeostasis and treat hypertension [70].

The discovery of new biomarkers related to lipid metabolism, glycemia, inflammation, and cardiac damage is a growing area of research. These biomarkers hold promises for better risk stratification and the development of new intervention targets in CVD management [71]. The role of cholesterol as a paracrine growth factor in atherogenesis is being re-evaluated, with implications for the early effects of lipidlowering drugs on atherosclerotic plaques [69].

Research continues to uncover new insights into the field. The role of nuclear receptors, such as ROR-α, in modulating CVD and inflammatory responses is under investigation [14]. The heart itself functions as an endocrine organ, producing hormones like GDF-15 and myostatin that influence systemic physiology [72]. The use of cardiac biomarkers, such as troponins and natriuretic peptides, in both human and veterinary medicine, highlights

species-specific differences that must be considered when interpreting results [73].
Ongoing controversies exist regarding the cardiovascular effects of calcium supplementation [74] and the impact of dipeptidyl peptidase IV inhibitors on heart failure risk [75]. Moreover, the field is expanding its scope to address global health challenges, particularly in emerging markets, by developing strategic brand frameworks for expanding access to cardiovascular and endocrinology treatments [76].
New therapeutic approaches, such as the use of cyclodextrin to reverse atherosclerosis, show promise in preclinical studies. This treatment enhances cholesterol metabolism and could be repurposed for human use, offering a novel strategy for managing atherosclerosis [77]. The potential of targeting ANGPTL3 for lipid management, similar to PCSK9 inhibitors, represents another innovative direction in cardiovascular endocrinology research [78].
While these emerging areas offer promising avenues for research and treatment, challenges remain in fully understanding the complex interactions between cardiovascular and endocrine systems. The need for more robust clinical trials and validation of novel biomarkers is critical to translating these findings into clinical practice. Additionally, the exploration of new mechanisms linking cardiovascular health with endocrine functions continues to be a fertile ground for future research, potentially leading to groundbreaking therapeutic interventions

Conclusion

While the field of cardiovascular endocrinology is advancing with promising research and therapeutic strategies, challenges remain. The complexity of hormonal interactions and their impact on cardiovascular health necessitates ongoing research to clarify these relationships and develop effective interventions. Additionally, the variability in healthcare infrastructure and economic conditions across different regions poses challenges for the implementation of new treatments, particularly in emerging markets. These factors highlight the need for tailored approaches that consider local contexts and patient needs.
One of the most transformative developments is the integration of artificial intelligence (AI) into cardiovascular endocrinology research and clinical practice. AI has the potential to revolutionize the way we diagnose, predict, and manage cardiovascular and endocrine disorders by leveraging large datasets, identifying patterns, and providing personalized treatment recommendations.
However, the integration of AI into cardiovascular endocrinology also presents challenges, including the need for robust data privacy measures, ethical considerations, and the validation of AI models in diverse populations. Collaborative efforts between researchers, clinicians, and AI experts will be essential to address these challenges and fully realize the potential of AI in this field. As we move forward, the synergy between cardiovascular endocrinology and AI holds great promise for advancing our understanding of hormonal influences on cardiovascular health and transforming the landscape of preventive and therapeutic interventions. By embracing these technological advancements, we can pave the way for a future where personalized, data-driven care becomes the cornerstone of cardiovascular endocrinology.

Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Pren Med Argent, 111(6), 274-284, 2025.

Resumen
La endocrinología cardiovascular es un campo en rápida evolución que investiga la compleja interacción entre los sistemas endocrino y cardiovascular. Esta área de estudio multidisciplinar es esencial para comprender cómo los desequilibrios hormonales pueden influir en la salud y las enfermedades cardiovasculares. El sistema endocrino, a través de la secreción de hormonas, desempeña un papel fundamental en la regulación de funciones cardiovasculares como la presión arterial, la frecuencia cardíaca (FC) y el tono vascular. Por otro lado, los eventos cardiovasculares pueden afectar la producción y liberación de hormonas, lo que pone de relieve la comunicación bidireccional entre estos sistemas. Esta revisión explora las interacciones fisiológicas y las consecuencias fisiopatológicas de las alteraciones de este delicado equilibrio, centrándose en hormonas clave como la vitamina D, la hormona del crecimiento y las hormonas tiroideas, y sus implicaciones para la salud cardiovascular. La revisión también profundiza en el papel de la programación del desarrollo en la configuración de la salud cardiovascular, haciendo hincapié en el impacto de factores de la vida temprana, como la nutrición materna, el estrés y las exposiciones ambientales, en los resultados cardiovasculares a largo plazo. Además, examina la influencia de las hormonas sexuales, el metabolismo de las lipoproteínas y áreas de investigación emergentes como el microbioma intestinal y nuevos biomarcadores sobre el riesgo de enfermedad cardiovascular (ECV). Se analizan estudios clínicos, incluyendo ensayos de referencia como el estudio cardíaco de Framingham (FHS) y la Iniciativa de Salud de la Mujer, para destacar la aplicación de los hallazgos de la investigación a la práctica clínica. La revisión concluye abordando los desafíos y las futuras direcciones de la endocrinología cardiovascular, subrayando la necesidad de investigación continua para desarrollar intervenciones eficaces y mejorar los resultados de los pacientes.

Palabras clave: Endocrinología cardiovascular, Programación del desarrollo, Regulación hormonal, Metabolismo de las lipoproteínas

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Measurement of Prothrombin Time, Activated Partial Thromboplastin Time and VIII Activity in a Sample of Iraqi Patients with Solid Tumors.

Medición del tiempo de protrombina, el tiempo de tromboplastina parcial activada y la actividad del factor VIII en una muestra de pacientes iraquíes con tumores sólidos.

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Abstract

Acquired thrombophilia is associated with a considerable risk of thrombosis which is highly encountered in malignancy, where both venous and arterial thromboembolism are not uncommon complications. Patients with malignant tumors, also present with hypercoagulability, even in the lack of thrombosis. Besides, activation of coagulation pathway may play a part in tumor progression. Around 15% of all patients with malignancy develops thrombosis during the course of their disease. Thrombosis can affect the morbidity and mortality of the underlying illness. Furthermore, complications of Thrombosis are one of the most common causes of death in patients with malignant tumors. Therefore, preventing thrombotic complications in cancer patients is a clinically significant concern. To study the effect of solid malignant tumors on blood coagulation via measurements of prothrombin time (PT), activated partial thromboplastin time (APTT) and factor VIII activity. Thirty patients diagnosed with malignant tumors attending the oncology consolatory out-patient clinic at Baghdad teaching hospital were investigated versus a control group of 30 healthy donors. PT, APTT and factor VIII activity were estimated, PT and APTT assessed by semi-automated technique and factor VIII activity was measured by clotting method. PT and APTT results were insignificantly related to control group 13.037 (±0.651) vs. 13.433 (±0.43) respectively. There was a significant correlation between PT with the stage of the malignant tumors. There was statistically significant difference in mean factor VIII activity between the patients and control group ($p < 0.000$). There was increase in factor VIII activity in cancer patients compared to the control group reflecting subclinical thrombophilia and higher risk of Venous thromboembolism (VTE) in patients with solid tumors due to activation of both prothrombotic and fibrinolytic pathways by malignant cells which is vital to consider primary prophylaxis by anticoagulants.

Keywords: Prothrombin time, Activated partial thromboplastin time, Factor VIII, Thrombophilia, Solid tumors.

Introduction

It is estimated that VTE disease occurs in about 6.8% of patients with an underlying malignancy [1, 2, 3]. A constellation of factors rather than a single event contributes to the hypercoagulable state of cancer.

Chemotherapy, surgery, immobilization, and the presence of comorbid conditions are associated with increased risk of clotting in these patients. However, the leading factor that predisposes cancer patients to thrombosis seems to be related to the interaction of tumor cells with the hemostatic system. Cancer cells possess a host of procoagulant properties mediated through excessive release of angiogenic factors, cytokine release as well as direct effect on the vessel wall [1, 4].

Thrombotic events can influence the morbidity and mortality of the underlying disease. Thrombotic complications are among the most common causes of death in patients

with cancer. Therefore, preventing these complications in cancer patients is a clinically relevant issue.
Recently, new approaches to the prevention and cure of thrombosis in cancer have been investigated, and the hypothesis that the strategies to inhibit clotting mechanism may favorably affect malignant disease is gaining increasing interest [2, 5, 6]. The study aimed to assess the effect of solid malignant tumors on blood coagulation via measurements of PT, APTT and factor VIII activity.

Methods

Patients

Over a two-month period, 30 patients (9 males and 21 females) were included and randomly selected in our study, attending the oncology consultatory out-patient clinic at Baghdad Teaching Hospital/Medical City. All patients were newly diagnosed with malignant solid tumors by reports of histopathology from governmental and private sectors. All the laboratory tests were completed at the hematology and biochemistry departments of The National Center for Teaching Laboratories/Medical City.

Exclusion criteria

All adult patients of age over 60 years, pregnant females or females with history of successive multiple abortions, diabetic and hypertensive, recent major surgery in the last 3 months, signs of active infection (no fever, no malaise, no focus of infection, etc.), on chemotherapy, aspirin and contraceptive pills or with positive history of prior thrombotic event.

Control group

Thirty healthy individuals, matched for sex and age. The subjects age of the control group ranged between 18 - 58 years and both nine males and twenty-one females were involved.

Data collection

Every patient was asked about age, residence, intake of drug including chemotherapy, personal and family history of any thrombotic or suspected thrombotic events, immobility, history of dehydration,
leg edema and history of diabetes mellitus or hypertension. Data were obtained from reports of histopathology about the definite histopathological type. malignant tumors Staging were taken from clinical and histopathological reports. ethical approval was acquired from all patients.

Sampling and sample handling

6 ml of blood were collected by a clean aseptic venipuncture from both patient and control group. The taken sample was then divided between three tubes as follows: 1.8 ml of blood in clean disposable capped plastic tube containing 0.2 ml of trisodium citrate dihydrate 109 mmol/l (32 g/l).

Platelets poor plasma was obtained after centrifugation of blood at room temperature with 2000 g for 15 min, then 0.5 ml of plasma collected from the upper part of the separated plasma leaving at least 0.5 ml plasma on top of the undisturbed red cell layer and the collected plasma were stored in toppered plastic tubes and frozen at -80 °C in deep freeze at the National Blood Transfusion Center for one to two weeks for performing VIII assay. The residual plasma was used for immediate performance of PT and PTT assay within 2 h of blood collection.

Coagulation tests

Manual measurement of PT and APTT tests were done by using (DIAGNOSTICA STAGO/France) kits [7, 8].

PT

The test measures the time of plasma clotting in the existence of an optimal concentration of tissue extract (thromboplastin) and specifies the overall competence of the extrinsic clotting system [9].

APTT

This test measures the clotting time of plasma after the activation of contact factors without tissue thromboplastin addition, and so indicates the overall effectiveness of the intrinsic pathway. The test depends on the contact factors, factors VIII and IX, and on the reaction with factors X, V, prothrombin and fibrinogen [9]. The APTT includes the recalcification of plasma after addition of standardized amount of cephalin (platelet substitute) and a factor XII activator (kaolin) [8]. Factor VIII one stage assay The one stage assay of factor VIII is grounded on the partial thromboplastin time. The assay compares the ability of dilution of the patient plasma and of standard plasma to correct the partial thromboplastin time of substrate plasma [9]. Normal pooled plasma was calibrated against STA® Unicalibrator (REF 00675) to sustain accuracy of one stage factor VIII assay [10].
Calibration was achieved by making 3 dilutions 1:10, 1:20, 1:40 of both unicalibrator and normal pool plasma, then by addition of 0.1 ml of STAGO-DEFICINT VIII and 0.1 ml of each dilution in plastic tube well mixed and 0.1 ml of cephalin kaolin was added. The mixture incubated for 3 min in water bath at 37 °C with gentle tilting every 1 min. Precisely at the end of the 3 min 0.1 ml of pre-warmed calcium chloride 0.025 mol/L added and a stop watch started concurrently to record the clotting time in seconds. The clotting time (APTT) of each dilution of unicalibrator and normal pooled plasma was recorded and plotted on a log paper as factor VIII activity against clotting time in seconds. The clotting times were plotted on a log-log paper to acquire a straight line refers to the parallel line bioassay [10].

Statistical analysis

Statistical analysis was performed with Minitab version 5 and Microsoft office excel 2007. Numeric data were

analyzed as mean, standard deviation and standard error of the mean, using student T-test, while nominal data were expressed as frequencies and were analyzed using chi-square, Pearson correlation was used to determine relation between two numeric variables. P value < 0.05 was considered significant.

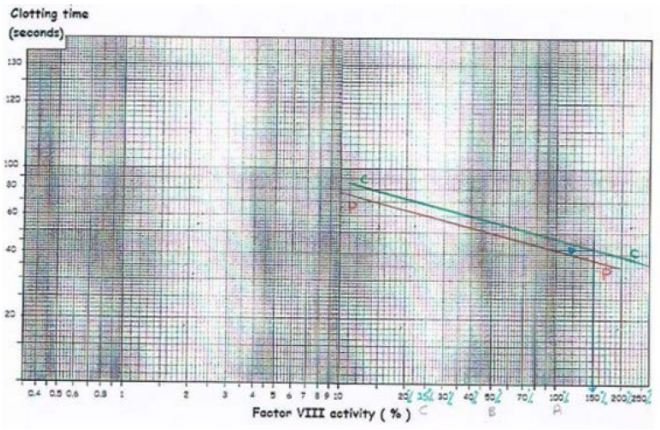

Figure 1: Factor VIII activity.

Stage	No	%
I	5	16.6
II	9	30
III	8	26.7
IV	8	26.7

Table 1: The percentages of each stage of malignant tumors in patients' group.

Results

The study was conducted on 30 patients (11 males and 19 females) and 30 healthy age and sex matched control subjects (11 males and 19 females).

Clinical data

The mean age for patients' group was 46.9 (±4.5) years and the mean age for the control group was 42 (±3.6) years. The range was (18 - 58) years for both groups. Patients group consisting of 9 males and 21 females control group consisting of 9 males and 21 females. Regarding patients' group the percentages and frequencies of each location of malignant tumor, breast cancer and bronchogenic malignancy were the most frequent malignancy among females and males respectively.
Stages' percentages of each malignant tumor with their frequencies are shown in table 1 which reveals that stage two is the most frequent.

Coagulation data

PT and APTT

The mean value of PT level was 13.037 (±0.651) and 13.433 (±0.43) seconds for patient and control groups respectively as shown in table 2.

There is insignificant difference in mean PT level between the patient and control group (p = 0.08). The mean value of APTT level was 28.23 (±2.5) and 29.083 (±0.683) seconds for patient and control groups respectively as shown in table 2. There is insignificant difference in mean PT level between the patient and control group (p = 0.08).

Factor VIII activity

The mean value of factor VIII activity was 181% and 99.3% for patient and control groups respectively as shown in table 3, and there is statistically significant difference in mean factor VIII activity between the patients and control group (p < 0.000), as shown in figure 2.

Correlations with stage

There is a negative correlation between PT level and stage of solid malignant tumors which is significant. There is a negative correlation between PTT level and stage of solid malignant tumors but didn't reach statistically significant level. There is a positive correlation between factor VIII activity and stage of malignant tumors which is insignificant (Table 4 and figure 3).

Discussion

Solid malignant tumors are often associated with modification of hemostasis and increased thrombotic risk in cancer patients. The mechanism of alteration of hemostasis is still not fully explained but many pathways seem to be involved. Yet, most of patients with malignancy have asymptomatic activation of hemostasis and discovered accidentally by laboratory tests [11, 12].
Hypercoagulability markers are less specific in older age, so in the current study, the age of both control and patient groups were selected below 60 years to avoid misinterpretation [13, 14]. There was significant correlation between PT with the stage of malignant tumor. There were insignificant correlations between APTT and factor VIII with the stage of neoplastic tumors. Ursavaş et al. [15] found that PT, APTT, factor VIII and fibrinogen levels didn't show any statistically significant differences between early and advanced disease groups which agree with the current study except for PT [15].
PT and APTT results of both patients and control groups were comparable, similar results were observed by Micco et al. [11] and Komurcuoglu et al. [16]. Factor VIII activity was significantly higher in patients with solid tumor than control group, similar results were found by Battistelli et al. [17], Lu et al. [18], Yigit et al. [19], and Deitcher and Gomes [20].
Elevated levels of procoagulants released by neoplastic cells leads to increased factor VIII activity associated with VTE risk seem to be persistent and not exclusively attributable to acute-phase response. Factor VIII activity levels above 1.5 IU/ml (150%) are associated with a threefold and a six-fold higher relative risk of VTE when compared with levels below 1.5 IU/ml (150%) and below 1.0 IU/ml (100%), correspondingly. VTE risk is 11-fold higher with factor VIII levels greater than 200% [21].

Tests	Mean PT (sec) ± SD	SE	P value
PT patients	13.037 ± (0.651)	0.12	0.08
PT control	13.433 ± (0.43)	0.079	
APTT patients	28.23 ± (2.5)	0.46	0.08
APTT control	29.083 ± (0.638)	0.12	

Table 2: Patient and control groups' results for PT and APTT.

Groups	Mean	SD	SE	P value
Patients	181	58.4	11	0.00
Control	99.3	11.1	2	

Table 3: Factor VIII activity results of patient and control groups.

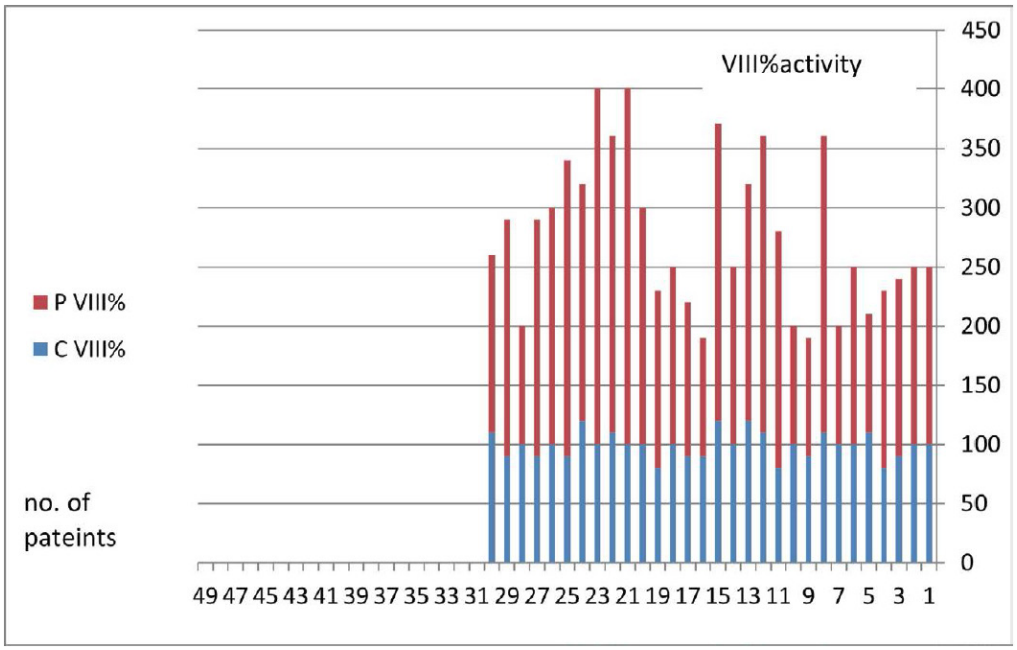

Figure 2: Factor VIII activity for control group (C) and patients' groups (P).

Stages	r	P value
PT	-0.422	0.025
PTT	-0.054	0.781
Factor VIII%	0.167	0.385

Table 4: Correlation between PT, APTT and factor VIII% with the stage of malignant tumors.

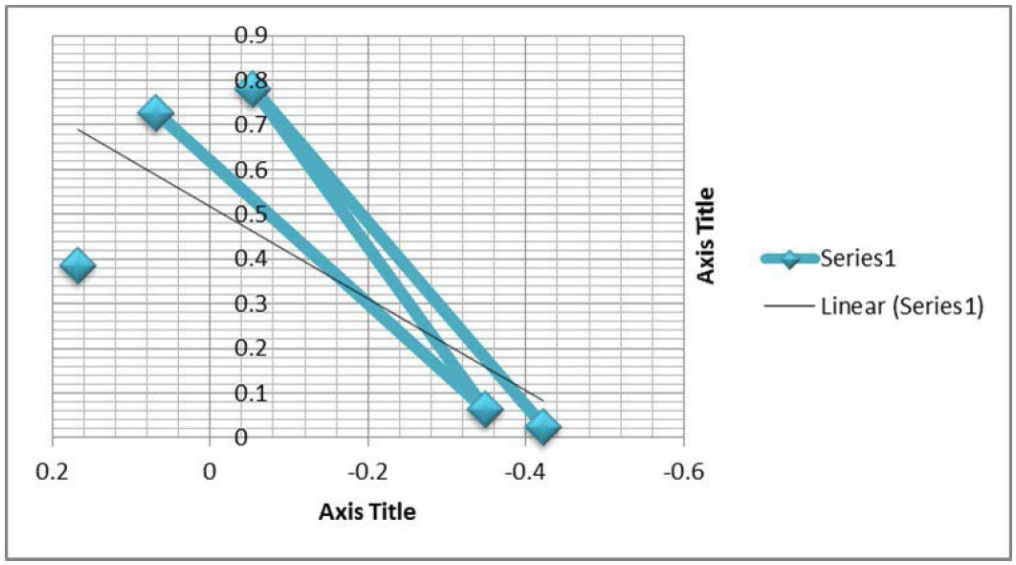

Figure 3: Correlations of coagulation data with the stage of malignant tumors.

Conclusion

There was significant elevation in factor VIII activity in patients with neoplastic tumors compared with the control group reflecting subclinical thrombophilia and increased VTE risk in patients with malignancy as a result of activation of prothrombotic and fibrinolytic pathways by neoplastic cells that is extremely necessary to take into consideration primary prophylaxis by anticoagulants.

Declarations

The authors declare that they have no conflicts of interest of any kind, that the work has been approved by the responsible ethics workplace´s committee, that the data and graphics present in the manuscript are original and were produced at their respective institutions with their due authorization and do not declare means of financing of the work done. The article referred with the consent of all authors for evaluation and publication. The authors also declare that there was/were obtained the informed consent/s of the patients/s for publication of their case/s. No artificial intelligence-assisted technologies were used in the preparation of this article.

Declaraciones

Los autores declaran no tener conflictos de interés de ninguna clase, que el trabajo ha sido aprobado por el comité de ética responsable en el lugar de trabajo, que los datos y los gráficos presentes en el manuscrito son originales y se realizaron en sus instituciones pertenecientes con su debida autorizacion y no declaran medios de financiación del trabajo realizado. El artículo fue remitido con el consentimiento de todos los autores para su evaluación y publicación. Los autores declaran, asimismo, que obtuvieron el/los consentimiento/s informado/s de/de los paciente/s para publicación de su/s caso/s. Para la confección de este artículo no se utilizaron tecnologías asistidas por Inteligencia Artificial.

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Resumen

La trombofilia adquirida se asocia a un riesgo considerable de trombosis, un problema frecuente en neoplasias malignas, donde la tromboembolia venosa y arterial son complicaciones frecuentes. Los pacientes con tumores malignos también presentan hipercoagulabilidad, incluso en ausencia de trombosis. Además, la activación de la vía de la coagulación puede influir en la progresión tumoral. Alrededor del 15 % de los pacientes con neoplasias malignas desarrollan trombosis durante su enfermedad. La trombosis puede afectar la morbilidad y la mortalidad de la enfermedad subyacente. Además, las complicaciones de la trombosis son una de las causas más comunes de muerte en pacientes con tumores malignos. Por lo tanto, la prevención de complicaciones trombóticas en pacientes con cáncer es una preocupación clínicamente significativa. El objetivo del estudio es estudiar el efecto de los tumores malignos sólidos en la coagulación sanguínea mediante mediciones del tiempo de protrombina (TP), el tiempo de tromboplastina parcial activada (TTPA) y la actividad del factor VIII. Se investigó a treinta pacientes con diagnóstico de tumores malignos que acudían a la consulta externa de oncología del Hospital Universitario de Bagdad, frente a un grupo control de 30 donantes sanos. Se estimaron el TP, el TTPA y la actividad del factor VIII. Ambos se evaluaron mediante una técnica semiautomatizada, y la actividad del factor VIII se midió mediante un método de coagulación. Los resultados de TP y TTPA mostraron una relación insignificante con el grupo control: 13,037 (±0,651) frente a 13,433 (±0,43), respectivamente. Se observó una correlación significativa entre el TP y el estadio de los tumores malignos. Se observó una diferencia estadísticamente significativa en la actividad media del factor VIII entre los pacientes y el grupo control ($p < 0,000$). Se observó un aumento de la actividad del factor VIII en pacientes con cáncer en comparación con el grupo control, lo que refleja trombofilia subclínica y un mayor riesgo de tromboembolia venosa (TEV) en pacientes con tumores sólidos debido a la activación de las vías protrombótica y fibrinolítica por células malignas, lo cual es fundamental para considerar la profilaxis primaria con anticoagulantes.

Palabras clave: Tiempo de protrombina, Tiempo de tromboplastina parcial activada, Factor VIII, Trombofilia, Tumores sólidos

LOGRA LAS METAS LIPÍDICAS

REOVEX

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- Reduce la injuria miocárdica en pacientes con síndrome coronario agudo.
- Estabiliza la placa aterosclerótica.
- Óptima tolerabilidad y seguridad.

REOVEX 5 **REOVEX 10** **REOVEX 20** **REOVEX 40**

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