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EDITORIAL
Consideraciones sobre los nuevos tratamientos para hemofilia.

La hemofilia es una enfermedad hemorrágica que afecta aproximadamente a una de cada 5 millones de personas en el mundo. Es causada por la mutación de un gen ubicado en el cromosoma X, por lo cual los varones sufren la enfermedad, tienen hijos varones sanos e hijas que son portadoras obligatorias de la misma. Cursa con manifestaciones hemorrágicas, cuya severidad depende de la concentración plasmática de los Factores VIII o IX de la coagulación sanguínea; estas manifestaciones pueden ser tan graves como la hemorragia intracraneal, tan limitantes como las hemartrosis a repetición y tan leves que la enfermedad puede pasar desapercibida y no descubrirse hasta que se produzca una injuria física o el paciente se someta a un estudio de coagulación. Se conocen tres tipos de hemofilia: la hemofilia A por deficiencia del factor VIII, la hemofilia B por deficiencia del factor IX y a la deficiencia hereditaria de factor XI se la ha denominado hemofilia C, aunque no está ligada al sexo y por lo general es poco severa.

El papel del factor VIII en la hemofilia A, se conoció a mediados del siglo XX, y hasta entonces el tratamiento de las crisis hemorrágicas había consistido principalmente de transfusiones más o menos frecuentes, con todos los riesgos y dificultades que ello implicaba. Una vez conocido que el FVIII o el IX estaban ausentes o deficientes en la hemofilia, se hizo frecuente el uso de plasma fresco congelado y del crioprecipitado. La calidad de vida de los pacientes hemofílicos, mejoró con la disponibilidad de concentrados de factores VIII y IX y el uso de desmopresina en casos más leves. El desarrollo de técnicas de laboratorio más precisas para la cuantificación de los factores de coagulación y para la determinación de anticuerpos neutralizantes influyó en una terapia más certera; se instituyó el tratamiento profiláctico y el uso de factor VII activado y complejo de protrombina en los pacientes con inhibidores. Estos avances en el tratamiento, disminuyeron la frecuencia y severidad de las hemorragias. Sin embargo, a pesar del enorme beneficio de los concentrados, la necesidad de administrarlos con frecuencia por vía endovenosa, sigue siendo el gran inconveniente, aparte de que llevan consigo el riesgo ya mencionado, del desarrollo de anticuerpos contra el factor administrado, y la posibilidad de transmisión de enfermedades infecciosas tan graves como la hepatitis y el síndrome de inmunodeficiencia adquirida. Con el desarrollo de los factores recombinantes, se pudo obviar el riesgo de infecciones y mejoró aún más la calidad de vida del paciente, pero siguió la necesidad de las frecuentes transfusiones y la posibilidad de desarrollar anticuerpos neutralizantes[1,2].

La búsqueda del tratamiento ideal, sin los inconvenientes mencionados, no ha cesado. Es así, como se han desarrollado los factores recombinantes de media vida alargada (EHL-rFVIII y EHL-FIX), para disminuir la frecuencia de las transfusiones[3]; la terapia con transferencia en el hepatocito, de genes normales adenoasociados a vectores virales, que permite la producción endógena del factor faltante, y por lo tanto, desaparece la necesidad de transfusiones, puesto que se admininistra una sola vez en la vida, por vía endovenosa[4]; la inyección de una pequeña

molécula de ARN y (si RNA) que va dirigida contra la antitrombina y que al eliminar este importante anticoagulante natural, ayuda a prevenir la hemorragia, con la ventaja de que se administra por vía subcutánea[5]. En esta misma dirección, de inhibir la anticoagulación, se encuentra otro anticuerpo monoclonal, dirigido contra el inhibidor el factor tisular de la coagulación[6,7]. Otro desarrollo importante, es el de un anticuerpo humanizado, bioespecífico, contra los factores de coagulación IX activado y X, que copia la actividad de cofactor del factor VIII activado. Se administra por vía subcutánea, a pacientes con hemofilia A e inhibidores, con una frecuencia semanal y aparentemente con pocos efectos secundarios[8].

La mayoría de estos novedosos tratamientos, se encuentra en etapa experimental, algunos de ellos ya en fase III. Se conocen algunos efectos secundarios, unos pueden causar reacciones en el sitio de la inyección, microangiopatías trombóticas, alteraciones de la función hepática, etc. Sin embargo, los efectos que pudieran causar a largo plazo, especialmente en lo que concierne a la terapia de transferencia de genes, puesto que se transfiere un gen extraño que va a permanecer en el huésped durante toda la vida, no se conocen.

El desarrollo de estas nuevas terapias, sin duda es altamente costoso y los laboratorios una vez culminada la etapa experimental y aprobado el producto, esperan recobrar con creces la inversión. Teóricamente, el costo tendría que ser asumido por el paciente. Sin embargo, los países con un sistema sanitario bien desarrollado, poseen estrategias para enfrentar esta situación y el paciente solo paga una pequeña fracción del costo y a veces nada. Nuestro país, Venezuela, tal como lo demuestra la minuciosa revisión de Ruiz-Sáez[8], cuenta con hematólogos de excelencia que se mantienen al día con los nuevos hallazgos médicos y la evolución de las diferentes terapias, pero no pueden trabajar con las manos vacías. La situación del paciente hemofílico sigue siendo precaria, sobre todo si reside fuera de la capital. El tratamiento profiláctico ya prácticamente, no existe. A falta de concentrados de factores, se ha vuelto a depender de los crioprecipitados y el plasma fresco congelado; en otras palabras, se ha regresado al tratamiento del principio de la década de los años 70 en el siglo XX. En situaciones de emergencia, los familiares tienen que habilitar la forma de conseguir los concentrados en la capital del país, porque estos son escasos o no existen en los Bancos de Sangre locales, mientras tanto, los pacientes siguen corriendo el riesgo de quedar incapacitados, o lo que es peor, morir a consecuencia de una hemorragia.

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Considerations on the new treatments for hemophilia.

The quality of life of the hemophilic patient, has improved significantly improved since the treatment with factors VIII or IX concentrates started being applied. It was improved further with the use of recombinant and extended half-life factor VIII and factor IX concentrates. Today, new therapies are emerging, that address the need of frequent intravenous injections (mainly by the transference of a normal gene in the human hepatocyte) and the presence of antibodies anti factors VIII or IX, or target the natural anticoagulant factors. All of these new treatments will be expensive and probably not affordable by the poor countries of the world. In Venezuela, the average patient with hemophilia, has great difficulty obtaining human factor concentrates and has to rely on old treatments such as fresh frozen plasma and cryoprecipitates.

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Relación del crecimiento sagital de los maxilares y el índice de maduración cervical.

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Palabras clave: vértebras cervicales; cefalometría; crecimiento mandibular; maduración esqueletal.

Resumen. El crecimiento del maxilar se manifiesta de manera diferente respecto a la mandíbula, la cual se caracteriza por un desarrollo sagital más tardío. El objetivo de esta investigación fue asociar el crecimiento sagital del maxilar superior e inferior con el índice de maduración cervical en radiografías cefálicas laterales de pacientes entre 8 a 20 años de la ciudad de Cuenca, Ecuador. Se realizó una investigación con enfoque cuantitativo de tipo descriptivo, correlacional y de corte transversal retrospectivo, con una base de datos de 10.586 radiografías cefálicas laterales. Se observó que el pico de crecimiento inicia alrededor de los 9 años en las mujeres y en los hombres a los 11 años, y este culmina a los 13 años en el sexo femenino y entre los 14 y 17 años en el sexo masculino. Además, se determinó una correlación baja ente el crecimiento sagital del maxilar superior y los estadios de maduración vertebral (r=0,338) así como con el maxilar inferior (r= 0,357). Finalmente, se concluyó que el crecimiento del maxilar superior se produce en los primeros estadios de maduración cervical, mientras que en el maxilar inferior el crecimiento longitudinal se produce a partir del estadio III de maduración cervical.

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Relationship between the sagittal growth of the maxillary and the cervical maturation index.

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Key words: cervical vertebrae; cephalometrics; mandibular growth; skeletal maturity.

Abstract. The growth of the maxilla manifests itself differently from the mandible, which is characterized by a later sagittal development. The objective of the research was to associate the sagittal growth of the upper and lower jaw and the cervical maturation index in lateral cephalic radiographs of patients between 8 and 20 years of age from the city of Cuenca. A descriptive, correlational and retrospective cross-sectional quantitative approach was conducted with a database of 10,586 lateral cephalic radiographs. It was observed that the peak of growth begins around 9 years of age in women and at 11 years in men, and culminates at age 13 in females, and between 14 and 17 years in males. In addition, a low correlation was determined between the sagittal growth of the upper jaw and the stages of vertebral maturation (r = 0.338) as well as with the lower jaw (r = 0.357). Finally, it was concluded that the growth of the upper jaw occurs in the first stages of cervical maturation, while in the lower jaw, longitudinal growth occurs from stage III of cervical maturation.

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INTRODUCCIÓN

El crecimiento y desarrollo craneofacial es un proceso evolutivo que comienza en la etapa de fecundación. Es derivado de una serie de sucesos morfogénicos que se inician en el segundo mes de vida intrauterina y continúan después del nacimiento hasta los dos años, que es cuando el individuo presenta mayor desarrollo [1].

El crecimiento del maxilar se manifiesta de manera diferente respecto a la mandíbula. Esta se caracteriza por un desarrollo sagital más tardío que produce variaciones en el patrón de crecimiento; tales variaciones influyen en el desarrollo craneofacial generando maloclusiones de tipo esqueletal [2,3].

Estudios realizados en cefalogramas demuestran que la radiografía cefalométrica es una herramienta valiosa que proporciona un análisis preciso en cuanto al crecimiento del maxilar y la mandíbula, describiendo extensas variaciones al inicio y durante el brote de crecimiento puberal [4].

La madurez esquelética de los pacientes puede ser valorada a través de diferentes indicadores biológicos, tales como el peso corporal, la altura, la maduración esquelética de la mano y muñeca, el desarrollo dental y la maduración vertebral cervical, entre otros [5,6]. Baccetti, Franchi y McNamara han demostrado la importancia de un diagnóstico previo del estado de maduración ósea para tomar la decisión de iniciar la intervención de algunas maloclusiones de consideración, dado que esta es una condición patológica que puede ser de origen esqueletal en la cual varios huesos participan en la ubicación de los dientes [7,8]. Los cambios del crecimiento normal de las estructuras óseas del complejo

maxilofacial pueden ser la base de la desarmonía oclusal, dando como resultado las diferentes clases de maloclusión, siendo estas Clase I, Clase II y Clase III [9].

Según Steiner, la clase esqueletal se puede establecer mediante el ángulo ANB, el cual determina la relación esquelética sagital de los maxilares, definiendo la gravedad de la discrepancia de los mismos [10,11]. El método de maduración de vértebras cervicales (CVM), descrito por Baccetti y col., se ha establecido como una técnica ampliamente confiable para la evaluación de las diferentes etapas en el crecimiento de los adolescentes, ya que las estapas de crecimiento varían significativamente entre hombres y mujeres [7,8].

El ser humano experimenta constantemente una serie de cambios físicos, psicológicos y sociales, desde su nacimiento hasta la muerte. El crecimiento, desarrollo y maduración son el resultado de la interacción genético-ambiental que provoca en los individuos diversos cambios en su desarrollo; debido a esto, en la población existen personas con diferentes picos de crecimiento y maduración, siendo esta rápida o tardía dependiendo de las condiciones raciales, étnicas, ambientales, costumbres y situación geográfica. No existen estudios a nivel de la población cuencana que registren estos parámetros, razón por la cual es necesario investigar sobre el ritmo de crecimiento de los maxilares, siendo el propósito de este estudio asociar el crecimiento sagital del maxilar superior e inferior y el índice de maduración cervical en radiografías cefálicas laterales de pacientes entre 8 a 20 años de la ciudad de Cuenca-Ecuador.

MATERIALES Y MÉTODOS

Se realizó una investigación con enfoque cuantitativo no experimental de tipo descriptivo, correlacional y de corte transversal, retrospectivo. Previo a su realización se obtuvo la aprobación del comité de bioética de la Universidad Católica de Cuenca.

Para el estudio se utilizó una base de datos de 10.586 radiografías cefálicas laterales provenientes del centro radiológico INNOVA de la ciudad de Cuenca; las mismas que fueron tomadas con el equipo radiográfico digital J. Morita vera View epocs 2d, con software i-dexel.

Para determinar la muestra se aplicó un nivel de confianza del 95%, precisión del 2% y una proporción del 5% conformando así un tamaño muestral de 398 radiografías. Sin embargo, se decidió ajustar el tamaño muestral a 400 radiografías.

Los criterios de inclusión aplicados fueron radiografías cefálicas laterales de pacientes de 8 a 22 años de edad, ASA I, en las cuales se observara de la primera a la sexta vértebra cervical y que tuvieran buena nitidez. Se excluyeron radiografías cefálicas laterales no estandarizadas, no tomadas con el mismo equipo y las provenientes de pacientes que presentan ausencia de piezas dentales o presenten exodoncias.

Para el proceso del trazado cefalométrico se analizaron 10 radiografías cefálicas laterales diarias durante 40 días consecutivos; las mismas fueron evaluadas por un especialista en el área de ortodoncia, mediante el uso de una computadora de escritorio tipo MacBook Air (13-inch, Early 2015), con una tarjeta de gráficos Intel HD Graphics 6000. Para el trazado cefalométrico se utilizó el software Nemochep 18.86. Una vez realizada la evaluación radiográfica, los datos se transfirieron a una ficha de recolección de datos en Excel para su posterior análisis estadístico.

Para determinar el error en las mediciones de las radiografías digitales se repitió el análisis de las mismas sobre el 10% de la muestra total seleccionada aleatoriamente y con el mismo operador, verificando así la coincidencia de los datos obtenidos, lo cual se realizó tres semanas después de la primera lectura radiográfica.

Técnica

Mediante el cefalograma de McNamara se determinó la longitud maxilar desde

el punto condíleo (Co) que corresponde al punto más posterosuperior del cóndilo mandibular hasta el punto A, punto más cóncavo del maxilar superior. La longitud mandibular se midió desde el punto Co hasta el punto gnathion (Gn), punto más anteroinferior de la sínfisis mandibular [12].

Para determinar los estadíos de maduración esqueletal se aplicó el método descrito por Baccetti, mediante el Indice de maduración cervical (CVM), basado en el análisis de la concavidad del borde inferior y la forma de los cuerpos vertébrales cervicales C2 a C4. Se establecieron 6 estadíos cervicales (CS), en los cuales el pico de crecimiento inicia en CS3, finalizando en CS4 o 12 meses antes. En CS3 y CS4 la anatomía de las vértebras pueden tener una forma rectangular horizontal o trapezoidal [8].

La clase esqueletal se determinó mediante el ángulo ANB del cefalograma de Steiner formado por el punto A, punto Nasion (N) (punto más anterior de la sutura frontonasal) y el punto B (punto más profundo de la concavidad del hueso alveolar inferior), representando así la relación anteroposterior del maxilar y la mandíbula. Cuando ANB se encuentra entre 0° y 4° indica una Clase I; si lo valores son mayores, corresponden a una Clase II y si los valores son menores, corresponde a una Clase III [10,11].

Finalmente, los resultados obtenidos se organizaron según las variables en una tabla de datos Excel, la misma que se trasladó al programa estadístico SPSS versión 18.0.0. Se aplicó estadística descriptiva para determinar la frecuencia de crecimiento maxilar, mandibular y el CVM, mediante tablas de frecuencia. Se determinó la relación entre crecimiento longitudinal de los maxilares, maduración cervical y clase esqueletal, mediante el análisis correlacional de Pearson en el cual se estableció el valor de p en ≤0.005 para comprobar significancia estadística.

Para establecer el tipo de relación según el correlacional de Pearson se determina la correlación según los siguientes valores: 1 correlación perfecta, 0,80 – 0,99 correlación muy alta, 0,60 - 0,79 correlación alta, 0,40 – 0,59 correlación media, 0,20 – 0,39 correlación baja, 0,01 – 0,19 correlación muy baja y 0,00 no existe correlación.

RESULTADOS

Se analizaron 400 radiografías cefálicas laterales, distribuidas en un rango de edad de 8 a 20 años. El total de radiografías del sexo femenino fue de 226 y del masculino 174. Del sexo femenino se analizaron 21 radiografías entre 8 y 13 años, mientras que de 11 y 17 años se analizaron 13 radiografías por cada edad. Respecto al sexo masculino se analizaron 18 radiografías en edades de 11 años y 10 radiografías en edades de 8 años, respectivamente.

Según los estadíos de maduración vertebral, se observa que el pico de crecimiento inicia en CS3 alrededor de los 9 años en las mujeres y en los hombres a los 11 años. Mientras que en CS4, el pico de crecimiento termina a los 13 años en el sexo femenino y entre los 14 y 17 años en el sexo masculino (Tabla 1).

En la Tabla 2 se observa que en la clase II esqueletal, la longitud maxilar aumenta de CS1 a CS3, mientras que en la clase I el aumento es a partir de CS4 a CS6 y en la clase III la longitud maxilar se encuentra siempre disminuida en relación a la clase I y II. La media total de la longitud maxilar para la clase I es de 74,61 mm para el sexo femenino y de 102,23 mm para el sexo masculino; para la clase II se obtuvo una media de 72,87 mm para las mujeres, mientras que para los hombres fue de 97,42 mm; en la clase III se observó una media total de 103,8 mm en mujeres y de 107,21 mm para varones.

En relación a la longitud mandibular se observó que, para el sexo femenino en la clase III, el aumento mandibular presentó valores mayores desde CS2 hasta CS5, en comparación con la clase I y II, a diferencia del sexo masculino en el que se encontró un crecimiento paulatino desde CS2 a CS6 dentro de la clase III, con respecto a las

Tabla 1
Distribución de la muestra según edad, sexo e índice de maduración cervical.

Edad	CS1		CS2		CS3		CS4		CS5		CS6	
	F	M	F	M	F	M	F	M	F	M	F	M
8 años	4	1	11	7	6	2	-	-	-	-	-	-
9 años	2	-	5	9	9	8	-	-	-	-	-	-
10 años	2	1	1	2	5	10	9	-	-	-	-	-
11 años	-	2	1	1	5	11	7	5	-	-	-	-
12 años	-	-	-	-	-	4	11	8	6	-	1	-
13 años	-	-	-	-	-	6	18	4	1	1	2	-
14 años	-	-	-	-	-	1	13	10	2	-	4	-
15 años	-	-	-	-	2	1	10	9	2	3	3	-
16 años	-	-	-	-	-	-	12	7	7	4	1	-
17 años	-	-	-	-	-	-	7	9	5	5	1	3
18 años	-	-	-	-	-	-	3	5	9	7	4	3
19 años	-	-	-	-	-	-	1	3	4	8	11	3
20 años	-	-	-	-	1	-	6	3	6	4	6	4
Total	8	4	18	19	28	43	97	63	42	32	33	13

CS: Estadío cervical.

Tabla 2
Longitud maxilar según índice de maduración cervical y clase esqueletal.

CVM	Sexo	Clase I		Clase II		Clase III	
		media	D.S	media	DS	media	DS
CS1	F	67,47	3,42	69,85	2,22	-	-
	M	-	-	71,1	2,98	-	-
CS2	F	68,04	2,44	67,83	3,26	74,4*	-
	M	66,06	2,74	70,57	2,62	67,23	2,27
CS3	F	68,53	4,84	70,11	5,02	68,15	3,6
	M	71,29	4,24	72,21	5,4	71,52	3,34
CS4	F	73,56	10,9	73,55	4,82	73,41	2,25
	M	77,45	5,28	77,12	4,66	77,81	3,95
CS5	F	78,06	17,22	74,94	3,88	63	13,68
	M	79,84	3,72	85,67	19,29	80,25	2,66
CS6	F	81,48	22,06	75,63	3,51	70,9	3,81
	M	81	2,56	79,8	2,59	74,4	0,28
Total	F	74,61	14,33	72,87	4,88	103,8	5,18
	M	102,23	9,57	97,42	14,99	107,21	9,59

CVM: Indice de maduración cervical. CS: Estadìo cervical. D.S: desvio estandar. * Presenta un solo caso.

otras clases. La media total de crecimiento mandibular en la clase I para el sexo femenino fue de 100 mm y de 102,23 mm para el masculino; la clase II presentó una media de 91,87 mm en mujeres a diferencia de los hombres que fue de 97,42 mm; en la clase III se encontró una media de 103,8 mm para el sexo femenino y 107,21 mm para el sexo masculino (Tabla 3).

El análisis correlacional de Pearson demostró la existencia de una correlación baja entre la longitud del maxilar superior y los estadìos de maduración cervical en el sexo femenino (r=0,31) y correlación media con el sexo masculino (r=0,58). Respecto a la longitud mandibular y los estadíos de maduración cervical se determinó, de igual manera, correlación baja con el sexo femenino (r=0,32) y correlación alta con el sexo masculino (r=0,60). Sin embargo, una vez aplicados los rangos de valores de correlación de Pearson, se pudo observar la existencia de una correlación baja en la Clase I para el sexo femenino, a diferencia del sexo masculino que presentó una correlación alta tanto para la longitud maxilar como mandibular. Con respecto a la Clase II tambien se observó una correlación media para ambos sexos dentro de la longitud maxilar, mientras que en la longitud mandibular, las mujeres presentaron una correlación muy baja a diferencia de los hombres que manifestaron una correlación media. Para la Clase III el grupo femenino demostró una correlación muy baja inversa, mientras que los varones presentaron una correlación alta respecto al crecimiento maxilar, a diferencia del crecimiento mandibular, en el que las mujeres presentaron una correlación media y los hombres una correlación alta (Tabla 4).

Tabla 3
Longitud mandibular según índice de maduración cervical y clase esqueletal.

CVM	Sexo	Clase I		Clase II		Clase III	
		media	DS	media	DS	media	DS
CS1	F	88,65	4,9	86,77	5,16	-	-
	M	-	-	89,8	5,27	-	-
CS2	F	89,23	5,57	87,53	5	92,9*	-
	M	86,12	3,35	87,62	2,67	97,84	6,43
CS3	F	88,76	6,92	88,14	4,93	98,45	0,07
	M	95,3	6,75	92,4	8,19	99,04	6,35
CS4	F	99,01	15,25	93,39	6,06	106,65	3,05
	M	103,91	8,47	98,15	8,63	111,61	8,05
CS5	F	105,63	23,38	96,22	5,79	105,03	1,81
	M	109,8	6,39	112,56	26,49	114,18	4,75
CS6	F	110,07	28,56	89,47	23,6	104,06	6,86
	M	107,76	3,82	104,2	3	115,4	2,26
Total	F	100	19,67	91,87	9,76	103,8	5,18
	M	102,23	9,57	97,42	14,99	107,21	9,59

CVM: Indice de maduración cervical. * Presenta un solo caso CS: Estadìo cervical. D.S: desvio estandar. F: femenino. M: masculino.

Tabla 4
Correlación de la longitud maxilar y mandibular con el índice de maduración cervical, según la clase esqueletal.

Clase esqueletal	Sexo	Longitud maxilar- CVM		Longitud mandibular- CVM	
		r	p	r	p
Clase I	F	0,299	0,001	0,344	0,00
	M	0,652	0,00	0,624	0,00
Clase II	F	0,443	0,00	0,181	0,038
	M	0,442	0,00	0,474	0,00
Clase III	F	-0,188	0,251	0,443	0,049
	M	0,657	0,00	0,704	0,00

CVM: Indice de maduración cervical. *r:* correlacional de Pearson. Significancia estadística $p \leq 0,05$.

DISCUSIÓN

La maduración ósea, es el proceso de osificación que presenta un hueso durante su desarrollo, la cual puede ser observada mediante el uso de radiografías con el fin de determinar el pico de crecimiento de los individuos.

Estudios realizados en Colombia en el año 2013 por Plazas y col. [13], en edades de 8 a 12 años, reportaron que el pico de crecimiento en mujeres ocurrió entre los 8 y 9 años dentro de CS3, mientras que, en el grupo de los hombres ninguno alcanzó su pico de crecimiento máximo. Tales resultados concuerdan con los obtenidos en el presente estudio, en el cual se encontró que el mayor pico de crecimiento cervical en las mujeres fue a los 9 años, mientras que los hombres alcanzaron su pico de crecimiento máximo a los 11 años, aunque existe una diferencia de edad para el sexo masculino con respecto al referido estudio**.** Perinetti y col. [14], determinaron que el pico de crecimiento se da entre CS3 y CS4, presentando una diferencia significativa entre el sexo masculino y femenino, en el cual la mujer manifiesta su pico de crecimiento entre los 11 y 12 años mientras que los hombres presentan su pico de crecimiento 1 año después; estos resultados son similares a los del presente estudio en el cual se observó que las mujeres mostraron su pico de crecimiento antes que los hombres. Además, en la muestra estudiada el pico de crecimiento se determinó a edades mas tempranas para ambos sexos, Bedoya y col. [6], estudiaron pacientes de 8 y 14 años y encontarron que el pico de crecimiento se manifestó a los 12 años en CS3 para ambos sexos. Tales resultados difieren con el presente estudio en el cual se observó que el pico de crecimiento para las mujeres se dio a los 9 años y para los hombres a los 11 años de edad dentro de CS3, esta diferencia de resultados pueden deberse a la procedencia de la muestra estudiada.

Armond y col. [15], en Brasil, utilizaron el método de Hassel y Farman y encontraron que los pacientes masculinos con maloclusión clase II, mostraron mayor crecimiento maxilar en CS1 y CS2 lo que está acorde con los resultados de la muestra estudiada en esta investigación, tanto para el sexo femenino como para el masculino. Los resultados de este estudio se corresponden a lo encontrado en la literatura existente, en la cual se hace referencia al patrón de crecimiento cefalocaudal, siendo las estructuras que están más cercanas al cerebro las que crecen antes; por lo tanto, el crecimiento del maxi-

lar se da antes que el mandibular dentro de los estadíos CS1 al CS3 [16].

Arriola y col. [17], reportan diferencias entre el sexo masculino y femenino respecto al crecimiento mandibular; la clase III esqueletal presenta mayor crecimiento longitudinal entre CS1 y CS2 respecto a la clase I y II que tuvieron valores menos significativos en dichos estadíos; el actual estudio demostró que, dentro de CS3 y CS4 se dio el mayor crecimiento mandibular en la clase III para el sexo masculino y femenino, presentado variaciones significativas frente a la clase I y II que tuvieron un menor crecimiento, dichas variaciones pueden deberse a que la clase III esqueletal presenta mayor crecimiento longitudinal de la mandíbula y el crecimiento es significativo durante el pico de crecimiento. Jeelani y col. [18], encontraron que el mayor crecimiento mandibular ocurrió en la clase III en CS3 para los hombres debido al inicio tardío del pico de crecimiento que ocurrió a los 13 años en comparación con las mujeres, difiriendo en edad con nuestro estudio en el que el brote de crecimiento en el sexo masculino se dio a los 11 años. Sin embargo, se reportó que el crecimiento mandibular es mayor para el sexo masculino respecto al femenino que presenta un menor crecimiento dentro de dicho estadío.

Baccetti y col. [19], reportaron que, en 1091 registros cefalométricos, el crecimiento mandibular fue mayor en la clase III para los niños respecto a las niñas que presentaron un menor aumento dentro del pico de crecimiento; tales resultados muestran similitud con los hallazgos del actual estudio, en el cual se encontró un aumento mandibular menor en las mujeres y mayor en los hombres dentro de los estadíos de maduración 3 y 4 para la clase III, estos hallazgos pueden pueden deberse a que, en el sexo masculino el periodo de crecimiento es mayor que en el sexo femenino. Generoso y col. [20], estudiaron radiografías de pacientes entre 7 y 12 años y establecieron que en CS2 y CS3 los niños con clase I presentaron un mayor crecimiento mandibular a diferencia de los niños de clase II, hallazgos que también son compatibles con el presente estudio, en el cual se encontró que el crecimiento mandibular era mayor en la clase I respecto a la clase II; de igual manera, las niñas con clase I presentaron un mayor aumento mandibular que las niñas de clase II únicamente en CS3.Esto último representa diferencias con relación al actual estudio, en el cual se observó que el mayor crecimiento mandibular se dio en la clase II dentro de dicho estadío, posiblemente estos hallazgos se deben a que en la población cuencana la clase II esqueletal se caracteriza por una longitud maxilar aumentada y no por un déficit mandibular. Colino-Gallardo y col. [21], en su revisión sistemática refieren que, en CS3 y CS4 se produce el máximo crecimiento mandibular dentro de la clase II respecto a la clase I para ambos sexos, difiriendo con el presente tema en el cual se encontró que, el mayor crecimiento de la mandíbula se dio en la clase I para ambos sexos respecto a la clase II que presentó un menor aumento dentro de dichos estadíos.

Al relacionar la longitud del maxilar superior e inferior y el estadío de maduración cervical en las clases esqueletales mediante el correlacional de Pearson, se determinó que existe relación tanto en el sexo masculino como en el femenino; lo que está en correspondencia con el estudio realizado por Akimoto y col. [22], en individuos de 6 a 14 años donde se encontró correlación entre el crecimiento del maxilar y la mandíbula para las clases I y II aplicando el mismo correlacional.

Los hallazgos del presente estudio en relación a las publicaciones antes mencionadas demuestran que el crecimiento craneofacial está ligado a factores genéticos y ambientales, los cuales varían con el tiempo debido a los diferentes cambios constantes en la nutrición y el estilo de vida. Estas características son las que influyen en la presencia de los estadíos de maduración y crecimiento longitudinal de los maxilares; por consiguiente, para futuros estudios se reco-

mienda ampliar el tamaño muestral que permita mejorar la información sobre el número de casos en las diferentes clases esqueletales, siendo trascendental realizar estudios que incluyan otras condiciones que puedan modificar el crecimiento y desarrollo.

En conclusión, el pico de crecimiento puberal está relacionado con la edad de los pacientes. Según aumentan los años, el crecimiento puberal va alcanzando su pico máximo, existiendo una diferencia significativa entre el sexo femenino y masculino, según la cual el pico de crecimiento en las mujeres inicia a los 9 años mientras que en los hombres de 2 a 3 años después. El crecimiento longitudinal de los maxilares, tanto superior como inferior, están en relación con el crecimiento puberal. Sin embargo, se debe tomar en cuenta que, en la clase I esqueletal se observa un crecimiento acorde para el maxilar que inicia en los primeros estadíos, mientras que la mandíbula recupera su crecimiento después del estadío 3. En la clase esqueletal II, se produce el máximo crecimiento maxilar en los primeros estadíos; en la clase III, el crecimiento mandibular se da a partir de CS3, estableciendo así la existencia de una correlación entre la longitud maxilar, mandibular y el estadío de maduración esqueletal para ambos sexos.

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Conflicto de competencia

Los autores declaran no presentar ningún conflicto de intereses o competencia con el trabajo de investigaciòn realizado.

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Evaluation of thyroid function and metabolic parameters in obese and overweight children: A prospective case-control study.

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Key words: body mass index; insulin; metabolic parameters; obesity; thyroid hormone.

Abstract. Obesity is considered an important global public health challenge, and its prevalence is rapidly increasing in children. We investigated in this study if the upper-normal TSH level may be associated with metabolic syndrome parameters, including obesity, high blood pressure, and dyslipidemia and changes in insulin sensitivity in overweight and obese children. We also investigated whether there is a relationship between BMI and these parameters. This prospective case-control study comprised 145 participants (74 females, 71 males) aged 5–18 years. Participants were divided into three groups according to their BMI z-score, as overweight, obese and control. The control group included 35 age and sex-matched healthy subjects. Thyroid stimulating hormone levels of control, overweight and obese groups were 2.14 ± 1.27, 2.97 ± 1.26 and 3.13 ± 1.11, respectively ($p<0.05$). There was a significant positive correlation between TSH and the BMI, BMI z-scores between overweight and obese groups ($r=0.302$, $p=0.000$), ($r=0.121$, $p=0.004$), respectively. The current study suggests that increased serum TSH levels, even within the normal range, in overweight and obese children is associated with the impairment of metabolic parameters, including dyslipidemia and insulin sensitivity. For that reason, TSH levels in the high-normal range should be considered as a risk factor for metabolic syndrome and its components.

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Evaluación de la función tiroidea y los parámetros metabólicos en niños obesos y con sobrepeso: Un estudio prospectivo de casos y controles.

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Palabras clave: índice de masa corporal; insulina; parámetros metabólicos; obesidad; hormona tiroidea.

Resumen. La obesidad se considera un importante desafío de salud pública mundial y su prevalencia está aumentando rápidamente en los niños. En este estudio, se investigó si el nivel normal superior de TSH puede estar asociado con los parámetros del síndrome metabólico, incluida la obesidad, la presión arterial elevada, cambios en los lípidos y la sensibilidad a la insulina, en niños con sobrepeso y obesidad. También investigamos si existe una relación entre el IMC y estos parámetros. En este estudio prospectivo de casos y controles se incluyeron a 145 participantes (74 hembras, 71 varones) de entre 5 y 18 años. Los participantes se dividieron en 3 grupos según el puntaje z del IMC, como sobrepeso, obesidad y control. El grupo de control incluyó 35 sujetos sanos emparejados por edad y sexo. Los niveles de hormona estimulante de la tiroides de los grupos de control, con sobrepeso y obesos fueron 2,14 ± 1,27, 2,97 ± 1,26 y 3,13 ± 1,11, respectivamente (p <0,05). Hubo una correlación positiva significativa entre la TSH y el BMI, la puntuación z del IMC entre los grupos con sobrepeso y obesidad (r = 0,302, p = 0,000), (r = 0,121, p = 0,004), respectivamente. Por esa razón, el nivel de TSH en el rango normal alto debe considerarse como un factor de riesgo del síndrome metabólico y sus componentes.

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INTRODUCTION

Obesity is considered an important global public health challenge, and its prevalence is rapidly increasing in children [1,2]. Obesity is defined as a body mass index (BMI) ≥ 95th percentile for children of the same age and gender [3]. It is believed that obese individuals are at an increased risk of metabolic syndrome and thyroid dysfunction [4,5].

There is a wide variation in reference values for thyroid stimulating hormone levels (TSH) in children [6]. Many laboratories use values of about 4.5 to 5.0 μIU/mL as the upper-normal range for TSH, and some experts suggest that the upper-normal TSH level in children should be lowered due to the risk of obesity, dyslipidemia, and changes in blood pressure (BP) and insulin sensitivity [7-10].

Thyroid hormone has a key role in regulating metabolism. It is well known that overt hypothyroidism may cause obesity in individuals; however, there is no clarity regarding subclinical hypothyroidism [11]. Subclinical hypothyroidism is defined biochemically as a normal serum free thyroxine level (FT4) concentration in the presence of an elevated serum TSH concentration [11]. Thyroid hormone regulates both basal metabolism and thermogenesis [12,13]. Moreover, it is involved in glucose and fat metabolism [12]. Because of these interactions between thy-

roid hormones and metabolic parameters, there is an increasing doubt of whether even mild thyroid dysfunction may induce obesity in children [14,15].

We speculated in this study that the upper-normal TSH level may be associated with metabolic syndrome parameters, including obesity, blood pressure, lipid and insulin sensitivity in overweight and obese children. We also investigated whether there is a relationship between BMI and these parameters.

MATERIALS AND METHODS

Study population

This prospective case-control study comprised 145 participants (74 females, 71 males) aged 5–18 years, and it was conducted in an ethnically homogeneous population between 2012 and 2015. Participants were divided into three groups according to their BMI z-score, as overweight (n=64), obese (n=46) and control. The control group included 35 age and sex-matched healthy subjects. Written informed consent and assent were obtained from participants and parents. Ethics approval was obtained from the Local Ethics Committee (protocol number/date:9204/09.04.-12) for this research, and the study was managed in accordance with the Declaration of Helsinki. Children with any known disease (any thyroid disease, cardiovascular disease, etc.) or using any pharmacologic treatment known to affect BMI z-score, thyroid hormones, blood pressure, lipid and glucose metabolism were excluded from the study.

Anthropometric measurements

Standing height (SH), body weight (BW), blood pressure measurement, waist and hip circumferences were obtained from all participants and made according to the World Health Organization recommendations [16]. Blood pressure was measured in the sitting position after five minutes of rest in a quiet environment with a mechanical sphygmomanometer. Blood pressure was measured twice and the average of the measurements was used as the final value. Standing height was measured with a Harpenden stadiometer, and participants were weighed in lightweight clothing. Body mass index was calculated as body weight in kilograms divided by the square of standing height in meters (BMI= kg/m^2). We used BMI z-scores to compare BMI values across different ages and by gender. Overweight was defined as $+1 <$ BMI z-score $\leq +2$ SDs, and obesity was defined as a BMI z-score over 2 SDs from the mean of natioanal charts [17].

Laboratory studies

The blood samples were obtained after an 8-12-hour overnight fast for analysis of the lipid profile, fasting plasma glucose (FPG), fasting insulin (FI), TSH and FT4. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were measured by an enzymatic colorimetric assay (Roche Cobas İntegra® 800, Mannheim, Germany). Low density lipoprotein cholesterol (LDL-C) was calculated for samples containing TG <400 mg/dL using the Friedewald formula. Fasting plasma glucose was measured by the hexokinase method (Roche Cobas İntegra® 800, Mannheim, Germany). Fasting Insulin, TSH and FT4 were measured by the electrochemiluminescence immunoassay method (The ADVIA Centaur® CP Immunoassay System, Erlangen, Germany). The reference values of TSH and FT4 in our center are 0.38-4.5 μIU/mL and 0.58-1.38 ng/dL, respectively. Insulin resistance was estimated by the homeostatic model [Homeostasis model assessment of insulin resistance (HOMA-IR) = fasting plasma glucose x fasting insulin /405] [9].

Statistical analysis

The data were evaluated using the Statistical Package for Social Sciences 21.0 program for Windows. Continuous variables were calculated as mean+standard

deviation. The normality of the distribution of continuous variables was confirmed by the Kolmogorov-Smirnov test. A one-way analysis of variance tests was used to evaluate comparisons between the groups. Pearson correlation analysis was used to evaluate the relationships. A p-value <0.05 was accepted as statistically significant.

The sample size estimation of the study was calculated by using G*Power 3.1.9.4 (with 90% power and 5% type I error rates).

RESULTS

The study included 110 overweight and obese participants and 35 healthy controls. The male/female ratio of overweight and obese groups was 31/33 and 22/24, respectively, while it was 18/17 for the control group (p >0.05). Mean age of control, overweight and obese groups were 9.7 ± 3.6; 10.3 ± 2.6; 10.8 ± 2.7 years, respectively (p >0.05). The anthropometric and laboratory characteristics of all participants are summarized in Table 1.

Table 1
Anthropometric and laboratory characteristics of the study participants.

Parameters	Control group (n=35)	Overweight group (n=64)	Obese group (n=46)	p
	Mean ± SD			
Age, yr	9.7 ± 3.6	10.3 ± 2.6	10.8 ± 2.7	0.12
Gender (M/F), (n,%)	18 (51.4)/17 (48.5)	31 (48.4)/33 (51.5)	22(47.8)/24 (52.1)	0.64
BMI (kg/m²)	20.94 ± 2.46	27.26 ± 1.29	32.98 ± 2.87	**<0.01**
BMI-Z score	0.63 ± 0.15	1.59 ± 0.48	2.47 ± 0.36	**<0.01**
WHR (cm/cm)	0.74 ± 0.03	0.82 ± 0.06	0.87 ± 0.07	**<0.01**
SBP (mmHg	106.6 ± 9.3	107.8 ± 12.2	110.3 ± 10.6	0.22
DBP (mmHg)	69.2 ± 5.9	69.1 ± 7.1	73.5 ± 9	0.13
TC (mg/dL)	156.1 ± 15.8	169.3 ± 38.3	171.93 ± 35.8	**<0.01**
TG (mg/dL)	89.6 ± 22.5	97.2 ± 49.3	101.8 ± 37	**<0.01**
LDL – C (mg/dL)	92 ± 14.5	97.4 ± 30	105.3 ± 31.6	**0.01**
HDL– C (mg/dL)	46.9 ± 10.3	48 ± 11.7	47.7 ± 12.9	0.90
FPG (mg/dL)	78.9 ± 12.7	89.6 ± 5.6	101.9 ± 6.2	**0.03**
Insulin (μU/mL)	13.32 ± 7.35	15.14 ± 6.32	21.69 ± 10.99	**<0.01**
HOMA-IR	1.12 ± 1.79	2.05 ± 1.45	2.44 ± 2.54	**<0.01**
TSH (μIU/mL)	2.14 ± 1.27	2.97 ± 1.26	3.13 ± 1.11	**<0.01**
FT4 (ng/dL)	1.21 ± 0.18	1.23 ± 0.14	1.18 ± 0.19	0.23

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

Thyroid stimulating hormone levels of the control, overweight and obese groups were 2.14 ± 1.27, 2.97 ± 1.26 and 3.13 ± 1.11, respectively ($p<0.05$), and the FT4 levels of control, overweight and obese subjects was 1.21 ± 0.18, 1.23 ± 0.14 and 1.18 ± 0.19, respectively ($p >0.05$). TSH levels were found to be slightly high in 13.6% (15 out of 110 subjects) of overweight and obese groups. There was a significant positive correlation between TSH and BMI, BMI z-scores between the overweight and obese groups ($r=0.302$, $p=0.000$), ($r=0.121$, $p=0.004$), respectively. Additionally, FT4 and BMI, BMI z-score between the overweight and obese groups ($r=-0.042$, $p=0.009$), ($r=-0.023$, $p=0.011$), respectively. Correlation between thyroid hormones and metabolic parameters in overweight and obese participants were summarized in Table 2.

Table 2
Correlation between thyroid hormones and metabolic parameters in overweight and obese subjects.

Parameters	TSH		FT4	
	r	p	r	p
Age	-0.023	**0.000**	0.010	0.231
BMI	0.302	**0.000**	-0.042	**0.009**
BMI-Z score	0.121	**0.004**	-0.023	**0.011**
WHR	0.130	**0.010**	-0.025	**0.018**
SBP	0.231	**0.006**	0.173	**0.014**
DBP	0.181	**0.023**	0.052	**0.031**
TC	0.227	**0.019**	-0.143	0.056
TG	0.021	**0.010**	-0.041	0.072
LDL – C	0.125	**0.016**	-0.055	0.133
HDL– C	0.031	0.235	-0.012	0.151
FPG	0.011	**0.018**	-0.013	0.068
Insulin	0.035	**0.044**	-0.019	0.124
HOMA-IR	0.023	**0.032**	-0.011	0.221

The overweight and obese groups had higher TC, LDL-C and TG levels than the control group ($p<0.05$), however, HDL-C level was significantly different between groups ($p >0.05$). We found a significant positive correlation between TSH and TC, LDL-C, TG ($r=0.227$, $p=0.019$), ($r=0.125$, $p=0.016$) and ($r=0.021$, $p=0.010$), respectively, but not with HDL-C ($r=0.031$, $p=0.235$).

Fasting plasma glucose, insulin and HOMA-IR values were significantly different among groups ($p <0.05$), (Table 1) and we found a significant positive correlation between TSH and FPG, insulin, HOMA-IR ($r=0.011$, $p=0.018$), ($r=0.035$, $p=0.044$), ($r=0.023$, $p=0.032$), respectively. However, there was not a significant correlation between FT4 and FPG, insulin, HOMA-IR ($r=-0.013$, $p=0.068$), ($r=-0.019$, $p=0.124$), ($r=-0.011$, $p=0.221$), respectively.

The correlation between thyroid hormones (TSH and FT4) and BMI, HOMA-IR in overweight and obese children can be seen in Fig. 1.

The anthropometric and laboratory characteristics of overweight and obese groups according to the gender and age are summarized in Tables 3 and 4.

DISCUSSION

Obesity is a critical public health problem associated with many chronic disorders, including metabolic syndrome and thyroid dysfunction [18,19]. The most common thyroid dysfunction is hyperthyrotropinemia, which is believed to be an adaptive process to excess body mass, energy expenditure and thermogenesis [3,20]. In the present study, we found a significant association and correlation between TSH and BMI, BMI z-scores in overweight and obese children. Thyroid stimulating hormone levels in these groups were higher than in the healthy control group. FT4 had a significant negative correlation with BMI, BMI z-scores, however, not a significant association. These findings are consistent with previous studies [16,21,22].

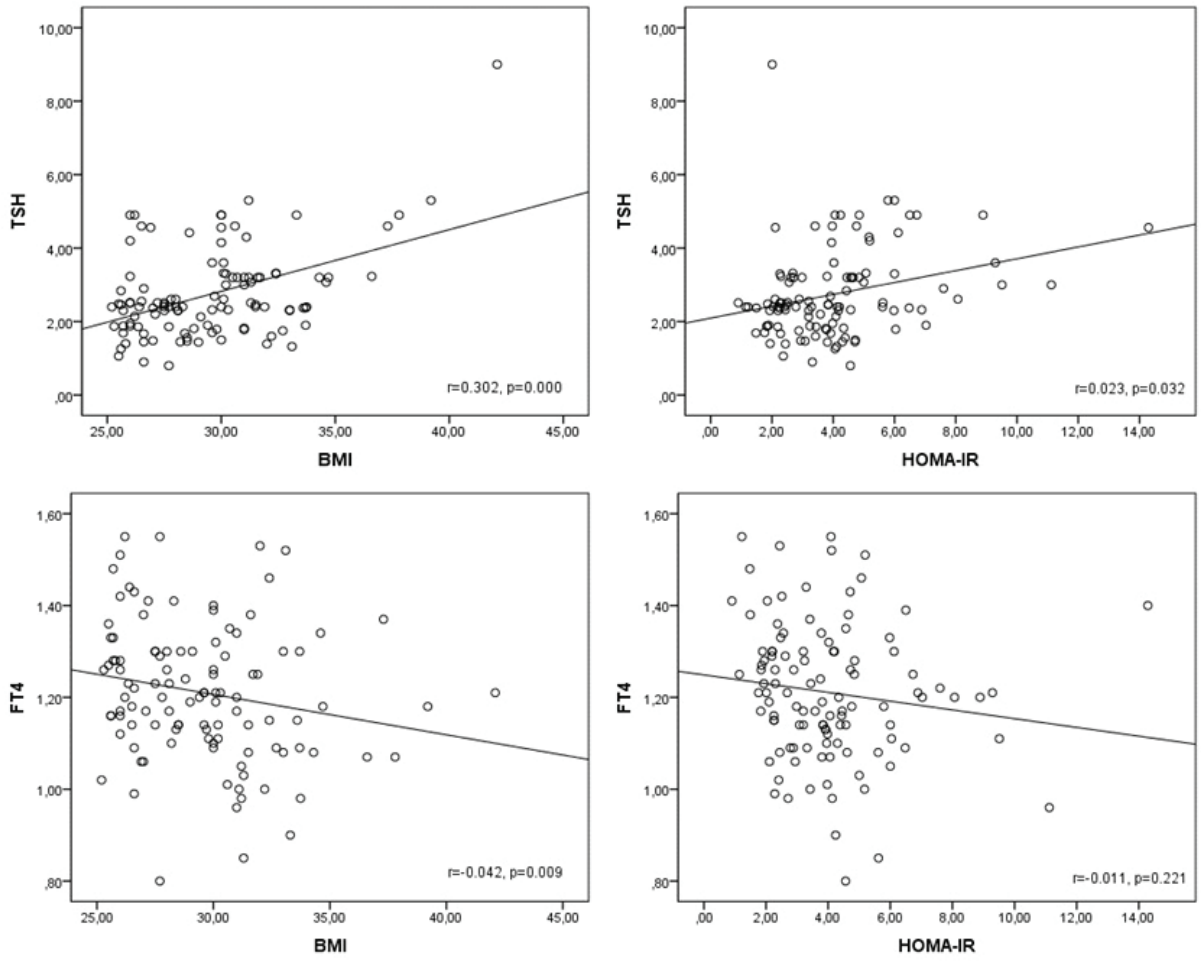

Fig. 1. Correlation between thyroid hormones (TSH and FT4) and BMI, HOMA-IR in overweight and obese children.

The mechanisms of the association between TSH and obesity is not definitely understood. However, several mechanisms have been proposed to explain this complex relationship, including derangement of the hypothalamic–pituitary axis, thyroid hormone resistance, changes in the activity of deiodinases, the impact of leptin and chronic low grade inflammation, etc. [23,24].

According to recent studies, the prevalence of isolated hyperthyrotropinemia in overweight and obese children is thought to be between 15% and 23% [25,26]. However, in our study, it was found to be only 15 out of 110 children (13.6%). The case selection and study design may be the reason for this discrepancy.

Classically, obesity-associated dyslipidemia is a well-known condition, and characterized by elevated TC, LDL-C, TG and decreased HDL-C level, and has been described both in overt and subclinical hypothyroidism [27,28]. Consistent with this, we found that TC, LDL-C and TG levels were higher in the overweight and obese groups than in the control group. However, the HDL-C level was significantly different between groups. That was confirmed in another study conducted by Aeberli *et al.* [24]. Additionally, we found a significant positive correlation between TSH

Table 3
Anthropometric and laboratory characteristics of overweight and obese groups according to the gender.

Parameters	Male	Female	p
	Mean ± SD		
Gender, n, (%)	53 (48.2)	57 (51.8)	-
Age, yr	10.2 ± 2.8	11.3 ± 3.3	0.09
BMI (kg/m^2)	29.36 ± 3.42	29.83 ± 3.59	0.50
BMI-Z score	2.01 ± 0.54	2.18 ± 0.46	0.16
WHR (cm/cm)	0.87 ± 0.05	0.84 ± 0.07	0.23
SBP (mmHg	108.5 ± 12.1	111.9 ± 12.7	0.89
DBP (mmHg)	71.1 ± 7.9	70.8 ± 8.4	0.85
TC (mg/dL)	167.5 ± 36.3	164.6 ± 37.2	0.10
TG (mg/dL)	99.9 ± 45.6	98.7 ± 44.1	0.88
LDL – C (mg/dL)	102.7 ± 31.6	98 ± 30.2	0.08
HDL– C (mg/dL)	47.7 ± 12.9	48 ± 11.8	0.93
FPG (mg/dL)	96.1 ± 6.7	94.2 ± 8.5	0.41
Insulin (μU/mL)	16.78 ± 8.48	19.12 ± 9.35	0.06
HOMA-IR	2.16 ± 1.96	2.28 ± 2.18	0.08
TSH (μIU/mL)	2.99 ± 1.08	3.09 ± 1.28	0.66
FT4 (ng/dL)	1.22 ± 0.17	1.19 ± 0.13	0.31

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

and TC, LDL-C, TG, and similar observations were reported by Le *et al.* and Canaris *et al.*[9,29]. In contrast to these findings, a retrospective analysis of a large community-based pediatric population in Rochester, which was conducted by Nader *et al.*, found only a significant positive correlations between TSH and TG [30]. These differences may be due to the sample size and diverse characteristics of the study participants.

The relationship between thyroid hormonal derangement and glucose metabolism in obesity is a complex interdependent interaction [31,32]. Recently, the study performed by Ambrosi *et al.* in Milan shown that TSH had a significant positive correlation with fasting insulin and HOMA-IR in 581 obese patients[33]. Similar results were reported by Reinehr *et al.*, and our findings were also in line with these studies [26]. However, in contrast to these findings, this association was not shown in some other studies [34,35].

In our study, metabolic parameters and blood pressure values were also compared between overweight and obese patient groups on the basis of age and gender. However, we did not find a significant association. These findings are consistent with previous studies [21,36,37].

The main strength of this study is that it was conducted prospectively in a healthy control group and in an ethnically homogeneous population. The limitations of the study include the relatively small sample size, a lack of evaluation of free triiodothyronine, thyroxine-binding globulin and thyroid peroxidase.

Table 4
Anthropometric and laboratory characteristics of overweight and obese groups according to the age.

Parameters	<11 years	≥11 years	p
	Mean ± SD		
Male/Female, n, (%)	22 (39.3) / 34 (60.7)	19 (35.2) / 35 (64.8)	0.40
Age, yr	8.39 ± 1.7	13.5 ± 1.9	**0.02**
BMI (kg/m²)	28.73 ± 2.31	30.64 ± 3.47	0.14
BMI-Z score	2.05 ± 0.57	2.24 ± 0.3	0.21
WHR (cm/cm)	0.83 ± 0.05	0.85 ± 0.07	0.12
SBP (mmHg	108.9 ± 12.8	112.8 ± 9.9	0.31
DBP (mmHg)	69.4 ± 7.1	70.5 ± 8.6	0.42
TC (mg/dL)	168.5 ± 39.1	169.6 ± 35.4	0.87
TG (mg/dL)	98 ± 44.9	104.4 ± 43.8	0.22
LDL – C (mg/dL)	103.6 ± 32.9	100 ± 29.2	0.58
HDL– C (mg/dL)	47.7 ± 10.9	48.1 ± 13.4	0.85
FPG (mg/dL)	91 ± 5.4	95 ± 6.5	0.39
Insulin (μU/mL)	17.88 ± 5.89	19.98 ± 10.79	0.22
HOMA-IR	2.35 ± 1.39	2.27 ± 2.51	0.34
TSH (μIU/mL)	2.94 ± 1.03	2.81 ± 1.37	0.87
FT4 (ng/dL)	1.22 ± 0.15	1.19 ± 0.13	0.22

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormoneL; FT4, free thyroxine.

The most important finding of this study is that increasing serum TSH level, even within the upper-normal level, in overweight and obese children can be associated with the impairment of metabolic parameters, including dyslipidemia and insulin sensitivity. Although the mechanism underlying this condition has not been fully elucidated yet, it is maybe an early sign of hypothyroidism, an autoimmune thyroid disease, or it may result from derangement of the hypothalamic–pituitary axis, the impact of leptin and chronic low grade inflammation, etc. [23,24,38,39].

As a result, the upper-normal serum TSH level should be considered as a risk factor of metabolic syndrome and its components in overweight and obese children, and this condition should be taken into account by researchers.

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Ethical approval

Given by Ethics Committee of Zeynep Kamil Maternity and Children's Health and Diseases Training and Research Hospital Ethics Committee (9204/09.04.2012).

Conflict of Interest

None.

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Author contributions

All authors made a significant contribution (concept and design of the study, acquisition of data, analysis and interpretation of the data, drafting or critically reviewing the manuscript, and final approval of the version of the article) to this article.

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Changes in chloremia, secondary to hydric reanimation during the first 24 hours, increases hospital stay and complications in patients with acute pancreatitis.

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Key words: Pancreatitis; chlorides; isotonic solutions; length of stay.

Abstract. Acute pancreatitis (AP) requires first-line treatment with intensive fluid resuscitation. Hydroelectrolyte changes secondary to this management could be related to an increase in hospital stay, complications, and mortality. The objective of this study was to correlate the increase in serum chlorine (> 8mEq / L) during the first 24 hours (ISC) with a longer hospital stay, complications and mortality in patients with AP. A total of 110 patients with AP admitted to the emergency room were included. Fluid management and serum chlorine were recorded on admission and after 24 hours; duration of hospital stay, complications and mortality, were also registered. 37 patients had ISC (age 56.4 ± 18.4 years; 51% women), there were no differences in age, sex or type of fluid management with patients without ISC. In bivariate analysis, ISC was associated with severe AP (30% vs 12%, p = 0.02), higher APACHE II score at admission (8 [6-15] vs 6 [4-9] points, p = 0.006), and longer hospital stay (9 [7-12] vs 7 [5-10] days, p = 0.03). The overall mortality and complications rate were 16% and 25%, respectively, with no differences between the groups (24% vs. 12%, p = 0.1 and 35% vs. 19%, p = 0.06). After multivariate adjustment, independent predictors of hospital stay were ISC> 8 mEq / L (p = 0.01) and APACHE II scores at 24 hours (p = 0.02). We conclude that ISC is associated with a longer hospital stay in patients with AP from a second-level hospital care population.

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Cambios en la cloremia secundaria a la reanimación hídrica, en las primeras 24 horas, incrementa la estancia hospitalaria y las complicaciones en los pacientes con pancreatitis aguda.

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Palabras clave: pancreatitis; cloruros; soluciones isotónicas; tiempo de internación.

Resumen. La pancreatitis aguda (PA) requiere tratamiento de primera línea con reanimación hídrica intensiva. Los cambios hidroelectrolíticos secundarios a este manejo podrían relacionarse a un incremento en la estancia hospitalaria, complicaciones y mortalidad. El objetivo de este estudio fue correlacionar el incremento de cloro sérico (>8mEq/L) en las primeras 24hrs (ICS), con una mayor estancia hospitalaria, complicaciones y mortalidad en pacientes con PA. Se incluyeron 110 pacientes con PA ingresados a urgencias, se registró el manejo hídrico y cloro sérico al ingreso y 24 horas después, la estancia hospitalaria, complicaciones y mortalidad. 37 pacientes tuvieron ICS (edad 56,4 ± 18,4 años; 51% mujeres) no hubo diferencias en edad, sexo o tipo de manejo hídrico en pacientes sin ISC. En el análisis bivariado, el ICS se asoció a PA grave (30% vs 12%, p = 0,02), mayor puntuación APACHE II al ingreso (8 [6-15] vs 6 [4-9] puntos, p = 0,006) y estancia hospitalaria más prolongada (9 [7-12] frente a 7 [5-10] días, p = 0,03). La tasa global de mortalidad y complicaciones fueron del 16% y el 25%, respectivamente, sin diferencias entre grupos (24% vs 12%, p = 0,1 y 35% vs 19%, p = 0,06). Después del ajuste multivariado, los predictores independientes de la estancia hospitalaria fueron ICS> 8 mEq/L (p = 0,01) y las puntuaciones APACHE II a las 24 horas (p = 0,02). Concluimos que el ICS se asocia a mayor estancia hospitalaria en pacientes con PA de una población de segundo nivel de atención hospitalaria.

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INTRODUCTION

Acute Pancreatitis (AP) is an inflammatory disease that frequently involves peripancreatic tissue and can englobe distant organs and systems [1,2]. The incidence varies between 4.9 and 73.4 cases per 100,000 people in the world [3]. Its etiology is mainly attributed to biliary lithiasis and alcoholism, and between 10 and 30% is classified as idiopathic [1]. There are prognostic factors of mortality, like the Ranson, Glasgow-Imrie, POP, BISAP criteria, and Hong Kong scale that is based in glycemia-urea and gives a prognosis with adequate accuracy [4].

Initial management of AP is based in hydric reanimation with intravenous liquids, mainly isotonic solutions, such as saline solution 0.9% (SS0.9%) and Ringer lactate (RL), and pain control [1,2,5].

The recommendation is to administer balanced solutions in a range of 200 to 500 milliliters per hour or 5 to 10 mL per kg of weight per hour, with a range of 2,500 and 4,000 mL in 24 hours. There are few studies to support the decision of what type of solution to administer [1]. A meta-analysis showed no statistically significant differences in the incidence of necrotizing PA comparing the use of SS0.9% or RL [6].

Retrospective studies suggest that aggressive administration of fluids in the initial 12-24 hours reduces morbi-mortality [1]. Being that the SS0.9% is used globally as the first line of therapy despite having an osmolarity of 308, and a pH 5.5, and supra physiologic concentrations of sodium and chloride, and that could increase patient morbi-mortality [7].

Chloride (Cl^-) is the main anion of human body, with functions maintaining oncotic pressure, acid-base equilibrium, muscular activity, osmosis, and immunomodulation.

The SS0.9% could induce pathologic hyperchloremia (Table 1) and hyperchloremic metabolic acidosis [8]. In intensive care units, hyperchloremia was associated as an independent factor of mortality in major trauma [9], acute kidney injury [10] and systemic inflammatory response syndrome [8,11].

Metabolic hyperchloremic acidosis in experimental studies with septic animals has demonstrated that it increases the production of interleukin 6, tumor necrosis factor, and nitric oxide; thus hyperchloremia is a pro-inflammatory modulator in sepsis [4,11].

In accordance to Kumpers *et al*, an infusion of two liters of SS0.9% reduces 12% of the blood supply in the renal cortex of healthy patients, as demonstrated with angiography [12]. The hyperchloremia, according to Marttinen *et al.*, associates with the risk of acute kidney injury, secondary to vasoconstriction of the afferent renal artery [10], decreasing the glomerular filtration rate, which leads to that exposed patients to non-guided chloride management, require more replacement therapy [13].

Associated mortality with hyperchloremia is between 30-40%, with concentrations

Table 1
Causes of hyperchloremia.

Pseudohiperchloremia	Loss of water and electrolytes
- High concentrations of solids in serum (fatty acids or proteins), dilutional - Bromide or iodide intoxication	- Certain forms of diarrhea - Osmotic diuresis - Certain cases of post-obstructive diuresis
Administration of fluids with high chloride containing	**Associated with metabolic acidosis**
- Saline Solution 0.9% - Albumin - Ammonium Chloride - Parenteral nutrition	- Certain forms of diarrhea - Tubular renal acidosis - Inhibitors of carbonic anhydrase - Ureteral deviation (for example, ileal bladder). - Administration of ammonium chloride. - Administration of arginine chlorhidrate, hydrochloric acid, or lysine. -Certain cases of chronic kidney disease. Organic acidosis with fast excretion of acid anion (for example: toluene overdose).
Net loss of water	**Respiratory alkalosis**
- Exercise - Severe dehydration - Fever - Hypermetabolic status - Insipidus diabetes	

of chloremia higher of 130mEq/L, having basal chloride levels of 80 and 120mEq/L in patients with systemic inflammatory response syndrome, demonstrating that the greater input of intravenous solutions, the greater hospital mortality [8].

In major trauma it was associated with 30-days mortality, analyzing chloremia at admission and 48 hours later, showing and elevation of serum levels in non-surviving patients, compared with survivors, with a chloride delta (ΔCl, that is the difference between chloremia at admission minus 48 hours chloremia) higher in the non-survivors (ΔCl 10.3±11.1mmol/L *vs* 1.7±5.2mmol/L, $p<0.001$). The administration of less than 1,500ml SS0.9% was not associated with mortality [9] and it has a limit of maximum 1 Liter in 24 hours [14].

The aim of this study was to correlate a significant increment of chloremia during the first 24 hours in patients with acute pancreatitis, with hospital stay and mortality of any cause, and to describe the presence of complications.

PATIENTS AND METHODS

Study design and patients

The present study was reviewed and approved by IMSS scientific and ethics committees with the number R-2017-2402-39 and was made with a database of IMSS Zone 50 Hospital registry, San Luis Potosi, Mexico. This database processed the registry of all consecutive admitted adults in the emergency room between January 2015 and December 2016, with diagnosis of acute pancreatitis. It includes demographic data and clinical information, medical procedures, etiology of pancreatitis, and subsequent laboratory findings. The data are periodically integrated, reviewed, and checked for accuracy.

For this retrospective, observational and analytic study, data from all patients admitted in the mentioned period was examined. We included patients who met the following criteria: (i) diagnosis of acute pancreatitis based in clinical characteristics, radiologic findings and pancreatic inflammation markers, following the 2012 Atlanta criteria revision, (ii) had serum basal electrolytes at admission and 24 hours later, (iii) underwent hospitalization without volunteer discharge. We excluded patients: (i) referred from other medical units with diagnosis of acute pancreatitis that received previous initial management, (ii) patients that had treatment with drugs that could affect chloremia, such as thiazides, diuretics, potassium-sparring diuretics, etc., and (iii) patients that had a disease that affected their renal function.

Outcome

The primary outcome of this study was hospital stay (measured in days); mortality for any cause, besides the presence of regional complications, such as peri-pancreatic collection, pancreatic and peri-pancreatic necrosis, gastric juice secretion, splenic infarct, colonic necrosis, pseudoaneurisms, splenic and portal vein thrombosis, and pancreatic ascites. Besides systemic complications defined as preexisting comorbidity exacerbation; coronary disease, pulmonary chronic disease, were registered and analyzed in the same complications category.

Laboratory procedures

The chloremia measures at admission and after 24 hours, was performed with indirect potentiometry (cobas c 501 analyzer, Roche Diagnostics, Indianapolis, IN, USA) and the results were expressed in milliequivalents per liter (mEq/L). We define ISC as the increment of >8 mEq/L through the first 24 hours, according to our observation in clinical practice and results of the data base.

Statistical analysis

Data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for normal distribution, and as median [inter-

quartile range] for non-normal distribution, while categorical variables were described as percentages and proportions. To evaluate differences, we used Student's t test/U-Mann Whitney test, and Chi-square/Fisher exact test, as appropriated. The primary outcome was the hospital stay in days, defined as the period between their emergency room admission and medical discharge; due to improvement or death (we excluded transferred patients and voluntary discharges). The chloremia delta was defined as chloremia after 24 hours minus chloremia at admission, expressed in mEq/L. Multivariate analysis was performed with multiple regression to determine the role of different variables with hospital stay in days. To estimate the power, we used post-study power-test with the pwr function, setting the significance in 0.05. All analyses were two-tailed and a P value of <0.05 was set for significance. R Studio version 3.4.1 statistical software was used for data analysis.

RESULTS

One hundred and ten patients were selected for the analysis, its baseline and clinic characteristics are shown in Table 2.

At 24 hours, 37 (33%) patients were classified with an ISC ($\Delta Cl>8mEq/L$). There were no differences in baseline characteristics (age, sex and pancreatitis etiology) between the two groups ($\Delta Cl>8mEq/L$, $\Delta Cl<8mEq/L$). (Table 3).

Table 2
Descriptive statistical. Baseline and clinical characteristics of the population.

	N=110 (%)	Median [Q1-Q3]	Mean ± SD
Age (years)		56 [42.2-69.7]	55.9±17.7
Sex (women)	63 (57)		
Etiology			
- Biliary	75 (68)		
- Alcoholic	9 (8)		
- Triglycerides	15 (14)		
- Drugs	1 (1)		
- Idiopathic	7 (6)		
- Others	3 (3)		
Severity			
- Mild	78 (71)		
- Moderate	12 (11)		
- Severe	20 (18)		
Chloremia at admission (mEq/L)		96.1 [93.5-99]	55.9±5.6
Admission APACHE II score		6 [4-7.7]	7.8±5.8
Used solution			
- SS0.9%	58 (53)		
- Hartmann	13 (12)		
- SS0.9%>Hartmann	24 (22)		
- Hartmann>SS0.9%	14 (13)		
- Others	1 (1)		
Quantity used (L)		4 [3.5-4.5]	4.06 ± 0.99

%: Percentage, Q1-Q3: Quartile 1 (P25) – Quartile 3 (P75), SD: Standard Deviation, h: hours, mEq/L: milliequivalents per liter, APACHE II: score of Acute Physiology and Chronic Health Evaluation II, SS0.9%: Saline Solution 0.9%, L: Liters.

Table 3
Bivariate analysis between increase in serum chlorine in 24 hours
ΔCl ≤8mEq/L vs ΔCl>8mEq/L.

	N=110 (%)	ΔCl ≤8mEq/L N=73 (%)	ΔCl >8mEq/L N=37 (%)	p
Age (years)				
Median [Q1-Q3]	56 [42.2-69.7]	56 [43-69]	56 [42-71]	0.81U
Mean ± SD	55.9 ± 17.7	55.6 ± 4.7	56.4 ± 18.4	
Sex (women)	63 (57)	44 (60)	19 (51)	0.37X
Etiology				
- Biliary	75 (68)	47 (64)	28 (75)	0.6F
- Alcoholic	9 (8)	5 (15)	4 (11)	
- Triglycerides	15 (14)	11 (15)	4 (11)	
- Drugs	1 (1)	1 (1)	0	
- Idiopathic	7 (6)	6 (8)	1 (3)	
- Others	3 (3)	3 (4)	0	
Severity				
- Mild	78 (71)	58 (79)	20 (54)	0.02X
- Moderate	12 (11)	6 (8)	6 (16)	
- Severe	20 (18)	9 (12)	11 (30)	
Chloremia at admission (mEq/L)				
Median [Q1-Q3]	96.1 [93.5-99]	97 [94.5-100]	96 [92-97.5]	0.03U
Mean ± SD	55.9 ± 5.6	97.1 ± 4.7	94.1 ± 6.6	
Chloremia after 24 h (mEq/L)				
Median [Q1-Q3]	103 [99.2-106]	102 [99-104.2]	105 [103.8-108]	0.0002U
Mean ± SD	102.9 ± 5.4	101.9 ± 5.1	105.1 ± 5.6	
Admission APACHE II (points)				
Median [Q1-Q3]	6 [4-7.7]	6 [4-9]	8 [6-15]	0.006U
Mean ± SD	7.8 ± 5.8	6.5 ± 4.5	10.2 ± 7.2	
24 hours APACHE II (points)				
Median [Q1-Q3]	5 [3-7.3]	5 [3-7]	6 [4-13]	0.13U
Mean ± SD	7.3 ± 7.4	6.3 ± 6.4	9.4 ± 8.8	
Hospital Stay (days)				
Median [Q1-Q3]	8 [6-9.5]	7 [5-10]	9 [7-12]	0.03U
Mean ± SD	9.5 ± 6.9	8.1 ± 4.2	12.3 ± 9.9	
Surgery				
- Elective	18 (16)	11 (15)	7 (19)	0.22F
- Urgency	1 (1)	0	1 (3)	
- Not surgery performed	60 (55)	38 (52)	22 (59)	
- Not needed	31 (28)	24 (32)	7 (19)	
Complications	27 (25)	14 (19)	13 (35)	0.06X
Mortality	18 (16)	9 (12)	9 (24)	0.10X

Table 3. CONTINUACIÓN

	N=110 (%)	ΔCl ≤8mEq/L N=73 (%)	ΔCl >8mEq/L N=37 (%)	p
Utilized solution				
- SS0.9%	58 (53)	34 (47)	24 (65)	
- Hartmann	13 (12)	12 (16)	1 (3)	
- SS0.9%>Hartmann	24 (22)	15 (21)	9 (24)	0.08χ
- Hartmann>SS0.9%	14 (13)	11 (15)	3 (8)	
- Others	1 (1)	1 (1)	0	
Quantity utilized (L)				
Median [Q1-Q3]	4 [3.5-4.5]	3.9 [3.5-4.3]	4.25 [3.6-5]	0.04ᵁ
Mean ± SD	4.06 ± 0.99	3.94 ± 0.86	4.31 ± 1.18	

%: Percentage, Q1-Q3: Quartile 1 (P25) – Quartile 3 (P75), SD: Standard Deviation, mEq/L: milliequivalents per liter, APACHE II: score of Acute Physiology and Chronic Health Evaluation II scale, SS0.9%: Saline Solution 0.9%, L: Liters. χ: Chi-Square test, ǂ: Exact Fisher Test, ᵁ: U-Mann-Whitney test, ᵀ: T-Student test.

Pancreatitis severity was stablished using the Atlanta criteria, and found as severe in the 30% of all patients with ΔCl>8mEq/L, compared with 12% of the patients with chloremia delta ≤8mEq/L (p=0.02). There were no differences in surgery indication in both groups.

Considering the clinical results, admission APACHE II score was higher in the group with ΔCl>8mEq/L (8 [6-15] *vs* 6 [4-9] points, p=0.006), but had no differences in APACHE II score 24 hours after (5 [3-7] *vs* 6 [4-13] points, p=0.13).

Hospital stay was longer in the group with ΔCl>8mEq/L (9 [7-12] *vs* 7 [5-10] days, p=0.03). The power (β) of this asseveration is 0.99 with a significance level (α) of 0.05.

There were not statistically significant differences in complications (35% vs 19%, p=0.06) and mortality (24% *vs* 12%, p=0.1).

Regarding the quantity of utilized solution in the first 24 hours from admission, we found that in the ΔCl>8mEq/L the median volume used was 4.25 [3.6-5] *vs* 3.9 [3.5-4.3] liters in the ΔCl≤8mEq/L group (p=0.04).

The Table 3 summarize the bivariated analysis of baseline and clinical outcomes of the patients, divided following their chloremia change.

In multivariate analysis modeling hospitalization days, final model was obtained with step-wise regression using backward variable elimination, showed that a ΔCl>8mEq/L (p=0.01) and 24 hours APACHE II score (p=0.02) stayed as the main predictors for longer hospital stay in patients with acute pancreatitis.

DISCUSSION

In this retrospective study of 110 patients with acute pancreatitis, we found that the significant chloremia increment in 24 hours (ΔCl>8mEq/L) could be an independent associated factor to prolong the hospital stay in the adult population. Chloremia concentration reflects patient's electrolyte and water balance; its change is attributed fundamentally to the management with crystalloid solutions. Thus, chloremia changes are intimately related with the kind and quantity of utilized solutions. Hyperchloremia at the same time is related with the acid-base equilibrium. In fact, the chloremia concentration increment is one of three causes of metabolic acidosis, which in animal studies increases the production of interleukin 6 and tumoral necrosis factor, as well as nitric oxide, therefore, chlo-

ride is a pro-inflammatory modulator [11]. It has been found that this ion is important in neutrophil functions, which requires constant influx through the chloride channels to produce hypochlorous acid from myeloperoxidase. For this reason, low extracellular chloride concentration is associated with neutrophil disfunction. This could provide a plausible pathophysiological link between the increment of chloremia and pro-inflammatory state and longer hospital stay in patients with acute pancreatitis. Recent studies in cells and animals indicate that hyperchloremic acidosis, through the increment of hydrochloric acid, significantly increases cytokines expression, besides the gene induction through κB nuclear factor and DNA junction. This seems to be especially relevant in states with important inflammatory response such as acute pancreatitis [11].

Previous studies had stablished the association between hyperchloremia and increased mortality in critically ill patients [8,9,11]. Isolated hyperchloremia has been recognized as an independent factor associated with acute kidney injury [10]. In our study, although it did not reach statistical significance, maybe because of the sample size, we can see a trend in the increment of mortality with significant changes in chloremia, as well as in the incidence of complications. Nevertheless, there is still controversy that chloremia changes are a consequence of aggressive fluid therapy in patients with deplored hydration level, or if they truly are the cause of mortality trough the inflammatory mechanisms mentioned before. Controlled prospective studies are needed to answer this question.

Regarding the use of solutions, Forsmark *et al* recommend administration of a range of 2.5 to 4 L in 24 hours; however, in our population the average was 4.07 ± 0.99 L, even reaching 7.2 L in the first 24 hours. Although recommendation is the use of crystalloids, either saline solution 0.9% or Hartmann solution, there is still no consensus as to which solution to use, although it has been seen that Ringer lactate may be associated with an anti-inflammatory effect [1].

In this population, a higher prevalence of biliary lithiasis as etiology (68%) of acute pancreatitis was noted. In the last 12 years, overweight and obesity, directly related to formation of biliary stones, have reached 71.3% in the adult population, an increase of almost 10% compared to the year 2000 [15].

In our study, the presence of ΔCl> 8mEq/L was an important predictor for hospital stay, even better than the APACHE II scale at admission and at 24 hours, only comparable with severity due to Atlanta classification in acute pancreatitis, even when it was adjusted in multivariate analysis.

We are aware that our study has limitations, mainly the lack of measurement of other electrolytes, acid-base and inflammatory balance parameters, such as sodium, potassium, calcium, magnesium, serum pH, bicarbonate (HCO_3) and C-reactive protein (CRP), even though several of these elements are routinely measured in this pathology.

Finally, the type of solution (Hartmann vs saline solution 0.9%), as well as the volume of liters used, should be evaluated in prospective controlled studies given its potential therapeutic effect and prognosis on days of hospital stay.

We conclude that changes greater than 8mEq/L of chloremia at 24 hours after admission identifies a subset of patients with acute pancreatitis with an increased risk of lengthening their hospital stay and probably mortality and complications, independently of other prognostic factors, such as APACHE II. Hyperchloremia remains a factor of poor prognosis, highly controllable with adequate fluid management, as well as being an easily measurable laboratory parameter that can better predict an increased probability of longer hospital stay in adult patients with acute pancreatitis.

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• RSO: participation in the design of the study, data acquisition final approval of the manuscript.

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Value of endorectal ultrasonography in the assessment of invasion staging of low rectal cancer with local progression after neoadjuvant radiochemotherapy.

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Key words: endorectal ultrasonography; low rectal cancer; local progression; neoadjuvant radiochemotherapy; invasion; staging.

Abstract. Although stages T3 and T4 rectal cancer can be reduced to T1 or T2 after neoadjuvant radiochemotherapy, the accuracy of the endorectal ultrasonography (ERUS) for the post-radiochemotherapy evaluation of low rectal cancer has seldom been reported. We aimed to investigate the value of ERUS in the assessment of invasion staging in low rectal cancer with local progression, and the factors affecting its accuracy, after neoadjuvant radiochemotherapy. A total of 114 patients administered with neoadjuvant radiochemotherapy for stages II and III low rectal cancer (local stage T3/T4) from February 2018 to December 2020 were enrolled in the study. The changes in local lesions were evaluated using ERUS before and after radiochemotherapy, and compared with the pathological T staging. The accuracy of post-neoadjuvant radiochemotherapy re-staging examined with ERUS was evaluated, and univariate analysis was used to identify the factors affecting the accuracy. After neoadjuvant radiochemotherapy, the blood flow distribution within the lesion significantly declined ($P<0.05$), the max length and max thickness of the longitudinal axis of the lesion were reduced ($P<0.05$), and the uT staging was decreased ($P<0.05$), when compared with lesions before the treatment. Compared with postoperative pathological T staging, the accuracies of ERUS in T1, T2, T3 and T4 stages were 11.11%, 28.57%, 27.27% and 100%, respectively. Univariate analysis

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indicated that review time of ERUS, post-operative T staging and Wheeler rectal regression stage were factors affecting the accuracy of ERUS re-staging. ERUS is more accurate for T4 re-staging, follow-up reviewed six weeks after neoadjuvant radiochemotherapy and low regression tumors, with a high application value for the assessment of the efficacy of neoadjuvant radiochemotherapy for low rectal cancer.

Valor de la ultrasonografía endorectal en la evaluación de la estadificación de la invasión del cáncer rectal bajo con progresión local, después de administrar radioquimioterapia neoadyuvante.

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Palabras clave: pancreatitis; cloruros; soluciones isotónicas; tiempo de internación.

Resumen. Aunque el cáncer de recto en estadios T3 y T4 se puede reducir a T1 o T2 después de la radioquimioterapia neoadyuvante, rara vez se ha informado la precisión de la ecografía endorrectal (ERUS) para la evaluación posterior a la radioquimioterapia del cáncer de recto inferior. Nuestro objetivo fue investigar el valor de ERUS en la evaluación de la estadificación de la invasión en el cáncer de recto inferior con progresión local, después de la radioquimioterapia neoadyuvante y los factores que afectan su precisión. Se incluyeron en el estudio un total de 114 pacientes a los que se les administró radioquimioterapia neoadyuvante para el cáncer de recto inferior en estadios II y III (estadio local T3/T4), desde febrero de 2018 hasta diciembre de 2020. Los cambios en las lesiones locales se evaluaron mediante ERUS antes y después de la radioquimioterapia y se compararon con la estadificación patológica T. Se evaluó la precisión de la re-estadificación examinada con ERUS, después de la radioquimioterapia neoadyuvante y se utilizó un análisis univariado para identificar los factores que afectan su precisión. Después de la radioquimioterapia neoadyuvante, la distribución del flujo sanguíneo dentro de la lesión disminuyó significativamente (P<0,05), la longitud máxima y el espesor máximo del eje longitudinal de la lesión se redujeron (P<0,05) y la estadificación uT disminuyó (P<0,05), en comparación con las lesiones antes del tratamiento. En comparación con la estadificación T patológica posoperatoria, las precisiones de ERUS en las etapas T1, T2, T3 y T4 fueron del 11,11%, 28,57%, 27,27% y 100%, respectivamente. El análisis univariable indicó que el tiempo de revisión de ERUS, la estadificación T postoperatoria y la etapa de regresión rectal de Wheeler fueron factores que afectaron la precisión de la re-estadificación con ERUS. ERUS es más preciso para la re-estadificación de T4, el seguimiento seis semanas después de la radioquimioterapia neoadyuvante y en tumores de baja regresión, con un alto valor de aplicación para la evaluación de la eficacia de la radioquimioterapia neoadyuvante para el cáncer rectal bajo.

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INTRODUCTION

Rectal cancer is a common malignancy of the digestive system, and the incidence rate exhibits an increasing trend annually[1]. Different stages of rectal cancer should be administered with different therapeutic strategies. Local resection is feasible for early-stage rectal cancer, and standard treatment mode, neoadjuvant radiochemotherapy combined with radical surgery, is recommended for locally advanced rectal cancer[2]. Neoadjuvant radiochemotherapy helps to reduce tumor size, degrade the staging, increase the sphincter preservation rate, reduce local recurrence rate and prolong the survival time of patients [3,4]. The "watch-and-wait" strategy can be adopted for rectal cancer patients with clinical complete response after neoadjuvant radiochemotherapy. Hence, tumors should be accurately re-staged after neoadjuvant therapy.

The endorectal ultrasonography (ERUS) offers an important means for preoperative staging of the primary lesion of rectal cancer, characterized by low cost, high efficiency, and accurate rectal wall stratification, and it is far superior to magnetic resonance imaging (MRI) in the differential diagnosis of T1 and T2 stages [5,6]. Although stages T3 and T4 rectal cancer will be reduced to T1 or T2 after neoadjuvant radiochemotherapy, there are currently only few reports on the accuracy of ERUS in the post-radiochemotherapy evaluation of low rectal cancer [7]. In this study, ERUS was utilized to evaluate the primary lesion of stage T3 and T4 low rectal cancer before and after neoadjuvant radiochemotherapy, aiming to evaluate the accuracy of ERUS after radiochemotherapy and before surgery, and to investigate the correlations between clinical indices and accuracy.

MATERIALS AND METHODS

A total of 114 patients diagnosed as low rectal cancer in our hospital from February 2018 to December 2020 were enrolled, including 69 males and 45 females, aged (57.3±6.2) years old. Digital anal examination showed that the distance between the tumor lower edge and the anal verge was 4-7 cm. The inclusion criteria were as follows: a) patients who were diagnosed with stage II or III low rectal cancer (regional stage T3/T4) by ERUS and MRI for the first time, and ultrasound probe could scan the tumor completely through the intestinal cavity. b) those who had no surgical contraindications, and were administered with surgery at eight weeks after neoadjuvant radiochemotherapy (2 Gy/time, 22 times, for a total radiotherapy dose of 44 Gy, while oral capecitabine 2500 mg/(m^2·d), bid for two weeks followed by one week rest as one cycle, for two cycles. And c) those who underwent neoadjuvant radiochemotherapy and total mesorectal excision, with ERUS examination at 4-8 weeks after neoadjuvant therapy and before surgery, and postoperative pathological staging and Wheeler rectal cancer regression grade (RCRG). The exclusion criteria involved: a) patients whose dosage of neoadjuvant radiochemotherapy did not reach the standard, or b) those whose radical excision did not reach the requirement. In the present study, the staging standard met the National Comprehensive Cancer Network (NCCN) guidelines of 2014.

METHODS

Philips iU 22 color Doppler ultrasound system (Netherlands) with C8-4V intracavitary ultrasonic probe was selected. The frequency of ERUS was 5-10 MHz. The probe was inserted into the rectal cavity to complete a "360-degree view" of the tumor. The location, length, diameter, shape, echo, and depth of invasion, followed by the number, size, and echo of the peri-intestinal lymph nodes were observed, and the blood flow distribution in the lesion, the max length of the longitudinal axis of the lesion, the max thickness of the tumor, and T staging (T1: hypoechoic shadow is confined to the first three layers; T2: hypoechoic shadow is present in the fourth

layer, but the fifth layer is smooth; T3: hypoechoic shadow is present in the fifth layer; T4: hypoechoic shadow is present in the intestinal lining and partly surrounding tissues or organs) were determined. Color Doppler blood flow imaging grading was performed according to the intensity of blood flow signals: grade 0: no blood flow signal, grade I: blood flow signals of focal region, grade II: multi-point and strip blood flow signals, and grade III: large amounts of dot and strip blood flow signals. ERUS was compared with pathological T staging to evaluate under-stage, over-stage and accuracy, and the correlations of patient's age, gender, distance between the lower edge of the tumor and the anus, review time of ERUS, nerve invasion, vascular invasion, lymph node metastasis, postoperative T staging and Wheeler rectal cancer regression grade with ERUS re-staging accuracy after neoadjuvant radiochemotherapy were subjected to univariate analysis to identify the factors affecting the accuracy.

STATISTICAL ANALYSIS

SPSS 20.0 software was employed for statistical analysis. Numerical data were expressed as percentage [n (%)] and analyzed using chi-square test. Measurement data were expressed as mean ± standard deviation ($\bar{\chi} \pm s$), and *t*-test was used for comparison between two groups. The factors affecting the accuracy of post-neoadjuvant radiochemotherapy re-staging examined with ERUS was evaluated by logistic regression analysis. $P<0.05$ indicated that the difference was statistically significant.

RESULTS

Changes in indices after neoadjuvant radiochemotherapy with ERUS

ERUS showed that the blood flow distribution within the lesion significantly declined ($\chi^2=159.723$, $p<0.001$) after neoadjuvant radiochemotherapy, when compared with the pre-treatment lesion. The max length of the longitudinal axis of the lesion and the max thickness of the tumor were reduced [(5.38±0.34) cm *vs.* (2.15± 0.14) cm, (3.03±0.24) cm *vs.* (0.96±0.12) cm] ($t=93.792$, $p<0.001$; $t=82.368$, $p<0.001$). Compared with before pre-neoadjuvant radiochemotherapy, uT staging had a significant difference after neoadjuvant radiochemotherapy ($\chi^2=58.455$, $p<0.001$) (Table 1).

Table 1
Changes in indices after neoadjuvant radiochemotherapy with ERUS (n=114).

Group	Pre-neoadjuvant radiochemotherapy	Post-neoadjuvant radiochemotherapy	χ^2/t	p
Blood flow (n)			$\chi^2=159.723$	<0.001
0	0	42		
□	0	51		
□	51	15		
□	63	6		
Max length (cm)	5.38±0.34	2.15±0.14	t=93.792	<0.001
Max thickness (cm)	3.03±0.24	0.96±0.12	t=82.368	<0.001
uT stage(n)			$\chi^2=58.455$	<0.001
T1	0	12		
T2	0	36		
T3	63	52		
T4	51	24		

ERUS and pathological T staging after neoadjuvant radiochemotherapy

Compared with postoperative pathological T staging, ERUS showed 88.89% of over-stage in T1 stage, 21.43% of under-stage and 50% of over-stage in T2 stage, 45.45% of under-stage and 27.27% of over-stage in T3 stage, 0 of under-stage and over-stage in T4 stage, and 21.05% of under-stage and 47.37% of over-stage in T stage (overall), and the accuracies of ERUS in T1, T2, T3, T4 and T stages (overall) were 11.11%, 28.57%, 27.27%, 100% and 31.58%, respectively (Table 2).

Clinicopathological factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy

Univariate and multivariate logistic analyses indicated that review time of ERUS, post-operative T staging and Wheeler rectal regression stage were factors affecting ERUS re-staging accuracy. ERUS was more accurate in patients with review time of ERUS ≥6 weeks after neoadjuvant radiochemotherapy, ypT4 and RCRG3 (Tables 3 and 4).

DISCUSSION

The incidence rate of low rectal cancer is higher among colorectal tumors. The anatomical structure of the low rectum is different from that of the high rectum, and the effect of radical surgery is poor for low locally advanced rectal cancer in the past, with a poor prognosis. With the extensive development, the role of neoadjuvant radiochemotherapy with the advantages of increasing the radical cure rate of low locally advanced rectal cancer, reducing the recurrence rate, increasing the sphincter preservation rate and prolong the survival time, has been confirmed [7,8]. In the NCCN guidelines, it has been definitely proposed to perform neoadjuvant radiochemotherapy for stages II and III low rectal cancer (regional stage T3 and T4). For low rectal cancer within 5 cm from the anus, ERUS has unique advantages [9]. In a previous study, it showed that the accuracy of ultrasound is 63-96% in the preoperative staging of low rectal cancer, which is 87-98% in MRI [10]. However, there are still few reports on the evaluation value of ERUS after neoadjuvant radiochemotherapy and before surgery.

The accuracy of ultrasound in different locations of rectal cancer differs greatly during the determination of the degree of invasion of the primary rectal cancer. Especially, ultrasound endoscopic scanning is required for middle and upper rectal cancer, which greatly affects the accuracy, but for low rectal cancer, intracavitary ultrasound probes can easily and completely scan the primary lesion to evaluate the length, thickness, depth of invasion, blood flow, and circumferential margins [11,12]. Under ERUS, the normal rectal wall is a 5-layer structure with a thickness of 2-3 mm with alternating high and low echoes, containing mucosa, mucosal muscle, submucosa, propria muscle, serous membrane and subserosal layer, surrounding with adipose tissues, mesangial fascia

Table 2
EURS and pathological T staging after neoadjuvant radiochemotherapy.

	EURS stage(n)				Total	EURS stage		
	uT1	uT2	uT3	uT4		Over staging	Underestimate staging	Accuracy
ypT1	3	9	15	0	27	0	88.89% (24/27)	11.11% (3/27)
ypT2	9	12	18	3	42	21.43% (9/42)	50.00% (21/42)	28.57% (12/42)
ypT3	0	15	9	9	33	45.45% (15/33)	27.27% (9/33)	27.27% (9/33)
ypT4	0	0	0	12	12	0	0	100.00%(12/12)
Total	12	36	52	24	114	21.05% (24/114)	47.37%(54/114)	31.58% (36/114)

outside the adipose tissues, and the primary lesion is characterized by irregularly shaped masses, with uneven low echoes, some multiple micro-calcifications, different depths of invasion into intestinal wall, disappearance of normal intestinal wall structure, abundant arteriovenous blood flow in the tumor, and high resistance of arterial blood flow [13,14].

Table 3
Univariate analysis results of factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy

Item	n	ERUS stage		χ^2	p
		Accurate (n=36)	Inaccurate (n=78)		
Age (years)				1.661	0.197
≤60	48	12	36		
>60	66	24	42		
Gender				3.013	0.083
Male	69	26	43		
Female	45	10	35		
Distance from low margin of tumor to anus (cm)				2.537	0.111
<3	60	15	45		
≥3	54	21	33		
Follow up check of ERUS (weeks)				9.204	0.002
<6	42	6	36		
≥6	72	30	42		
Nerve invasion				0.506	0.477
Negative	93	28	65		
Positive	21	8	13		
Vessel invasion				0.050	0.822
Negative	27	9	18		
Positive	87	27	60		
Lymph node metastasis				0.201	0.654
Negative	51	15	36		
Positive	63	21	42		
Post-operation stage				37.948	<0.001
ypT1	27	3	24		
ypT2	42	12	30		
ypT3	33	9	24		
ypT4	12	12	0		
PCRG				21.732	<0.001
PCRG1	33	3	30		
PCRG2	39	9	30		
PCRG3	42	24	18		

Table 4
Multivariate logistic analysis results of factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy.

Item	Regression coefficient	Standard error	Wald χ^2	OR	95% CI	p
Review time of ERUS ≥6 weeks	2.203	0.297	5.389	1.727	1.063~2.804	0.004
ypT4	2.687	0.172	6.835	2.010	1.928~4.400	0.000
PCRG3	2.236	0.238	4.623	2.581	1.689~3.479	0.022
Constant term	1.784	0.348	76.436	6.053		0.006

After neoadjuvant radiochemotherapy, the primary tumor is prone to pathological features such as necrosis, fibrosis, reduced density, and decreased blood supply, and the original 5-layer structure of the intestinal wall is destroyed, so that MRI or ERUS re-staging accuracy is poor [15]. Compared with before pre-neoadjuvant radiochemotherapy, ERUS showed that the blood flow distribution within the lesion significantly declined, the max length of the longitudinal axis of the lesion and the max thickness of tumor were significantly reduced, most stage T3 or T4 rectal cancer was reduced to T1 or T2, and the uT staging was decreased after neoadjuvant radiochemotherapy.

These results demonstrated that ERUS is of clinical guiding significance in the evaluation of tumor length, thickness and blood flow after radiochemotherapy, and can effectively evaluate the efficacy of adjuvant therapy. Compared with postoperative pathological T re-staging, the results displayed that ERUS showed 88.89% of over-stage in T1 stage, 21.43% of under-stage and 50% of over-stage in T2 stage, 45.45% of under-stage and 27.27% of over-stage in T3 stage, 0 of under-stage and over-stage in T4 stage, and 21.05% of under-stage and 47.37% of over-stage in T stage (overall), and the accuracy of ERUS in T1, T2, T3, T4 and T stage (overall) was 11.11%, 28.57%, 27.27%, 100% and 31.58%, respectively. The above results suggested that ERUS has extensive under-stage in T1 and T2 stages, and the accuracy is extremely poor. The reason may be that neoadjuvant therapy is absolutely effective for the primary lesion of T1 and T2 re-staging, and the 5-layer structure of the intestinal wall is difficult to distinguish. Because of tumor regression, fibrous interstitial tissue proliferation, reduced distribution of tumor cells in the interstitium, and decreased blood flow of the tumor, the accuracy of the stratification of the mucosal layer, mucosal muscle, submucosal layer and muscularis propria is poor, and the fibrous interstitial tissue with incomplete shrinkage may be mistaken for residual tumors, resulting in excessive staging [16]. A previous study indicated that the total accuracy of ERUS T staging after neoadjuvant radiochemotherapy is 48%, with 38% of over-staging and 14% of under-staging, tumor regresses notably in the primary tumor that is sensitive to radiochemotherapy, and the accuracy of re-staging is poor [17], similar to the results of this study. The results of this study showed that ERUS was more accurate for T4 re-staging, because T4 re-staging indicates ineffective or extremely poor effect of neoadjuvant radiochemotherapy. Studies have displayed that the accuracy of ERUS and MRI is close to 100% in T4 stage with larger tumor, so the depth of invasion is more accurate, and the evaluation accuracy is higher. Further univariate analysis showed that review time of ERUS, postoperative T staging and Wheeler rectal cancer regression grade are factors

affecting ERUS re-staging accuracy in low rectal cancer. The accuracy is higher in patients with review time of ERUS ≥6 weeks. The reason may be that the edema begins to subside 4 weeks after radiotherapy, and the boundary of tumor regression is more obvious, achieving the maximum effect at 6-8 weeks. Hence, ERUS can more accurately distinguish the intestinal wall level after six weeks. Patients with ypT4 and PCRG3 have poor response of tumor to radiochemotherapy, consistent with RCR3 of regression, and higher accuracy of T4 staging mentioned above. ERUS is poorly accurate for regional re-staging of obvious regression after radiochemotherapy, and more accurate for T4 re-staging of unobvious regression after radiochemotherapy. Besides, different operators with experience, different types of probes and fuselages are also factors that affect the results of ERUS.

In conclusion, ERUS can effectively allow the evaluation of the efficacy of low rectal cancer after neoadjuvant radiochemotherapy, including length, volume and blood flow. However, it is poorly accurate for those with prominent effect of neoadjuvant radiochemotherapy and T staging with effective regression, and more accurate for those primary lesions with non-prominent effect of neoadjuvant radiochemotherapy and poor tumor regression. Besides, ERUS has a higher accuracy for the review time at 6 weeks after neoadjuvant radiochemotherapy. Regardless, this study still has limitations. First, the sample size is small, and further verification is needed with a large population. Second, the scan range of ERUS is limited, which cannot display tumors in the upper rectal segment. Third, ERUS does not work well for rectal cancer in the immediate vicinity of the anus or mesorectal lymph nodes. Particularly, patients after receiving neoadjuvant radiotherapy probably cannot tolerate the pain during examination because the mucosa is damaged.

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Authors contribution

SG and CS designed this study and prepared this manuscript; LY, HY, JH, ZY and XW performed this study and analyzed the clinical data. All authors have approved the submission and publication of this manuscript.

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Clinical value of combined detection of thrombus precursor protein and P-selectin in the diagnosis of acute coronary syndrome.

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Key words: acute coronary syndrome; thrombus precursor protein; P-selectin; molecular markers of prethrombotic state.

Abstract. Acute coronary syndrome (ACS), including acute myocardial infarction (AMI) and unstable angina (UA), is the most threatening and lethal form of coronary heart disease. ACS has an abrupt onset and rapid development, which may lead to fatal conditions at any time. Thus, it is never too early to detect and diagnose patients with ACS. The objective of this work was to explore the significance of the combined detection of plasma thrombus precursor protein (TpP) and serum P-selectin (Ps), in the detection and diagnosis of patients with early ACS. A total of 126 subjects were included in the study, 64 ACS patients, 30 individuals with stable angina (SA) and 32 healthy persons who were selected as the control groups. There were no differences in gender, age, ethnicity, or blood glucolipid levels among the groups. Enzyme linked immunosorbent assay (Elisa) was used to quantitatively determine the plasma levels of TpP and Ps. The levels of the two biomarkers in the case group were significantly higher than those in the control groups. Among the ACS patients, the levels of TpP and Ps were higher in AMI patients than in the UA patients. In addition, there was no significant differences in the levels of Ps between SA patients and healthy persons. In conclusion, plasma TpP and serum Ps are remarkably increased in patients with ACS. Therefore, TpP and Ps may serve as ACS indicators, and their measurement may provide a support for an early clinical identification of ACS.

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Valor clínico de la detección combinada de proteína precursora de trombo y selectina P en el diagnóstico del síndrome coronario agudo.

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Palabras clave: síndrome coronario agudo; proteína precursora de trombo: P-selectina; marcadores moleculares de estado pretrombótico.

Resumen. El síndrome coronario agudo (SCA), que incluye el infarto agudo de miocardio (IAM) y la angina inestable (AI), es la forma más amenazante y letal de enfermedad coronaria. El SCA tiene un inicio abrupto y un desarrollo rápido, lo que puede conducir a condiciones fatales en cualquier momento. Por lo tanto, nunca es demasiado pronto para detectar y diagnosticar pacientes con SCA. El objetivo de este trabajo fue explorar la importancia de la detección combinada de la proteína precursora de trombos plasmáticos (TpP) y la selectina P sérica (Ps), en la detección y diagnóstico de pacientes con SCA precoz. Se incluyeron en el estudio un total de 126 sujetos, 64 pacientes con SCA, 30 individuos con angina estable (AE) y 32 personas sanas que fueron seleccionadas como grupos de control. No hubo diferencias en el género, la edad, el origen étnico o los niveles de glucolípidos en sangre entre los grupos. Se usó el ensayo inmunoabsorbente ligado a enzimas (Elisa) para determinar cuantitativamente los niveles plasmáticos de TpP y Ps. Los niveles de los dos biomarcadores en el grupo de casos (SCA) fueron significativamente más altos que los de los grupos de control. Entre los pacientes con SCA, los niveles de TpP y Ps fueron más altos en los pacientes con IAM que en los pacientes con AI. Además, no hubo diferencias significativas en los niveles de Ps entre pacientes con SA y personas sanas. En conclusión, la TpP plasmática y la Ps sérica están notablemente aumentadas en pacientes con SCA. Por lo tanto, TpP y Ps pueden servir como indicadores de SCA y su medición puede proporcionar un apoyo para una identificación clínica temprana de SCA.

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INTRODUCTION

Acute Coronary Syndrome (ACS) refers to a group of clinical syndromes with acute myocardial ischemic events due to a sudden obstruction of the coronary blood flow. It is almost always associated with the rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery.

ACS generally is divided into ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The occurrence of ACS is primarily due to plaque erosion or plaque rupture after coronary atherosclerosis, and can cause incomplete occlusion of blood vessels or secondary complete occlusive thrombosis, which ultimately leads to acute myocardial

ischemia[1]. ACS is easy to be missed in the clinical area due to the fact that its signs and symptoms usually begin abruptly. ACS progresses rapidly, which affects the survival time and quality of life of ACS patients [2,3]. Therefore, an early diagnosis is very important for ACS.

Thrombosis is one of the leading causes of atherosclerotic plaque formation. The detection of thrombus markers can identify whether the patient is in the prethrombotic state, which is of particular significance to assess the risk of ACS. The thrombus precursor protein (TpP) is a marker, and the most direct evidence, of impending thrombosis [4]. P-selectin (Ps) is a member of the selectin family of cell adhesion molecules, which plays a vital role in the initiation of inflammation, the mediation of leukocyte adhesion and aggregation on the endothelium, and the formation of thrombus [5]. In this study, through the determination of the above two biomarkers in healthy individuals and patients with ACS or SA in our hospital, we comprehensively analyzed the differences in the levels of the two factors in each studied group and investigated the significance of combined detection of TpP and Ps in the early diagnosis of ACS.

MATERIALS AND METHODS

Subjects and study design

Sixty-four patients with ACS treated in the Shanghai Xinhua Hospital Chongming Branch, from October 2019 to October 2020, were randomly selected as the case groups (including 30 patients with unstable angina (UA) and 34 patients with acute myocardial infarction (AMI) (18 patients with NSTEMI, 16 patients with STEMI)). Thirty patients with stable angina (SA) and 32 healthy people corresponding to the case group in terms of gender, age, ethnicity, etc. were selected as the control groups. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Xinhua Hospital Chongming Branch. All subjects gave their informed consent for inclusion before participating in the study (on admission). After admission, patients in each group received a routine electrocardiogram (or dynamic electrocardiogram), and the grouping was determined after the measurement of myocardial enzymes. Patients receiving platelet therapy, or with an abnormal coagulation function (DIC, hemophilia, leukemia, abnormal coagulopathy caused by severe liver disease, vitamin K deficiency) were excluded.

Baseline data were collected, including gender, age, nationality, blood glucose, blood lipids, and myocardial enzyme indexes. All the candidates had 4 ml of fasting venous blood drawn at 8:00 in the morning after admission. The Ps tube was immediately centrifuged at 3,000 rpm for 10 minutes to collect serum. The TpP tube was added with sodium citrate for anticoagulation and centrifuged at 3,000 rpm for 10 minutes to collect plasma. The collected serum and plasma were stored at –70° for testing.

Biomarker assays

Serum P-selectin was determined using a kit provided by Wuhan USCN Business Co., Ltd., and plasma TpP was measured with a kit provided by Wuhan Cusabio Technology LLC. The model of the microplate reader was Shanghai Kehua st-360.

Statistical analyses

The data obtained from the experiment were analyzed by SPSS 22.0 statistical software. The measurement data were expressed by $\bar{\chi} \pm$ SD. The comparison between means was made by the Student's t-test (analysis of variance was used to compare more than two groups). The counting data was represented by the composition ratio, and comparison between groups was by the χ^2 test. $P<0.05$ indicated that the difference was statistically significant.

RESULTS

Basic characteristics of the study participants

The details of demographic data of the 126 study participants are listed in Table 1. The results showed that there were no significant differences in age and sex among the groups.

Comparison of results between Stable Angina patients and healthy people

The results in Table 2, show that there were no statistically significant differences in age, blood glucose concentration, blood lipid concentration or the serum Ps levels between stable angina patients and healthy people ($P>0.05$). The serum TpP level of patients with SA was higher than that of the healthy people ($P<0.05$).

Comparison within case groups

In the case groups, there was no significant difference in the baseline data between patients with UA, STEMI and NSTEMI ($P>0.05$). The serum levels of Ps and TpP of patients with NSTEMI and STEMI were higher than those of patients with UA ($P<0.05$). See Table 3.

Comparison of results between case and control groups

The demographics, clinical, and laboratory data (age, gender, blood glucose, blood lipids, etc.) between case groups and control groups had no significant difference ($P>0.05$). The Ps and TpP levels of case groups were significantly higher than those of control groups ($P<0.05$). See Table 4.

Table 1
Basic information of patients.

Index		ACS			Control Groups		p
		UA (n=30)	NSTEMI (n=18)	STEMI (=16)	SA (n=30)	Healthy (n=32)	
Age		67.40±10.669	61.44±14.454	65.00±8.990	65.97±10.361	62.22±14.988	NS
Gender	Male (n/%)	21/70	13/72	22/73	22/73	19/60	NS
	Female (n/%)	9/30	5/28	8/27	8/27	19/60	

ACS: Acute coronary syndrome; UA: unstable angina; NSTEMI: non–ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SA: stable angina.

Table 2
Comparison of results between Stable Angina patients and healthy people.

Index	SA Group (30 cases)	Healthy Group (32 cases)	p
Age (years)	65.97±10.361	62.22±14.988	NS
Blood glucose (mmol/L)	6.54±1.946	6.30±2.257	NS
Blood lipid (mmol/L)	1.69±1.544	1.60±1.069	NS
Ps (ng/mL)	45.74±28.427	58.12±36.322	NS
TpP (ng/mL)	4.27±1.932	2.73±1.159	0.001

SA: stable angina Ps: P-selectin TpP: Thrombus precursor protein.

Table 3
Comparison of the results of UA, NSTEMI and STEMI within the case group.

Index	UA (30 cases)	NSTEMI (18 cases)	STEMI (16 cases)	p		
				(a and c1)	(a and c2)	(c1 and c2)
Blood glucose (mmol/L)	6.57±2.253	8.52±4.150	7.09±2.041	NS	NS	NS
Blood lipids (mmol/L)	1.81±1.504	1.91±1.198	1.99±1.168	NS	NS	NS
Ps (ng/mL)	39.09±12.139	87.40±37.413	93.39±39.000	<0.001	<0.0010	NS
TpP (ng/mL)	6.03±2.033	9.82±3.659	10.93±3.725	0.001	0.001	NS

UA: unstable angina NSTEMI: non–ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction Ps: P-selectin TpP: Thrombus precursor protein.

Table 4
Comparison of results between case and control groups.

Index	Case	Control	p
Age (years)	65.23±11.396	64.03±12.990	0.581
Blood glucose (mmol/L)	7.20±2.886	6.41±2.103	0.090
Blood lipids (mmol/L)	1.89±1.326	1.64±1.318	0.319
Ps (ng/mL)	66.25±38.39	52.13±33.07	0.029
TpP (ng/mL)	8.32±3.69	3.47±1.746	<0.001

Ps: P-selectin TpP: Thrombus precursor protein.

DISCUSSION

Many studies have confirmed that ACS is caused by unstable plaque, surface rupture, and breakage in the coronary arteries, which cause bleeding and thrombosis, leading to partial or complete occlusion of the coronary arteries. Platelet adhesion, activation, aggregation, and thrombosis are central to its pathogenesis [6]. Through the detection of related factors involved in thrombosis, the early recognition of ACS can be improved.

TpP is a high molecular weight soluble fibrin polymer, formed by the polymerization of fibrin monomers produced by the action of thrombin on fibrinogen and is the direct precursor of insoluble fibrin. Studies have confirmed that when the TpP level rises, it means that the thrombus has started, and the fibrin monomer has begun to polymerize, which can be used as a predictor of thrombosis [7]. Because of the specific antigenic determinants on the structure, this antigenic determinant does not exist on fibrinogen and fibrin degradation products. It may be more clinically significant than other indicators for diagnosing various thrombotic diseases [8].

Ps is a member of the selectin family of adhesion molecules. It plays a vital role in the process from leukocyte recruitment to plaque rupture. Related experiments have shown that Ps expression in platelets near the ruptured plaque was significantly increased, and there were a large number of mononuclear macrophages and T lymphocytes around it [9]. Many studies have also confirmed that the level of Ps can be used

to determine the incidence and severity of coronary heart disease [10,11].

The levels of the two indicators in the case group, were generally higher than those of healthy individuals and SA patients, which were similar to the results of Atalar [12] and Kayikcioglu et al. [13]. In addition, this study found that the levels of Ps and TpP in patients with acute myocardial infarction were significantly higher than those in patients with unstable angina. This indicated that there is a significant correlation between the changes in the levels of the two and AMI, but there is little difference between petients with STEMI and NSTEMI. There was no significant difference between healthy people and SA patients. Ps and TpP may play a role in early detection of ACS, but they cannot distinguish between NSTEMI and STEMI.

The concentration of TpP in plasma reflects the activity of thrombin in circulation. The increase of TpP indicates that the fibrin monomer has polymerized, which indicates that the thrombus is about to form (and is an indicator of thrombus activity this is a repetition). Stimulated by hypoxia, free radicals, and thrombin, the expression of Ps increases, which mediates the adhesion of leukocytes and endothelial cells and plays a central role in thrombosis [14,15]. Therefore, in patients with ACS caused by thrombosis, the expression levels of TpP and Ps may be significantly up-regulated. TpP is of great significance not only for the early diagnosis but also for the severity and prognosis of ACS [16]. Thus, TpP cannot only be used for the diagnosis but also for the classification of ACS in the future.

In summary, through the detection of molecular markers of the prethrombotic state, the early diagnosis of ACS can be achieved. It provides crucial guidance for further decisions on treatment options in clinical work, reduces the risk of premature death, improves the survival rate of patients, and brings greater benefits to the clinical response in the occurrence of acute cardiovascular events.

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Concomitant acute lower extremity arterial and deep vein thrombosis developing in a patient under anticoagulant therapy after COVID 19 infection.

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Key words: Covid 19; thrombosis; hypercoagulability; thromboprophylaxis.

Abstract. The hypercoagulable state continues after the Coronavirus 2019 (Covid 19) infection and prophylactic anticoagulants are recommended in this period. However, arterial and venous thromboembolic events can be observed during the convalescence period after the Covid 19. Here, we present the case of acute lower extremity arterial and venous thromboembolism developed in the post-Covid 19 period in a 77-years-old patient, under therapeutic doses of anticoagulant therapy (enoxparin 1mg/kg of weight every 12 hours). The patient, who had no previous history of arterial or venous thrombosis, was taken to emergency surgery with the diagnosis of ALI (acute limb ischemia) due to acute arterial thrombosis. An arterial thrombectomy was performed with the help of a 4F Fogarty catheter inserted from the left femoral artery under local anesthesia. All distal pulses of the patient were palpable in the postoperative period. After the platelet count became >100,000 mm^3, 100 mg of acetylsalicylic acid daily was added to the therapeutic dose of enoxaparin sodium treatment. The patient was discharged, uneventfully, except for a minimal diameter increase secondary to deep venous thrombosis (DVT) on the fifth postoperative day, with a combination of enoxaparin and acetylsalicylic acid treatment. Endothelial injury, chronic immuno-thrombogenicity, and increased platelet aggregation in the post-Covid 19 recovery period can cause major thrombotic events, even weeks after the recovery. Anticoagulant therapy is recommended for thromboprophylaxis when the following statuses exist: ≥65 years, critical illness, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer. Combination treatment with long-term antiaggregant therapy may be prudent in thromboembolic events developed under anticoagulant therapy.

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Trombosis arterial aguda y trombosis venosa profunda concomitantes de extremidad inferior en un paciente bajo terapia anticoagulante después de infección por COVID 19.

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Palabras clave: COVID 19; trombosis; hipercoagulabilidad; tromboprofilaxis.

Resumen. El estado de hipercoagulabilidad continúa después de la infección por Coronavirus 2019 (Covid-19) y la anticoagulación profiláctica se recomienda durante este período. Sin embargo, eventos tromboembólicos arteriales y venosos se pueden observar durante el período de convalecencia posterior al Covid-19. Se presenta el caso de trombosis venosa profunda (TVP) y arterial agudas de una extremidad inferior en una paciente de 77 años, bajo terapia anticoagulante (enoxparin 1mg/kg de peso, cada 12 horas), en el período post-Covid 19. La paciente, sin historia previa de trombosis arterial ni venosa, fue llevada a cirugía de emergencia con el diagnóstico de isquemia aguda de extremidades por trombosis arterial aguda. Se le realizó trombectomía arterial con la ayuda de un catéter Fogarty 4F insertado desde la arteria femoral izquierda bajo anestesia local. Todos los pulsos distales del paciente fueron palpables en el periodo postoperatorio. Después de que las plaquetas llegaron a ser mayores a100.000 mm^3, 100 mg de ácido acetilsalicílico diarios se añadieron a la dosis terapéutica del tratamiento con enoxaparina sódica. La paciente fue dada de alta sin incidencias, excepto por un mínimo aumento de diámetro secundario a la TVP, al quinto día postoperatorio con la combinación de enoxaparina y ácido acetilsalicílico. La lesión endotelial, la inmunotrombogenicidad crónica y la agregación plaquetaria aumentada en el período de recuperación posterior a Covid-19 pueden causar eventos trombóticos importantes incluso semanas después de la recuperación. La combinación con terapia antiagregante a largo plazo puede ser prudente en los casos de eventos tromboembólicos desarrollados en pacientes con terapia anticoagulante.

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INTRODUCTION

Due to Coronavirus 2019 (Covid 19) infection, mostly pulmonary and cardiovascular complications develop. It has been demonstrated that patients with Covid 19 infection are in a hypercoagulable state, which causes arterial and venous thrombosis[1]. The hypercoagulable state continues after Covid 19, and long-term anticoagulant therapy is recommended for its treatment [2]. Acute limb ischemia (ALI) and venous thromboembolism are among the most common vascular complications seen after Covid 19 infection [1,3]. Especially in the patients that develop ALI, high amputation and mortality rates are reported [3].

Here, we present a case of concomitant lower extremity arterial and venous thrombosis that developed under anticoagulant therapy in the early period after Covid 19 infection. A written informed consent was

obtained from the patient for the report of the details and images related to her case.

CASE REPORT

On September 27, 2021, a 77-year-old female patient was referred to us from the emergency department of the Isparta City Hospital with complaints of tightness and swelling in the left leg that had been present for a day, and sudden coldness, pallor, and severe pain below the knee for the last two hours. As a result of physical examination, signs of coldness, pallor, prolongation of capillary refill time, tightness, increase in diameter and Homans sign were found in the left lower extremity (Fig. 1). While all pulses were palpable in the right lower extremity, only the femoral pulse was palpable in the left lower extremity. Monophasic flow pattern was determined with manual Doppler in the popliteal artery, but flow could not be determined with manual Doppler in the distal pulses. An electrocardiogram revealed sinus tachycardia at a rate of 105 per minute. Urgent blood test results were found as follows: white blood cell 10,720/mm^3 (normal range <10,000), lymphocyte 680/mm^3 (normal range 800-4,000), eosinophil 10/mm^3 (normal range 20-50), platelet 84,000/mm^3 (normal range 100,000-400,000), hemoglobin 9.5 g/dL (normal range 12-16), D-dimer value 0.92 mg/L (normal range 0-0.55), prothrombin time 12.4 seconds (normal range 10.5-14.5), activated partial thromboplastin time 21.6 seconds (normal range 21.6-35), and international normalized ratio 1.11 (normal range 0.8-1.2). Other biochemical parameters were found normal. A computed tomography angiogram (CTA) taken on the patient revealed an intraluminal thrombus extending from the distal part of the left superficial femoral artery to the tibioperoneal trunk (Figs. 2a, 2b). In addition, calibration increases were observed in the main and superficial femoral veins (Fig. 2c). Acute deep venous thrombosis (DVT) extending from the popliteal vein to the external iliac vein was determined by venous Doppler ultrasound.

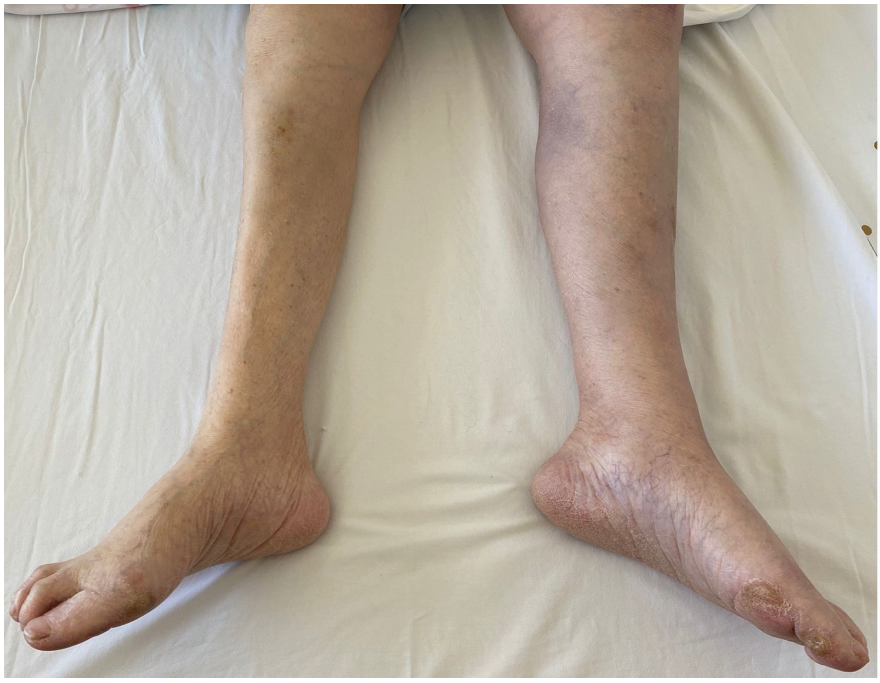

Fig. 1. Significant increase in the diameter and cyanotic areas in patches in the left lower extremity.

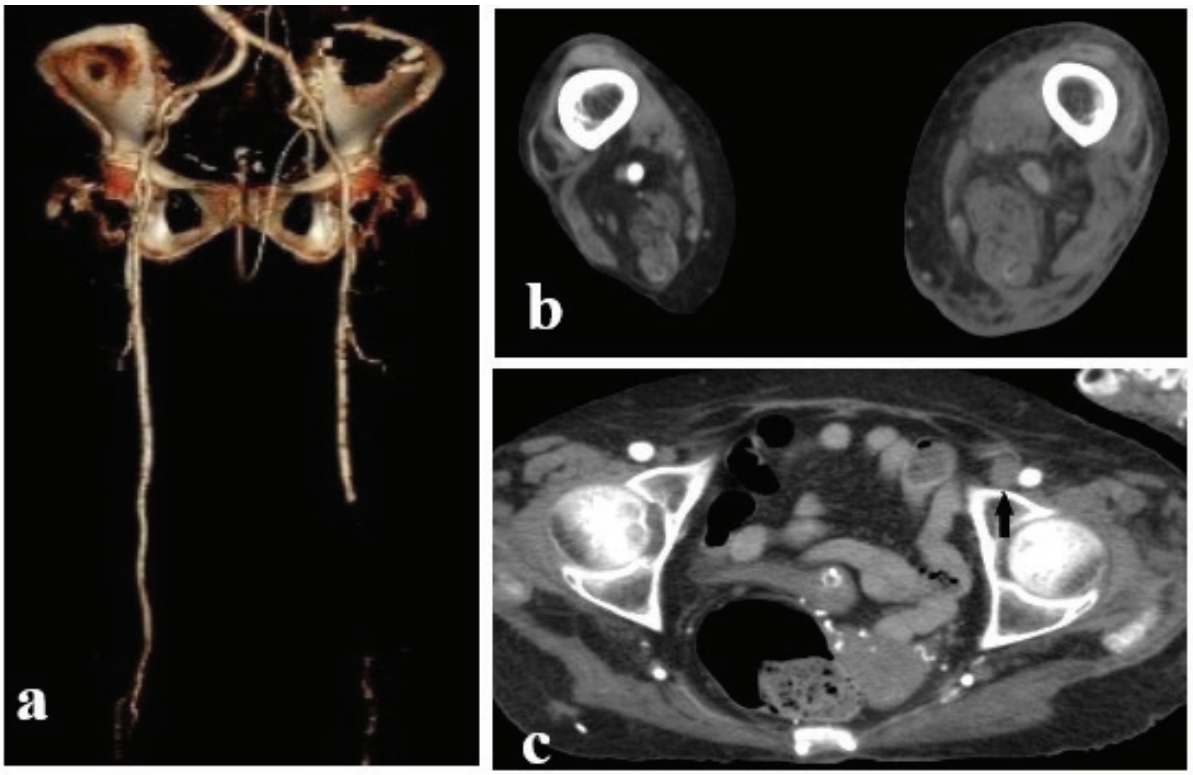

Fig. 2. Computed tomography angiogram a) and b) acute thrombus material in the left superficial femoral artery c) Calibration increase in the left common femoral vein due to acute thrombus material.

In the patient's medical history, there was a diagnosis of Covid 19 pneumonia confirmed by reverse transcription-polymerase chain reaction test and chest computed tomography 36 days before the thrombotic event. After 21 days of intensive care and 11 days of chest diseases service follow-up, the patient was discharged from the hospital a with therapeutic dose of enoxaparin sodium treatment (1mg/kg of weight every 12 hours) (Fig. 3). D-dimer value was found as 0.78 mg/L (normal range 0-0.55) and platelet was found as 202,000 mm3 (normal range 100,000-400,000) at discharge. The patient had not been vaccinated against Covid 19 infection prior to the event.

The patient, who had no previous history of arterial or venous thrombosis, was taken to emergency surgery with the diagnosis of ALI due to acute arterial thrombosis. An arterial thrombectomy was performed with the help of a 4F Fogarty catheter inserted from the left femoral artery under local anesthesia. The catheter was introduced to a 70 cm distal length. Abundant and fresh thrombus material was removed. All distal pulses of the patient were palpable in the postoperative period. After the platelet count became >100,000 mm3, 100 mg of acetylsalicylic acid daily was added to the therapeutic dose of enoxaparin sodium treatment. Leg elevation was applied. The patient was discharged from the cardiovascular surgery service uneventfully on the fifth postoperative day with the combination of enoxaparin and acetylsalicylic acid, except for a minimal diameter increase secondary to DVT.

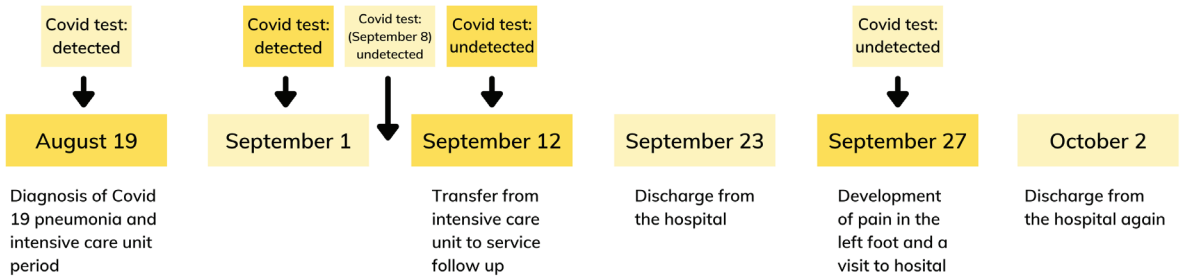

Fig. 3. Timeline of patient of this article.

DISCUSSION

Apart from pulmonary involvement, coagulopathy and cardiovascular effects, which cause significant increases in morbidity and mortality rates due to Covid 19 infection, are relatively common [4]. As detected in our case, increased fibrin degradation products, as well as high D-dimer and low platelet levels, may be an indicator of thrombotic complications that develop or may develop [5].

ALI is less common than venous thrombosis in patients with Covid 19. ALI due to arterial thrombosis can be seen after Covid 19 infection as well as during the acute infection period. Borrelli et al. reported cases of arterial thrombosis that developed 15-45 days after respiratory symptoms in the patients whose Covid 19 treatment was completed and nasopharyngeal swab test was negative [6], and Bozzani *et al* reported cases of arterial thrombosis that developed after 41-149 days in the patients with the same conditions [7]. In our case, the swab test was negative during the convalescence, and arterial and venous acute thrombosis was detected under therapeutic dose of anticoagulant therapy on the 19th day.

Virchow's classic triad for thrombosis consist of stasis, endothelial injury, and a hypercoagulable state. Hypercoagulability and stasis particularly affect acute thrombogenesis. This may play a lesser role in the arterial and venous events seen in convalescent Covid 19 patients. The most important mechanism here may be endothelial injury and dysfunction. The multisystem inflammatory syndrome, which includes myocarditis and inflammatory vasculopathy and seen in the recovery period after Covid 19 in children, is an indicator of endothelial dysfunction and injury [8]. Chronic immuno-thrombogenicity, which develops and accumulates especially after mild or asymptomatic Covid 19 infection, may also cause major thrombotic events even weeks later [2]. Another cause of thrombogenicity may be increased platelet aggregation. Zaid *et al* showed severe acute respiratory syndrome coronavirus 2 RNAs and high platelet-associated cytokine levels in platelets in their 115 cases studied. In this study as well, platelet aggregation occurred at lower concentrations of thrombin than it was expected [9].

There is no consensus on long-term thromboprophylaxis following Covid 19 infection. Guidelines for COVID 19 are derived from recommendations in medically ill populations. Although therapeutic doses of low molecular weight heparin (LMWH) have been recommended for the patients with Covid 19 and standard thromboprophylaxis, by taking the high incidence of venous thromboembolism (VTE) into consideration, the American College of Chest Physicians recommends standard prophylactic LMWH due to the lack of clinical trial data [10]. On the other hand, the International Society on Thrombosis and Hemostasis (ISTH)

guidelines recommend thromboprophylaxis with LMWH and a direct oral anticoagulant (DOAC) in patients with low bleeding and high VTE risks. ISTH has identified as high-risk factors the age older than 65 years, critical illness, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer. The ISTH suggests a duration of 14 to 30 days for post discharge thromboprophylaxis, although optimal duration remains unclear [11]. Although prophylaxis was initiated with a therapeutic dose of LMWH treatment in our case, who was considered with high risk due to high D-dimer level and advanced age, antiaggregant agent was added to the treatment in the postoperative period, considering possible increased platelet aggregation due to the simultaneous occurrence of arterial and VTE.

More systematic, randomized controlled studies on Covid 19-related thrombosis are needed. Results of ongoing clinical trials, such as the ACTIV-4 trial (NCT04498273), which have specifically evaluated prophylactic antiaggregant and anticoagulant therapy, are awaited.

In conclusion, anticoagulant agents and thromboprophilaxis should be considered especially in high-risk patients after Covid 19 infection. The combination of anticoagulant and antiaggregant prophylaxis should also be kept in mind in patients with low bleeding risk. It may be rational to add a long-term antiaggregant to the treatment, especially in thromboembolic events developed under anticoagulant therapy.

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Epidemiología del virus del papiloma humano.

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Palabras clave: virus del papiloma humano; taxonomía; nomenclatura; epidemiología; cáncer de cuello uterino; cáncer de vulva; cáncer de vagina.

Resumen. La presente revisión narrativa fue realizada con el objeto de investigar y recopilar la información más reciente y relevante sobre la epidemiología del Virus del Papiloma Humano y su relación con las patologías asociadas a él, en especial la patología maligna del área genital femenina. La revisión de la literatura fue realizada electrónicamente en PubMed, Medline, ISI, DOAJ, Springer, Embase. Web of Knowledge, DOAJ, y Google Scholar para los artículos escritos en el idioma inglés. Los portales Scielo, Latindex, Imbiomed-L, Redalyc y Google Scholar fueron revisados en búsqueda de artículos escritos en el idioma español. La búsqueda incluyó las palabras claves: epidemiología del virus del papiloma humano, taxonomía viral, estructura del virus del papiloma humano, clasificación del virus del papiloma, nomenclatura del virus del papiloma humano, patologías asociadas al virus del papiloma humano, virus papiloma humano y cáncer del cuello uterino, virus del papiloma humano y cáncer de vulva, y virus del papiloma humano y cáncer de vagina. Se buscaron, revisaron y analizaron las publicaciones desde enero de 1987 hasta agosto de 2021. Esta revisión narrativa investigó la epidemiología del virus del papiloma humano y sus patologías asociadas, en especial las malignas del área genital femenina.

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Epidemiology of human papillomavirus.

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Key words: human papillomavirus; taxonomy; nomenclature; epidemiology; cervical cancer; vulvar cancer; vaginal cancer.

Abstract. The present narrative review was conducted to investigate and to compile the most recent and relevant information about the epidemiology of the Human Papilloma Virus and its relationship with the pathologies associated with it. Literature searches were performed electronically in PubMed, Medline, ISI, DOAJ, Springer, Embase. Web of Knowledge, DOAJ, and Google Scholar for original articles written in the English language and Scielo, Latindex, Imbiomed-L, Redalyc, and Google Scholar for original articles written in the Spanish language. The searches included the keywords: epidemiology of human papillomavirus, viral taxonomy, the structure of human papillomavirus, classification of human papillomavirus, the nomenclature of human papillomavirus, pathologies associated to human papillomavirus, human papillomavirus and cervical, human papillomavirus and vulvar cancer and human papillomavirus and vaginal cancer Publications from January 1987 to August 2021 reviewed. This narrative review researched the epidemiology of the human papillomavirus and its pathologies associated especially the female genital area.

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INTRODUCCIÓN

Los virus del papiloma (VPs) son virus muy antiguos que infectan a los vertebrados como los mamíferos, peces, reptiles, y aves. Muestran una gran diversidad genotípica y una amplia variación en la presentación fenotípica de la infección[1]. Los VPs tienen preferencia para infectar epitelios escamosos diferenciados o estratificados y en los humanos, la piel es uno de ellos[2]. Las lesiones cutáneas producidas por los VPs fueron mencionadas previamente por los griegos y los romanos[2]. La palabra papiloma viene del latín moderno papilloma, término formado por papilla, "pezón de mama de mujer", que a la vez es el diminutivo de pápula, que se traduce como "inflamación que adopta la forma de una protuberancia en forma de pezón", y el sufijo castellano "oma", derivado del griego "omá", en este caso con el significado de tumor, como en melanoma, mieloma, etc. Probablemente esta voz latina se vincule con la vieja raíz indoeuropea "pap", "hincharse", de la que quizá derivaron: "pippalaka" en sánscrito, hace unos 2500 años y la palabra latina "pappa", muy difundida en el lenguaje infantil como "comida", imitando el sonido que emite un niño cuando tiene hambre; en la lengua griega pappas, "padre y pappos, abuelo, pappe, teta", en el idioma inglés de los años 1100 a 1500 d.C.; o "pap", en el alto germano hablado entre los siglos XII y XVI d.C.; "papas", en lituano; "pape", en el antiguo francés (siglos IX al XIV d.C.), una especie de alimento acuoso a base de cereales y carne; y "papa" en español y portugués. Existen registros de que "papilla y su plural

papillae", ya aparecían en escritos médicos a finales del siglo XVII, mientras que papula, como inflamación, hacia los inicios del siglo XVIII, y papiloma entre 1855 y 1870. De este modo, papiloma (papilloma) se traduce como "tumor en forma de pezón o tetilla". La palabra "papilomatosis" deriva de la palabra "papilloma, papillomat", más el sufijo griego "osis", que denota enfermedad[3].

Los VPs pertenecen a la familia *Papillomaviridae* y son una familia de virus pequeños, heterogéneos, con 55 nm de diámetro, no envueltos con un genoma de doble cadena de ADN (ADNc) con 5.748 a 8.607 pares de bases (bp) y está compuesto en aproximadamente en un 42 % de Guanina-Citosina (36%-59%). Los VPs pueden infectar epitelios mucosos y queratinizados y puede coevolucionar con su huésped sin producir enfermedad, sin embargo, algunos de estos virus son patógenos capaces de intervenir en la producción de cáncer[4,5]. En los viriones no se han encontrado componentes de naturaleza lipídica ni glucídica y contienen el ADNc[4-6]. La cápside viral o envoltorio que cubre o protege el ADNc tiene aproximadamente 600 Å de diámetro y consiste de 360 copias arreglados en 72 capsómeros arreglados a su vez en un enrejado icosahedral[7-10]. Cada capsómero es un pentámero compuesta por 2 proteínas: la proteína mayor o L1 y la proteína menor o L2. La proteína L1 contiene 5 monómeros de 55-kDa y, la proteína L2 tiene 12 copias de 74-kDa, posiblemente asociadas con 12 capsómeros pentavalentes[7,10,11]. Cada cápside envuelve una copia del ADNc asociado a las histonas centrales: histonas H2a, H2b, H3 y H4[12-14]. El genoma de los VPs en especial los que afectan al humano ha sido dividido en tres regiones principales: 1- La región reguladora no codificante de aproximadamente entre 400 a 1.000 bp, la cual se denomina región no codificante o región larga de control (LCR) o región reguladora superior (URR); esta región pose el promotor principal p97 junto con la secuencia del potenciador o aumentador y del silenciador que regulan la replicación del ADN a través del control de la transcripción de los marcos de lectura abiertos (ORF) y esta región posee el más alto grado de variación en el genoma viral; 2- La región que incluye genes de expresión temprana (E), como los ORF E1, E2, E4, E5, E6 y E7 que intervienen en la replicación del virus y dan origen a proteínas no estructurales y, 3- La región que contiene los genes de expresión tardía (L), que dan origen a dos proteínas estructurales de la cápside viral L1 y L2[15-17]. En total se encuentran 9 ó 10 ORFs y en todos los papilomavirus están localizados en una sola de las 2 cadenas del ADN genómico[12,16]. La LCR contiene elementos de respuesta para factores de transcripción celulares, tales como AP1, SP1, Oct1, etc., así como para las proteínas virales E1 y E2, que controlan la replicación y la expresión del genoma viral. En algunos papilomavirus se pueden identificar dos ORF denominados E3 y E8[18]. Las proteínas codificadas en el genoma que forman parte de la estructura de la cápside del virión son solo dos: L1 y L2. Las demás proteínas virales cumplen diferentes funciones durante el ciclo replicativo del VPH. En la Tabla 1 se pueden observar las proteínas codificadas en el genoma del virus y sus funciones.

La clasificación de los papilomavirus ha sido algo complicada debido a varios factores. A diferencia de otros virus, los papilomavirus no generan una respuesta inmunitaria humoral adecuada y persistente, tanto en humanos como en otros mamíferos, por lo cual no ha sido posible desarrollar un sistema de clasificación por serotipos, a lo que se agrega la ausencia de modelos de infección celulares o de animales de laboratorio[5,12]. Para la clasificación de los PVs se han tomado dos criterios básicos: a) el huésped, estos virus son altamente específicos de especie, y, b) la secuencia genética, que permite la diferenciación entre los virus aislados; la secuencia más utilizada para la clasificación de los papilomavirus es la del gen L1. Se establece un nuevo tipo de VP cuando la secuencia del gen L1 varía en más de 10% respecto a tipos virales ya conocidos. Si la diferencia es de 2 a 10 %, se les

Tabla 1
Funciones de las proteínas del VPH.

No estructurales	**E1.** Esencial para la replicación y transcripción.
	E2. Esencial para la replicación, segregación genómica y encapsidación.
	E4. Regula la expresión de genes tardíos, controla la maduración viral y la salida de los viriones.
	E5. Estimula la actividad transformante de E6 7 E7, promueve la fusión celular originando aneuploidía e inestabilidad inestabilidad cromosómica y contribuye a la evasión de la respuesta inmunitaria.
	E6. Se une e induce la degradación de la p53 inhibiendo la apoptosis, interactúa con proteínas del sistema inmunitario innato, contribuye a la evasión de la respuesta inmune y a la persistencia del virus, activa la expresión de la telomerasa.
	E7. Se une e induce la degradación de la pRB, incrementa la actividad de las cinasas dependientes de ciclinas, afecta la expresión de los genes de la fase S por interacción directa de factores de transcripción E2F y con la histona deacetilasa, contribuye a la evasión de la respuesta inmune.
Estructurales	**L1.** Proteína principal o mayor de la cápside. Reconoce los receptores de la célula huésped, es latamente inmunogénica e induce anticuerpos neutralizantes.
	L2. Proteína secundaria o menor de la cápside, participa en la unión y en la entrada del virión a la célula y en el transporte al núcleo, en la liberación del genoma y ensamble de los viriones.

E: Early o temprana; L: late o tardía.

clasifica como subtipos virales y si la diferencia es menor a 2% se definen como variantes virales[19,20]. En los primeros VPs se empezó a utilizar la palabra tipo y un número, para denominar a los diferentes virus descubiertos, lo cual puede llevar a pensar que un tipo es equivalente a una especie de VPs[15,21].

Los virus de la familia *Papillomaviridae* fueron clasificados inicialmente como una subfamilia de los *Papovaviridae* en 1962, pero se reclasificaron en 2002 como una familia independiente. De acuerdo al International Committee on Taxonomy of Viruses (ICTV) en su actualización del 2020, la familia *Papovaviridae* está dividida en 2 subfamilias: la *Firstpapillomaviridae* y la *Secondpapillomaviridae*. La subfamilia *Firstpapillomaviridae* tiene 53 géneros y 133 especies y la subfamilia *Secondpapillomaviridae* tiene 1 genero[22-25] (ver Tabla 2).

En relación a los VPs que afectan al humano, Virus del Papiloma Humano (VPH) el Centro Internacional de Referencia del Virus del Papiloma Humano del Instituto Karolinska ha reportado hasta el 2021, la identificación de 228 diferentes tipos de VPHs. Los VPH que afectan el área genito-anal pertenecen al género *Alphapapillomavirus*; este género ha sido dividido en dos grupos: los de bajo riesgo, que se asocian principalmente con verrugas genitales benignas y los de alto riesgo que se asocian y consideran por su alto potencial oncogénico como agentes etiológicos del cáncer del cuello uterino, vagina, vulva, pene y ano[12,20].

MATERIAL Y MÉTODOS

Se realizó la búsqueda en las páginas electrónicas de Pub Med, Google Scholar,

Tabla 2
Sub-Familia *Firstpapillomaviridae*.

Géneros	
1	*Alphapapillomavirus*
2	*Betapapillovirus*
3	*Chipapapillomavirus*
4	*Deltapapillomavirus*
5	*Dyochipapillomavirus*
6	*Dyodeltapapillomavirus*
7	*Dyoepsilonpapillomavirus*
8	*Dyoetapapillomavirus*
9	*Dyoetapapillomavirus*
10	*Dyoiotapapillomavirus*
11	*Dyokappapapillomavirus*
12	*Dyolambdapapillomavirus*
13	*Dyomupapapillomavirus*
14	*Dyonupapapillomavirus*
15	*Dyoomegapapillomavirus*
16	*Dyoomiokronpapillomavirus*
17	*Dyophipapillomavirus*
18	*Dyopipapillomavirus*
19	*Dyopsipapillomavirus*
20	*Dyorhopapillomavirus*
21	*Dyosigmapapillomavirus*
22	*Dyotaupapillomavirus*
23	*Dyothetapapillomavirus*
24	*Dyoupsilonpapillomavirus*
25	*Dyoxipapillomavirus*
26	*Dyozetapapillomavirus*
27	*Epsilonpapillomavirus*
28	*Etapaillomavirus*
29	*Gammapapillomavirys*
30	*Iotapapillomavirus*
31	*Kappapapillomavirus*
32	*Lambdapapillomavirus*
33	*Mupapapillomavirus*
34	*Nupapillomavirus*
35	*Omegapapillomavirus*
36	*Omikronpapillomavirus*
37	*Phipapapillomavirus*
38	*Pipapillomavirus*
39	*Psipapillomavirus*
40	*Rhopapillomavirus*
41	*Sigmapapillomavirus*
42	*Thaupapillomavirus*
43	*Thetapapillomavirus*
44	*Treisdeltapapillomavirus*
45	*Treisepsilonpapillomavirus*
46	*Treisetapapillomavirus*
47	*Treisiotapapillomavirus*
48	*Treiskappapapillomavirus*
49	*Treisthetapapillomavirus*
50	*Treiszetapapillomavirus*
51	*Upsilonpapillomavirus*
52	*Xipapapillopmavirus*
53	*Zetapapillomavirus*

Sub-Familia *Secondpapillomaviridae*.

Género
Alphapapillomavirus

Springer, Web of Knowledge, DOAJ, Hinari, Oxford Academic, JAMA Network, Embase, Research Life en la literatura de habla inglesa y en Scielo, Latindex, Imbiomed-L, Redalyc y Google Scholar en la literatura de habla española. Se emplearon los términos y/o palabras claves (DeCS/MESH): epidemiologia del virus del papiloma humano, taxonomía viral, estructura del virus del papiloma humano, clasificación del virus del papiloma, nomenclatura del virus del papiloma humano, patologías asociadas al virus del papiloma humano, virus del papiloma humano y cáncer del cuello uterino, virus del papiloma humano y cáncer de vulva, y virus del papiloma humano y cáncer de vagina. La búsqueda se realizó usando palabras solas o usando la combinación de AND/Y o OR/O. Dentro de los criterios de inclusión se consideraron: a) artículos de fuentes primarias publicados en revistas indexadas, con naturaleza de revisión, artículos originales de investigación, estudios comparativos, estudios de evaluación, capítulos de libros y meta-análisis de acceso abierto; b) artículos en idioma inglés y español. Fueron excluidos de la revisión: cartas al editor, reportes de casos y estudios sin control. Igualmente, fueron excluidas las publicaciones que no tenían libre acceso. Cuando se encontraron dos publicaciones con la misma población estudiada, se analizó la publicación más reciente o con mayor número de pacientes estudiados. Se revisaron los artículos publicados desde el año 1995 hasta junio de 2021.

Se encontraron 452 artículos durante la búsqueda primaria de la investigación. Se excluyeron 325 de ellos por no poseer acceso libre al texto completo y no reunieron ciertos criterios de inclusión para la revisión. De los 127 artículos para la revisión y consulta del texto completo, 65 fueron elegidos para la revisión, los restantes 62 fueron excluidos por no reunir los criterios de inclusión. Se encontraron 19 artículos repetidos por lo que los restantes 46 artículos fueron revisados para la elaboración del artículo de revisión narrativa.

Epidemiología del VPH

Los estudios epidemiológicos realizados en la última década sobre el VPH han demostrado que es la enfermedad de transmisión sexual más común y diseminada en el mundo[26,27]. Chesson y col.[28] estimaron que la mujer y el hombre tienen una probabilidad del 49,1% de adquirir el VPH desde su inicio de la actividad sexual hasta los 44 años, teniendo un solo compañero y hasta un 99,9% de probabilidad cuando el número de parejas sexuales es mayor de 5, con un promedio de 80,9% para las mujeres y un 89,1% para los hombres. Los mismos autores[28] reportaron que el riesgo promedio de adquirir una infección por VPH desde su debut sexual hasta los 70 años es del 82,2% al 86,2% en las mujeres y del 89,9% al 92,2% en los hombres; siendo un 100% de probabilidad en aquellas personas que tuviesen más de 15 parejas sexuales durante el año. Sin embargo, muchas de estas infecciones son transitorias y no presentan ningún impacto clínico; en las mujeres se estima que el 90% de las infecciones por el VPH son eliminadas o aclaradas en un 90% en un término de 2 a 3 años[26,29,30]. Ochoa-Carrillo[22] ha mencionado que el 42,5% de las mujeres en el mundo tienen la presencia del VPH en cualquier momento de su vida. Bruni y col.[26,31] reportaron que un promedio de 11,7% (rango: 6,1%-35,5% dependiendo del área geográfica del mundo y de la edad) de la población femenina a nivel mundial con citologías cérvico-vaginales normales (CCV), presenta la infección del VPH.

La prevalencia del VPH en las mujeres con CCV negativa está muy asociada a la edad. Bruni y col. [26] han reportado que hay 3 patrones de distribución de la infección por el VPH de acuerdo a la edad; en el primer patrón, muy similar en casi todos los países desarrollados del mundo, ocurre una elevación de la prevalencia dentro del primer año del comienzo de la actividad sexual, generalmente durante la adolescencia y la década entre 20 a 30 años, generalmente en personas de 25 o menos años, para comenzar a

descender y estabilizarse, formando una meseta o *plateau* a partir de los grupos etarios de edad mediana. El otro patrón de comportamiento de la infección por VPH es aplanado a través de todos los grupos etarios, y se observa en los países asiáticos en especial India. El tercer patrón bimodal consiste en una primera elevación de la prevalencia en el primer año del comienzo de la actividad sexual, seguido de una meseta o *plateau* en las edades medias de la vida de la mujer y una segunda elevación o repunte de la prevalencia de la infección después de los 40 años; este patrón se observa sobre todo en el continente americano y africano[26,31].

Alrededor del mundo, el pico de la infección por VPH se observa en mujeres jóvenes, menores de 25 años, y comienza a declinar hasta que llegan a la madurez cuando se alcanza el *plateau* o meseta de la infección; sin embargo, en Centro y Suramérica, se observa un segundo pico en mujeres alrededor de los 40 años y en África Occidental alrededor de los 55 años. Este segundo repunte es menos acentuado en el Sur-Este Asiático, Sur de Europa, y Sur de África; en el resto de las regiones del mundo no se observa este repunte[31].

Como se mencionó anteriormente para el año 2010, la prevalencia de la infección del VPH en mujeres con CCV negativas era 11,7% (rango:11,65% a 11,7%): para los países o regiones subdesarrollados es 11,8% (rango:11,6% a 12,0%) y para los países o regiones desarrollados es 11,3% (rango:11,2% a 11,3%). Para el continente africano la prevalencia es 21,1% (rango: 20,2% a 22,0%), siendo la región del África del Este la que presenta la mayor prevalencia con 33,6% (rango: 30,2% a 37,1%). El continente asiático presenta una prevalencia de 9,4% (rango: 9,2% a 9,6%), el sureste asiático presenta la prevalencia más elevada de la región con 14,0% (rango: 13,0% a 15,0%) y la parte occidental del continente como Turquía, Bahréin, y Emiratos Árabes Unidos presenta la prevalencia más baja del mundo con 1,7% (rango: 1,1% a 2,5%). Europa presenta una prevalencia del 14,2% (rango: 14,1% a 14,4%). Europa del Este presenta la prevalencia más elevada del continente europeo con 21,4% (rango: 20,1% a 22,7%). El continente americano presenta una prevalencia de 11,5% (rango: 11,4%–11,6%) y el área o región del Caribe presenta le prevalencia más elevada de la región con 35,4% (rango: 29,0% a 42,2%) y la región de Norteamérica presenta la prevalencia más baja del continente con un 4,7% (rango: 4,6% a 4,7%). En Venezuela, Núñez-Troconis y col.[32] reportaron una prevalencia del 14,6% de infección del VPH en CCV negativas, sin embargo, en el 2017, Toro y López[33] reportaron una presencia de la infección del VPH en el 28,5% en mujeres con CCV negativas para malignidad.

El VPH puede llegar a afectar hasta 20% de la población en un momento dado; la incidencia de la infección varía dependiendo del tipo de VPH, del grupo etario de la población y la predilección del virus por el tejido mucoso o el tejido cutáneo[22,34]. Este tipo de infección afecta al 10.4% de la población femenina, alrededor del mundo. Diferentes autores[34,35] han mencionado que los VPH que afectan el área ano-rectal también están asociados a lesiones verrugosas no malignas en piel y mucosa.

En 2019, Bruni y col.[36] reportaron una prevalencia ajustada actualizada de la infección del VPH de un 9,9% a nivel global. McQuillan y col.[37] reportaron en los Estados Unidos de Norteamérica (EEUU) para los 2013 y 2014 una prevalencia de cualquier tipo de VPH genital del 42,5% en los adultos comprendidos entre los 18 a 59 años de edad, independientemente de los resultados de la CCV: 45,2% de prevalencia en los hombres y 39,9% en las mujeres. En el año 2009, Núñez-Troconis[38] reportó en una prevalencia del VPH del 15,6% en Venezuela.

Basados en su capacidad oncogénica los VPH se han clasificado en bajo y alto riesgo. Entre los de bajo riesgo (BR) tenemos que los VPH: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, y CP6108 se asocian con el condiloma acuminado, la neoplasia intraepitelial

de bajo grado y las infecciones asintomáticas. Entre los de alto riesgo (AR) tenemos los VPH: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 y 82. Hay tres tipos de VPH de probable alto riesgo: 26, 53 y 66 que se relacionan con el cáncer del cuello uterino, vagina y vulva[12,22].

Los genotipos de BR más comunes en el continente americano y europeo son el 6 y el 11, aunque son menos frecuentes en África y Asia[39]; el VPH 6 es el más común de los tipos de BR en el continente americano: 0,9% en Latinoamérica y 2% en Norteamérica; es menos frecuente en Asia con un 0,2%.

Los tipos de VPH más comunes a nivel mundial, en mujeres con CCV normal son los tipos de AR o de mayor capacidad oncogénica, tales como los tipos 16, 18, 52, 31, 58, 39, 51, y 56. McQuillan y col.[37] reportaron en EEUU que la prevalencia de los VPH-AR fue de 22,7% en adultos en edades comprendidas entre los 18 y 59 años: 25,1% de prevalencia en los hombres y 20,4% en las mujeres. A nivel mundial, se estima que el 22,5% (95% intervalo de confianza: 21.9% a 23.2%) de las infecciones producidas por el VPH, es a causa del VPH-16. Las regiones del mundo que tienen menor incidencia de infecciones por el VPH-16 son África del Sur con 13,7%, África del Este con 11,3% y África del Oeste con 11,1%; le siguen Norteamérica con 24,3%, Oeste de Europa con 24,4%, el Sur de Europa con 28,9% y el Sureste Asiático con el porcentaje más alto con 32,3%[31]. El VPH de AR más frecuente después del VPH-16 a nivel internacional es el 18 y, el VPH-45 es el menos frecuente con un 0,5% entre los VPH-AR. El VPH-31 es especialmente más frecuente en Europa con un 2,3%; el VPH-52 se encuentra en un 2,3% en Norteamérica, un 2,4% en África y en un 0,7% en Asia[31].

Patologías asociadas al VPH

Los VPHs se dividen en 2 grupos de acuerdo a su preferencia epitelial: 1. los que afectan el epitelio cutáneo o la piel y 2. los que afectan los epitelios cutáneos mucosos[2]. Los VPHs que afectan a la piel o epitelio cutáneo pertenecen al género beta y algunos miembros de los géneros gamma, mu y un, mientras que al género alfa pertenecen los que afectan los epitelios mucosos y algunos que afectan el epitelio cutáneo[2,21]. También han sido agrupados de acuerdo al área del cuerpo donde producen la infección: 1. región de la piel; 2. región ano-genital y 3. región oral. A su vez, los VPHs que afecta los epitelios muco-cutáneos han sido subdivididos en BR, principalmente asociados con las verrugas y los AR, que son los VPHs asociados a procesos malignos.

Las infecciones por el VPH puede ser clínicas, sub-clinicas y latentes tanto en la piel como en las áreas muco-cutáneas. Las lesiones clínicas son las que pueden ser observadas como las verrugas. Las sub-clinicas son aquellas que necesitan elementos adicionales para su diagnóstico tales como aplicaciones de ácido acético, colposcopia del cuello uterino, anoscopia de canal anal y estudios microscópico de las lesiones. Las infecciones latentes se detectan con la demostración de la presencia del ADN del VPH en muestras clínicas de piel o mucosas histológicamente normales[2].

Las lesiones clínicas están asociadas con la expresión genética completa del virus y la producción de partículas virales completas y cuando la infección se hace persistente, las funciones celulares normales son anuladas o abolidas y se interrumpen los eventos tardíos en el ciclo de vida del virus.

Aproximadamente el 70% de las infecciones por VPHs se resuelven o curan espontáneamente en 1 año y el 90% en un plazo de 2 a 3 años[26,29,30,40]. El aclaramiento o cura del virus depende de una respuesta inmune celular efectiva y adecuada, mientras que en las infecciones persistentes existe una falla en la respuesta inmune celular contra el virus, y en el caso de los VPH-AR se traduce en el riesgo de progresión de la infección hacia lesiones cancerosas[41].

En la Tabla 3 se puede observar las patologías producidas por el VPH y los tipos involucrados.

Tabla 3
Patologías asociadas al VPH.

Enfermeted	Patología	Tipos de VPH más frecuentemente asociados
Verrugas Comunes		2,4,7
Verrugas Planas		3,10 en ocasiones: 26,27,28,29,41
Verrugas Plantar		1,2,4
Epidermodisplasias Verruciformes	Verrugas Planas	3,10
	Placas parecidas a Pitiriasis	5,8; menos comunes 9,12,14,15, 17, 19,20, 21–25, 36–39, 47,49
	Carcinoma Escamo-celular por exposición al sol	5, 8, menos comunes 14,17,20,47
Verrugas Anogenitales	Verrugas Externas	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89
	Papilomas del Cuello Uterino	6,11
	Tumor de Buschke–Lowenstein	6
	Papulosis Bowenoide	16,55
Precanceres y Cánceres Anogenitales	Grupo 1: Carcinogénicos para los Humanos	16,18, 31, 33, 45, 51, 52
	Grupo 2A: Probablemente Carcinogénicos para los Humanos	68
	Grupo 2B: Posiblemente Carcinogénicos para los Humanos	26, 53, 64, 65, 66, 67, 69, 70, 73, 82
Lesiones Orales	Papilomas Orales	2,6,7,11,16,18,32,57
	Papilomas Laríngeos	6,11
	Hiperplasia Focal (Enfermedad de Heck	13,32
	Carcinoma Orofaríngeo	16,18

Cánceres asociados al VPH

Los canceres asociados al VPH en el área genital del sexo femenino se ubican, como se mencionó anteriormente, en vulva, vagina y cuello uterino.

Según la Agencia Internacional para la Investigación del Cáncer (IARC) para el año 2018, el VPH causó el 31,1% de los cánceres para ambos sexos alrededor del mundo, representando la segunda causa de tipo infeccioso causante de cáncer (CA) después del *Helicobacter pylori* (36,3%). En el continente africano representó la primera causa con un 48,4% de todos los CAs; en Asia fue la segunda causa con el 24,4%; en Europa ocupó el segundo lugar con 38,6% y en Oceanía y el continente americano fue la primera causa con un 46,9% y un 43,6%, respectivamente[42].

Según la misma agencia, el VPH fue la primera causa de CAs atribuibles a infecciones a nivel mundial para el sexo femenino con un 56,1% de los canceres. Asimismo, representó la primera causa de CA para el sexo femenino en todos los continentes: África: 71,4%, Asia: 50,3%, Europa: 56,8%; Oceanía: 67,9% y América: 63,4%[42].

En lo que respecta nuestro continente, la zona del Caribe ocupa el primer lugar con una incidencia del 67,2%, Suramérica con

64%, Norteamérica con 60,6% y Centroamérica con 60,3%[42].

De acuerdo a la IARC, el VPH representó el 71,7% de las causas de CA producidas por infecciones en el sexo femenino en los países con bajo nivel de ingresos; para los países de bajo a medianos ingresos fue el 72,8%, en los países de medianos a elevados ingresos fue del 46,3% y en los países de ingresos elevados representó el 45,7%[42].

El Centro para el Control y Prevención de Enfermedades de EEUU (CDC) reportó un promedio de 45.330 casos de CAs asociados al VPH entre los años 2013 y 2017; 25.405 casos ocurrieron en mujeres y 19.925 en hombres; el 96% de ellos, se debieron a VPH-AR [43,44].

Cáncer de Vulva

El 43% de los CAs de vulva a nivel mundial son atribuibles al VPH. La vulva tiene 2 tipos histológicos de CAs con factores de riesgo diferente: 1. el tipo verruga basaloide y 2. el tipo queratinizante. Los primeros son más comunes en mujeres jóvenes y se consiguen generalmente con una lesión intraepitelial vulvar adyacente (NIV) y en un 86% están asociados al VPH, y tienen factores de riesgo muy similares a los del cáncer del cuello uterino (CaCu). Los tipos queratinizantes representan la mayoría de los canceres de vulva (CaV), en más del 60%; estas lesiones se originan a partir de lesiones crónicas vulvares como el liquen escleroso y la hiperplasia escamosa. Sus precursores VIN son lesiones más diferenciadas y no están relacionadas con la infección del VPH. Estas lesiones cancerosas son más frecuentes en mujeres de mayor edad y están raramente asociadas al VPH, en un 6%, o con otros de los factores de riesgo característicos del CaCu[38,45].

Según la IARC para el 2020, se registraron 45.240 casos del CaV a nivel mundial y, su distribución por continente fue la siguiente: Europa: 36,5%, Asia: 26,90%, América: 24.1%, África: 11,4%, y Oceanía: 1,2%. El CaV causo la muerte de 17.427 mujeres, con la siguiente distribución por continente: Europa: 37,3%, Asia: 27,7%, América: 17,9%, África: 16,4% y Oceanía: 0,65%[46]. Para el continente americano, la IARC reportó una incidencia para el año 2020 de 10.870 casos que se distribuyeron de la manera siguiente: Norteamérica con el 64,8% y resto del continente americano con el 35,2%. Se reportaron 3.127 decesos: 55,8% correspondieron a Norteamérica y 44,2% para el resto del continente[46.]

de Martel y col.[45] reportaron para el año 2012 a nivel global que el VPH estaba involucrado en la producción del CaV en un 24,9% y en el 72,6%, los tipos 16 y 18 contribuyeron en el origen de este CA. Los autores reportaron que los tipos 6/11/16/18/31/33/45/52/582 contribuyeron en un 87,1% en el origen del CaV. La prevalencia del VPH en los casos de NIV 2/3 es del 85,3% (33), siendo el tipo 16 el más frecuentemente aislado en estas lesiones premalignas. El CDC de EEUU[40,41] reportó un promedio anual de 4.114 casos de CaV, representando el 16,2% de 25.405 CAs genitales del sexo femenino atribuidos al VPH de CaV entre 2013 y 2017.

Según Bruni y col.[36] el tipo 16 es la causa más frecuente de CaV y NIV 2/3 atribuibles al VPH con 19,4% y 67,1% a nivel mundial, respectivamente. En el continente africano representa el 58% de los VPHs causantes o atribuible al CaV. En América, se aisló en el 26,5% de los CaV y en el 56,7% de los NIV 2/3. En Asia, representó el 18,1% y el 80% para el CaV y los NIV 2/3, respectivamente. En Europa, se encontró en el 13,8% de los CaV y en el 69,9% de los NIV 2/3. En el continente de Oceanía es encontrado en el 27,3% de los CaV y en el 71,2% de los NIV 2/3.

Cáncer de vagina

El cáncer de vagina (CaVa) comparte los mismos factores de riesgo del CaCu y es aceptado que comparten la misma etiología como es la infección por el VPH, aunque hay evidencias limitadas sobre ello. Las mujeres con CaVa tienen más probabilidad de tener

antecedentes de tener otros CAs anogenitales en especial del CaCu. El ADN del VPH es aislado en el 70% de los CaVa invasivos y en el 91% de las neoplasias intraepiteliales vaginales (NIVa) 2/3[45,47].

Según la IARC para el 2020, se registraron 17.908 casos del CaVa a nivel mundial y, su distribución por continente fue la siguiente: Asia: 54,5%, América: 17,1%, Europa: 16,5%, África: 11,2%, y Oceanía: 0,8%. El CaVa causó la muerte de 7.995 mujeres, siendo la distribución por continente la siguiente: Asia: 57,6%, Europa: 15,8%, África: 13,8% América: 12,1%, y Oceanía: 0,7%[46]. Para el continente americano, la IARC reportó una incidencia para el año 2020 de 3.061 de casos que se distribuyeron: Norteamérica con el 53,2% y el resto del continente americano: 46,8%. Se reportaron 965 decesos: 48,8% correspondieron a Norteamérica y 51,2% para el resto del continente[48].

de Martel y col.[45] reportaron para el año 2012 que el VPH estaba involucrado en la producción del CaVa en un 78% y, los tipos 16 y 18 contribuyeron en un 63,7% en el origen de este CA, a nivel global. Los autores reportaron que los tipos 6/11/16/18/31/33/45/52/582 contribuyeron en un 85,3% en el origen del CaV. El ADN del VPH se encontró en el 70% de la CaVa invasivos. El CDC de EEUU[44] reportó un promedio anual de 867 casos de CaVa, atribuidos al VPH, representando el 7,3 % del total de CAs genitales del sexo femenino entre 2013 y 2017[43-45].

Según Bruni y col.[36] el VPH 16 fue el tipo más frecuente de VPH, causante de CaVa y NIVa 2/3 con 43,6% y 56,1% a nivel mundial, respectivamente. En el continente africano representa el 31,6% de los VPHs causantes o atribuible al CaVa. En América, se aisló en el 42,4% de los CaVa y en el 46,3% de los NIVa 2/3. En Asia, representó el 39,4% y el 53,8% para el CaVa y los NIVa 2/3, respectivamente. En Europa, se encontró en el 47,4% de los CaVa y en el 65,6% de los NIVa 2/3. En el continente de Oceanía es encontrado en el 46,2% de los CaVa y en el 53,8% de los NIV 2/3.

Cáncer del cuello uterino

Según la IARC para el 2020, se registraron 604.127 casos del CaCu a nivel mundial y, su distribución por continente fue la siguiente: Asia: 58,2%, África: 19,4%, América: 11,7%, Europa: 9,6%, y Oceanía: 0,4%. El CaCu causó la muerte de 341.831 mujeres, siendo la distribución por continente la siguiente: Asia: 58,5%, África: 22,5%, América: 11,1%, Europa: 9,2%, y Oceanía: 0,4 %[49.] Para el continente americano, la IARC reportó una incidencia para el 2020 de 74.410 casos que se distribuyeron: Norte-América con el 20,1% y resto del continente americano: 79,9%. Se reportaron 32.925 decesos: 16,7% correspondieron a Norte-América y 83,3% para el resto del continente[49].

de Martel y col[.45] reportaron para el año 2012 a nivel global, 630.000 casos de cáncer atribuidos al VPH: 570.000 en mujeres y 60.000 en hombres. Quinientos treinta mil casos de los 570.00 casos ocurridos en mujeres (93%) correspondieron al CaCu. Según los autores, el 70,8% de los CaCu debido al VPH se atribuyeron a los tipos 16 y 18, igualmente reportaron que los tipos 6/11/16/18/31/33/45/52/582 contribuyeron en un 89,5% en el origen del CaCu.

Bruni y col.[36] reportaron en el año 2019 que la prevalencia de los VPH 16/18 a nivel mundial en pacientes con CCV normales fue 3,9%, con lesiones de bajo grado (LBG) 25,8%, con lesiones de alto grado (LAG) 51,9% y en CaCu fue de 69,4%. En los países subdesarrollados, la prevalencia fue de 3,8% en pacientes con CCV normales, 25,1% en mujeres con LBG, 46,7% en pacientes con LAG y un 69,5% en mujeres con diagnóstico de CaCu. Las cifras para los países desarrollados fueron: citologías normales: 3,8%, LBG: 25,9%, LAG: 54,1% y cáncer: 71,8%. La distribución por continente se observa en la Tabla 4. Los hallazgos a nivel global de acuerdo al tipo histológico del CA fueron los siguiente: el CA epidermoide o escamoso: 68,4%, el adenocarcinoma: 71% y en los CA no especificados: 72,8%.

Tabla 4
Prevalencia de la infección por los VPH tipos 16/18
Porcentaje

Continente	Citología Normal	LBG	LAG	Cáncer
África	3,8	24,9	38,6	67,2
América	4,5	26,7	56,9	68,2
Asia	3,4	21,2	42,1	68,9
Europa	3,8	27,1	54,5	74,0
Oceanía	8,3	27,1	59,1	76,6

LBG: Lesión de bajo grado; LAG: Lesión de alto grado.

CONCLUSIÓN

Los CAs del área genital femenina presentan cofactores importantes en su origen y evolución, siendo uno de los importantes el VPH. Es importante conocer bien su epidemiologia y comportamiento para poder controlar este virus y por lo tanto disminuir la incidencia y mortalidad por estos CAs, en especial el del cuello uterino. La prevención primaria de la infección por este virus es esencial y en eso está basada la vacuna que nos permitirá reducir en una alta proporción de CAs, en especial al del cuello uterino.

Conflicto de Interés

El autor declara que no existen.

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Effect of video games training on the gross motor skills of children with cerebral palsy: systematic review and meta-analysis.

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Key words: video games training; gross motor skills; cerebral palsy; intervention; randomized controlled trial.

Abstract. The purpose of this work was to systematically evaluate the intervention effects of video games training (VGT) on the gross motor skills (GMS) development of children with cerebral palsy (CP). Seven Chinese and English databases (PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, EBSCO) were searched. Data were retrieved from randomized controlled trials on the GMS among individuals with CP. The retrieval was from the inception of each database to March 16, 2021. The included studies were evaluated quantitatively using the PEDro Scale. Then, relevant data were inputted and analyzed in Review Manager 5.4. Thirteen papers were included: seven written in English and six in Chinese. In the three subordinate concept of GMS, VGT could significantly improve locomotor skills (LS) (standardized mean difference = 0.80, 95% confidence interval 0.55–105, P<0.00001), and non-locomotor skills (NLS) (standardized mean difference = 0.83, 95% confidence interval 0.38–1.28, P=0.0003) in CP. However, there was no significant difference in object control skills (OCS), when compared with the control group (standardized mean difference = 0.55, 95% confidence interval -0.01–0.72, P=0.05). VGT can improve LS and NLS in CP, but the effect on OCS is uncertain; therefore, it is recommended that additional high-quality literature be included in the future. In general, VGT has been proven an effective intervention tool on the GMS development in CP.

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Efecto del entrenamiento con videojuegos en la motricidad gruesa de niños con parálisis cerebral: revisión sistemática y meta-análisis.

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Palabras clave: entrenamiento con videojuegos; habilidades motoras gruesas; parálisis cerebral; intervención; prueba controlada aleatoria.

Resumen. Este artículo intentó evaluar sistemáticamente el efecto de la intervención del entrenamiento con videojuegos (VGT) en el desarrollo de las habilidades motoras gruesas (GMS) de niños con parálisis cerebral (CP), basándose en un cuerpo de datos logrado de las conclusiones de pruebas controladas aleatorias sobre las habilidades motoras gruesas de niños con CP, obtenidos de la búsqueda sistemática en siete bases de datos chinos y extranjeros, tales como PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang y EBSCO. El lapso de búsqueda fue desde la fecha de establecimiento de cada base de datos hasta el 16 de marzo del 2021. Se aplicó la escala PEDro para realizar un estudio cuantitativo y después, se analizaron los datos relevantes con Review Manager 5.4. Se incluyeron 13 publicaciones, 7 artículos escritos en inglés y 6 en chino. En el marco del concepto de los tres subordinados de GMS, la VGT podría mejorar significativamente la habilidad locomotora (LS) (diferencia de medias estandarizada = 0.80, intervalo de confianza del 95%: 0.55-105, P<0.00001), y las habilidades no locomotoras (NLS) (diferencia de medias estandarizada = 0.83, intervalo de confianza del 95%: 0.38-1.28, P= 0,0003) en PC; pero no hubo una diferencia significativa en las habilidades de control de objetos (OCS), cuando se compararon con el grupo control (diferencia de medias estandarizada= 0,55, intervalo de confianza del 95% -0,01-0,72, P= 0,05). En conclusión, el VGT puede mejorar las LS y NLS en CP, pero el efecto sobre OCS es incierto; por lo que se recomienda la inclusión de literatura adicional de alta calidad en el futuro. De este modo se pudo demostrar que el VGT es una herramienta de intervención eficaz en el desarrollo de las GMS en niños con CP.

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INTRODUCTION

Cerebral palsy (CP), is a group of persistent central motor and postural developmental disorders and activity limitation syndrome, which is caused by non-progressive brain damage in developing fetuses or infants [1]. According to the statistics of the World Health Organization (WHO), the incidence rate of CP is around 0.2%-0.3% worldwide, and there are more than forty thousand new CP children in China every year [2]. Most of the children with CP have problems such as dyskinesia, abnormal posture and abnormal hemiplegic gait [3]. The damage to the advanced central nervous system of children with CP may cause secondary injuries, such as physical spasm, amyotrophy, skeletal

deformities and developmental coordination disorder, which constrain the children's ability to move, thereby impacting upon their development of gross motor skills (GMS) [4-6]. The good development of GMS will promote children and adolescents to participate in activities actively, but the GMS disorder is an important factor hindering children with CP from participating in physical activities [7]. If they do not participate in physical activities for a long time, children with CP will not only lag behind their peers in strength, coordination and endurance, but also face the risk of many mental diseases, such as depression, social phobia, and so on [8]. Therefore, it is very important to pay attention to the development of GMS in children with CP.

People pay great attention to and support various sports activities to improve the physique and abilities of special groups [9]. The quantity and quality of motor experience are important for brain plasticity and functional recovery [10], so motor skill intervention is often provided to develop the gross motor function of children with CP. However, traditional motor intervention therapy often requires the help of various games and facilities, and requires a large activity space and experienced therapists to accurately control the treatment process, so as to ensure the participants' interest in the treatment process and the smooth progress of the treatment [6]. Most importantly, the level of motor skills of children with CP is very poor, and the highly structured and repetitive activities of traditional rehabilitation are difficult to adhere to and to motivate their participation [11]. A potential area of intervention may lie in the attractiveness of playing and children's preference for and participation in technology [12].

"Active video games" (AVGs), also known as "exergaming" or "virtual reality games" realize sports entertainment with the help of high-tech technologies, such as human–computer interaction, motion sensing and virtual reality [13]. AVGs can provide an ecological environment similar to that in the real world, where participants can practice specific tasks, and the difficulty of tasks can be adjusted readily in the game and provide sufficient challenges [14]. Such immersive experience in a safe, enjoyable, and playful environment is associated with less fatigue and more relaxation, which may attract children, including those with CP [15]. Simultaneously, due to the characteristics and animation effects of the game, it can also increase children's motivation and participation in the gaming process, attract users to immerse themselves in the sports environment [16], and improve their cognitive function and motor skills. Hence, video games training (VGT) are very suitable as rehabilitation tools for children, and gradually have developed into a popular therapy of motor skill intervention for special populations [17]. A review of the literature on children with cerebral palsy suggests that AVGs interventions can improve GMS development, including their balance, coordination and other physical fitness [18].

Many scholars have done research on video game training to improve the GMS of children with CP. However, the past research often focused on one aspect of GMS, such as the impact on stability skills, the impact on upper limb skills, etc., and they lack of a summary and discussion of the effects of video games to improve the overall GMS of children with CP. GMS refers to the movement generated by large muscles or muscle groups of the body, including walking, running, jumping, throwing, etc. According to the change of spatial position and the control of external tools, the GMS can be divided into locomotor skills (LS), object control skills (OCS) and non-locomotor skills (NLS) [19]. It can be seen that GMS is a general term that includes three subordinate concepts. This research was aimed to explore the effects of VGT on the GMS development of children with CP by employing a systematic review and meta-analysis, and demonstrate the effectiveness of VGT in intervening the three subordinate concepts of GMS in children with CP. In addition, if one aspect of

GMS is significantly improved, the dose effect of intervention duration, intervention frequency and intervention cycle will be discussed by subgroup analysis.

METHODS

Criteria for including studies

The criteria for including literature were: (i) the study population was aged 3–14 years with CP; (ii) at least one of GMS was objectively measured and reported separately; (iii) the intervention was not a single intervention; (iv) the study was published and peer-reviewed in English or Chinese; (v) the study was a randomized controlled trial (RCT).

Criteria for excluding studies

The criteria for excluding studies were: (i) evaluation of motor skill is a combination of gross motor skill and fine motor skill; (ii) data on the change of GMS before and after the test (e.g., mean ± SD) were absent; (iii) the subjects were not 3-14 years old.

Outcome indicators

(i) Index of LS, including walking, running, jumping, shuttle run, etc.; (ii) Index of OCS, including throwing, catching, hitting and beating, etc.; (iii) Index of NLS, including balance beam standing, on one or both feet, etc.

Literature-retrieval strategy

The databases we used were PubMed, Cochrane Library, Embase, Elton Bryson Stephens Company, Web of Science, China National Knowledge Infrastructure, and Wanfang. We retrieved data from randomized controlled trials (RCTs) from the inception of each database to March 16, 2021.

The search strategy was based on the principle of PICOS (Population, Intervention, Comparison, Outcomes and Study design). We employed three groups and used search terms for them.

Group 1 was based on VGT: "active video game*" (视频游戏), OR "exergam*", (体感游戏) OR "virtual realit*" OR "virtual therap*", OR "virtual environment*", OR "video game*", OR "computer game*", OR "serious gam*", OR "Wii", OR "Kinect", OR "PlayStation", OR "EyeToy", OR "GestureTek", OR "IREX".

Group 2 was based on GMS: "gross motor"(粗大动作) OR "motor coordination", OR "motor skill". OR "movement skill", OR "fundamental motor skill", OR "fundamental motor skill", OR "fundamental movement skill", OR "motion capture", OR "balance".

Group 3 was based on the subject: "children with CP" (脑瘫儿童), OR "children with cerebral palsy" (脑性瘫痪儿童), OR "spastic diplegia*", OR"spastic diplegic", OR"spastic quadriplegic".

Literature screening

Two researchers used independent double-blind methods to screen the literature based on the inclusion and exclusion criteria stated above, and relevant data were extracted. If there was a disagreement on the review, screening, and data-extraction stages, a third researcher discussed whether to include the data.

Data extraction

The data extracted from the literature was the author names, year of publication, and the basic characteristics of samples (gaming platform, game type, outcome indicators, and intervention environment/period/duration/frequency) (Table 1).

Quality evaluation

All the literature included in our study consisted of RCTs. The PEDro Scale was used for evaluation of literature quality, and comprised 11 items. The PEDro scale has a total score of 10 points: <4 indicates "poor" quality; 4–5 indicates "medium" quality; 6–8 indicates "good" quality; 9–10 indicates "high" quality (Table 2).

Table 1
List of basic characteristics of the included documents.

Researchers	Subjects		Intervention Setting	AVGs Platform	AVGs Category	Control group	Intervention			Outcome Indicators	GMS
	E/C	Age (y)					Cycle	Time	Frequency		
Alsaif *et al.* (24) 2015	20/20	6-10	Home	Nintendo Wii Fit	Unreported	Non-intervention	12	20	7	MABC, BOT-2	②③
Arnoni *et al.* (25) 2019	7/8	5-14	Unreported	Xbox 360 Kinect	Jumping, Loading exercises	Regular Exercise	8	45	2	GMFM-88, BSA	①③
Chen *et al.* (26) 2013	15/15	3-6	Medical Clinic	Q4 Scene Interactive Training System	Billiard Ball, Hopscotch	Regular Exercise	12	30	5	BBS,GMFM-88	①③
Chen *et al.* (27) 2016	20/20	3-6	Medical Clinic	Q4 Scene Interactive Training System	Billiard Ball, Hopscotch	Regular Exercise	12	40	5	BBS,GMFM-88	①③
Chiu *et al.* (28) 2014	30/27	6-13	Home	Nintendo Wii Sports	Bowling, Aerial sports, Frisbee and Basketball	Regular treatment	6	40	3	TT	②
Pourazar *et al.* (29) 2019	10/10	7-12	Medical Clinic	Xbox 360 Kinect	Dance rehabilitation training	Regular treatment	6	85-100	1	SEBT	③
Ren *et al.* (30) 2016	19/16	3-6	Medical Clinic	Q4 Scene Interactive Training System	Unreported	Regular Exercise+ Occupational Therapy	12	40	5	BBS,GMFM-88	①③
Rojas *et al.* (31) 2017	16/16	7-14	Rehabilitation centre	Nintendo Wii Balance Board	Snowboard, Penguin Slide, Super Hula Hoop,Yoga	Standard Physiotherapy	6	30	3	COP	③

Table 1
CONTINUATION

Researchers	Subjects		Intervention Setting	AVGs Platform	AVGs Category	Control group	Intervention			Outcome Indicators	GMS
	E/C	Age (y)					Cycle	Time	Frequency		
Urgen *et al.* (32) 2016	15/15	7-14	Unreported	Nintendo Wii Fit	Jogging plus, Penguin slide, Heading, Ski jump, Snowball fight, Tilt city, Perfect 10, Segway circuit play	Routine Physiotherapy and Rehabilitation	9	45	2	GMFM, PBS, TUGT	①③
Uysal *et al.* (33) 2016	12/12	6-14	Rehabilitation centre	Nintendo Wii Balance	Basketball, Tennis, Boxing	Routine Physiotherapy	12	30	2	PBS	③
Zhang *et al.* (2) 2019	20/20	3-6	Rehabilitation centre	KMC1	Cycling game	Regular treatment	12	20	5	GMFM-88	①
Zhao(a) *et al.* (34) 2018	21/21	3-6	Rehabilitation centre	Xbox 360 Kinect	Boxing, Javelin bowling , Universe bubble ball,Bounce ball	Regular treatment	3	40	5	GMFM-88, QUEST	①②
Zhao(b) *et al.* (35) 2018	21/21	3-6	Rehabilitation centre	Xbox 360 Kinect	Dance music imitation	Regular treatment	3	40	5	GMFM-88, PBS	①③

E= Experimental group; C= Control group; CP = cerebral palsy; MABC-2 = Movement Assessment Battery for Children-2; BBS = Berg Balance Scale; PBS = Pediatric Balance Scale; TUGT = Timed Get Up and Go Test; COP = Center Of Pressure; BOT = Bruininks–Oseretsky Test of Motor Proficiency; QUEST=Quality of Upper Extremity Skill Test; ①Locomotor Skills; ②Object Control Skills; ③Non-locomotor skills.

Table 2
Methodological Quality Assessment for Included Studies.

Included Studies	A	B	C	D	E	F	G	H	I	J	K	Score
Alsaif *et al*. 2015	1	1	0	1	0	0	0	1	1	1	1	6
Arnoni *et al.* 2019	1	1	1	1	1	1	0	1	1	1	0	8
Chen *et al.* 2013	1	1	0	1	0	0	0	1	1	1	1	6
Chen *et al.* 2016	1	1	0	1	0	0	0	1	1	1	1	6
Chiu *et al*. 2014	1	1	0	1	0	0	1	1	1	1	1	7
Pourazar *et al.* 2019	1	1	0	1	1	1	0	1	1	1	0	7
Ren *et al.* 2016	1	1	0	1	0	0	0	1	1	1	1	6
Rojas *et al.* 2017	1	1	0	1	0	0	0	1	1	1	1	6
Urgen *et al.* 2016	1	1	0	1	0	0	0	1	1	1	0	5
Uysal *et al.* 2016	1	1	0	1	0	1	0	1	1	1	1	7
Zhang *et al.* 2019	1	1	0	1	0	0	0	1	1	1	1	6
Zhao(a) *et al.* 2018	1	1	0	1	0	0	0	1	1	1	1	6
Zhao(b) *et al.* 2018	1	1	1	0	0	0	0	1	1	1	1	6

a. eligibility criteria were specified; b. subjects were allocated randomly to groups; c. allocation was concealed; d. the groups were similar at baseline with regard to the most important outcome indicators; e. there was blinding of all subjects; f. there was blinding of all therapists; g. there was blinding of all assessors; h. measures of at least one key outcome were obtained from >85% of subjects initially allocated to groups; i. all subjects for whom outcome measures were available received treatment or, if this was not the case, data for at least one key outcome were analyzed by intention-to-treat; j. the results of between-group statistical comparisons were reported for at least one key outcome; k. the study provided point measures and measures of variability for at least one key outcome.

Statistical analyses

We employed Review Manager 5.4 for data processing. The boundary value of "small", "medium", and "large" effect sizes was 0.2, 0.5, and 0.8 [20]. Also, 75%, 50%, and 25% denoted the proportion of "high", "medium" and "low" inter-study heterogeneity, respectively [21]. If significant heterogeneity between the studies was not observed ($P > 0.1$, $I^2 < 40\%$), then we used a fixed-effects model for analyses. If there was significant heterogeneity between studies ($P < 0.1$, $I^2 \geq 40\%$), then a random-effects model was used for analyses, and further subgroup analyses were carried out to discover the source of heterogeneity.

If ≥2 tasks had been used to measure the GMS of CP, the effect size is selected from the most commonly used tasks [22]. If the study reported multiple measurements on the same task (e.g., the ability to balance in left, right, front, and back directions), the standard deviation and variance were averaged to represent the outcome of the task [23].

RESULTS

Literature characteristics

A total of 840 Chinese and English studies were obtained from seven Chinese and English databases. Six studies were added through other means, so 846 studies were imported into Endnote™ X9 (https://endnote.com/). After removal of duplicates, 631 studies were obtained. Then, 126 studies were removed after reading the title and abstract, which left 113 studies. Then, the full text was read. According to the inclusion and exclusion criteria stated above, 13 studies using RCTs were included: seven written in English and six in Chinese (Fig. 1). The

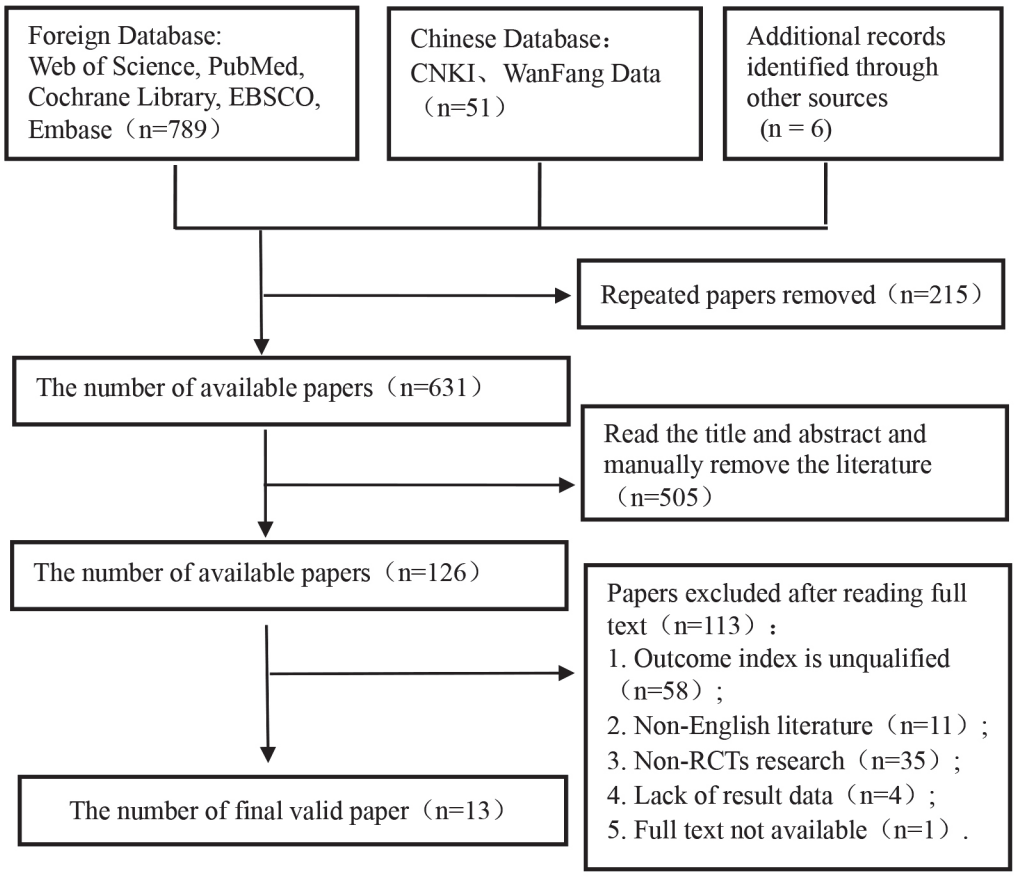

Fig. 1. The flow chart of literature screening.

characteristics of the studies are shown in Table 1.

The 13 studies involved 447 subjects. Overall (male and female) samples were used in all studies, and the sex ratio was approximately equal. The sample size of one study was >50, in the other 12 studies it was between 20 and 40. In our meta-analysis, Nintendo (Kyoto, Japan) Wii™ was the dominant and most frequently used gaming platform. Five studies used Nintendo gaming platforms, including Wii Balance, Wii Fit (or Wii Fit Plus) and Wii Sports. The KMC1 (INNOVAID, Denmark) virtual situational movement system was used in one studies ,Q4 Scene Interactive Training System was used in three studies, and four studies used the Xbox™ 360 gaming platform from Microsoft (Redmond, WA, USA). Except for two studies that did not mention explicitly the intervention environment, medical institutions such as rehabilitation hospitals and children's clinics were the main intervention venues (nine studies) and two studies used family homes as the intervention environments.

In terms of the types of active video games, it covered almost all sports, including routine sports such as dancing, table tennis, basketball, boxing, bowling, ski jumping, obstacle course, skateboarding and so on. Compared with traditional sports intervention methods, the content scope of games is broader, providing more choice space for participants.

Literature Quality Evaluation

Among the 13 RCTs, only one study was rated as "medium" quality (PEDro Scale

score = 5), and the other 12 studies were rated between 6 and 8, all of which denoted "good" quality. The most prevalent problem in the included RCTs was a lack of blinding. A lack of blinding in the subject intervention or evaluation of the final outcome can increase the risk of bias in the selection and evaluation of participants, and may impinge an artificial influence on the experimental results [36]. The quality evaluation of studies included in our meta-analysis is shown in Table 2.

RESULTS OF META-ANALYSIS

Meta-analysis of the intervention effects of VGT on LS of Children with CP

Eight randomized controlled experiments were included in the study on the intervention of VGT on LS of CP, including 274 subjects. The analysis results are shown in Fig. 2. Heterogeneity test results showed that there was low heterogeneity between studies (X^2=4.43, I^2=0%, P=0.73), the fixed-effect model was used to combine effect size and effect size [SMD=0.80, 95%CI(0.55,1.05), P<0.00001], the difference was statistically significant, indicating that VGT could significantly improve the LS of CP, and the LS were significantly improved compared with the control group. To further explore the source of potential heterogeneity, a subgroup analysis of potential moderators was conducted (Table 3).

Meta-analysis of the intervention effects of VGT on OCS of Children with CP

Only three studies reported the intervention effect of AVGs on OCS of children with CP. The heterogeneity test showed (Fig. 3) a high degree of heterogeneity between studies (X^2 = 5.21, I^2 = 62%, P = 0.07), the random-effect model was used to combine effect size and effect size [SMD=0.55,95%CI(-0.01,0.72),p=0.05], the difference was not statistically significant. Indicating that VGT had no significant difference in improving OCS of Children with CP when compared with the control group.

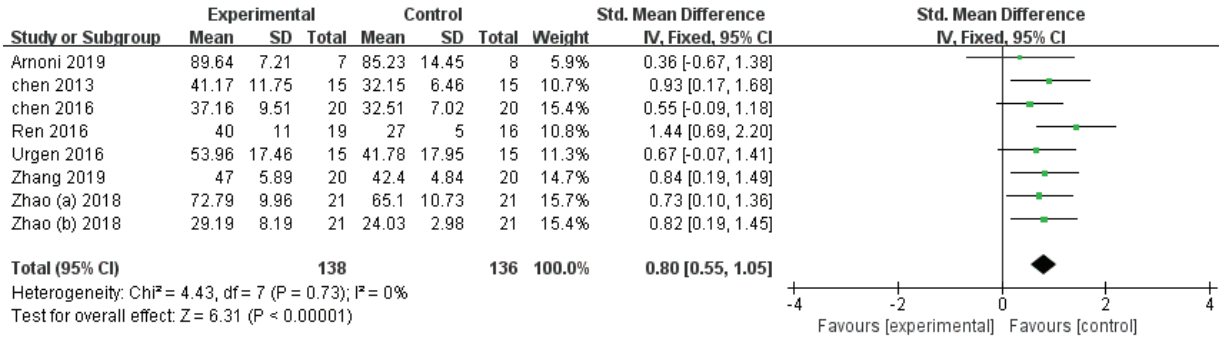

Fig. 2. Effects of VGT on LS of Children with CP.

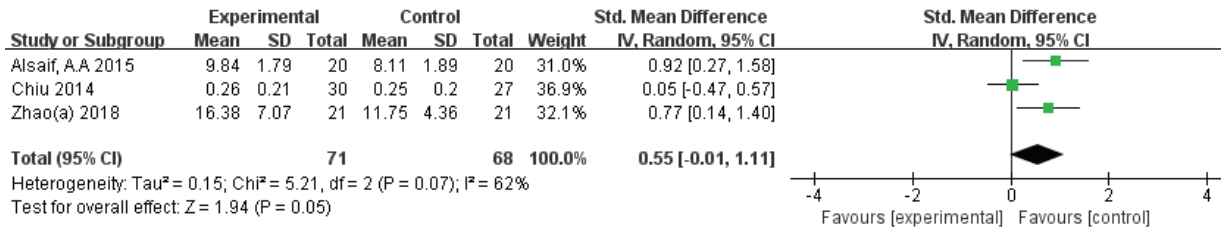

Fig. 3. Effects of VGT on OCS of Children with CP.

Table 3

Subgroup analyses of the intervention effects of VGT on LS of Children with CP.

Moderator variable	Subgroup	Included literature	Heterogeneity test			Effect size	95% CI	Two-tailed test	
			$\chi 2$	P	I2			Z	P
Gaming platform	Nintendo Wii™	1	0	0.00	0	0.67	(-0.07,1.41)	1.78	0.08
	Xbox™ 360	3	0.58	0.75	0%	0.71	(0.30,1.12)	3.40	**0.0007****
	Q4 Scene Interactive Training System	3	3.20	0.20	37%	0.94	(0.42,1.46)	3.54	**0.0004****
	KMC1	1	0	0.00	0	0.84	(0.19,1.49)	2.53	**0.01***
Intervention cycle	≤8 weeks	3	0.58	0.75	0%	0.71	(0.30,1.12)	3.40	**0.0007****
	9-12 weeks	5	3.53	0.47	0%	0.85	(0.54,1.17)	5.35	**<0.00001****
Duration of single intervention	≤30 min	2	0.03	0.86	0%	0.87	(0.38,1.37)	3.47	**0.0005****
	≥40 min	6	2.78	0.73	0%	0.57	(0.29,0.86)	3.93	**<0.0001****
Intervention frequency	<3 times/week	2	0.24	0.63	0%	0.56	(-0.04,1.16)	1.84	0.07
	3-5 times/week	6	3.46	0.63	0%	0.85	(0.58,1.12)	6.10	**<0.00001****

*: $p<0.05$; **: $p<0.01$.

Meta-analysis of the intervention effects of AVGs on NLS of Children with CP.

VGT were the most widely studied intervention on NLS of Children with CP, and 10 randomized controlled experiments were included in the study on the intervention of VGT on NLS of Children with CP, including 298 subjects. The analysis results are shown in Fig. 4. The heterogeneity test showed a high degree of heterogeneity between studies (X^2 = 28.42, I^2 = 68%, P=0.0008), the random-effect model was used to combine effect size and effect size [SMD=0.83,95%CI(0.38,1.28),p=0.0003], the difference was statistically significant, indicating that VGT could significantly improve NLS of Children with CP, and the NLS were significantly improved compared with the control group. To further explore the source of potential heterogeneity, a subgroup analysis of potential moderators was conducted (Table 4).

DISCUSSION

With the continuous development and improvement of virtual-reality technology, VGT are increasingly applied in the field of sports rehabilitation, and the intervention of VGT in special children is centered on the mobility, balance and motor development of children with autism [37-39], CP [23-35] and developmental coordination disorder [40,41]. However, there are few meta-analyses on the intervention of gross motor skills and their subordinate concepts in VGT, and the main purpose of this study is to evaluate quantitatively the results of VGT on the development of GMS in children with CP to verify its intervention effect.

Analyses of the intervention effect of VGT on LS of CP

Locomotor Skills refers to the ability to move and change body direction and position quickly and effectively under control, which requires the integration of independent motor abilities including balance, coordination, speed, reflection, strength and endurance, and is the embodiment of comprehensive ability. Meta-analysis of eight papers included in this study with LS as an indicator, showed that VGT had a significant effect on LS of CP (SMD=0.80). This is consistent with the results of the study conducted by Wuang *et al*. on 155 patients with Down syndrome aged 7-12 years. After a 24-week, 2,880 minute virtual-reality game intervention, they found that the AVGs intervention group showed significant improvements in speed and agility compared with the non-exercise group and the standard occupational therapy group [42].

In video game training, the standing posture is often used to complete a lot of weight fluctuation control, standing-squatting, standing-sitting and other exercises,

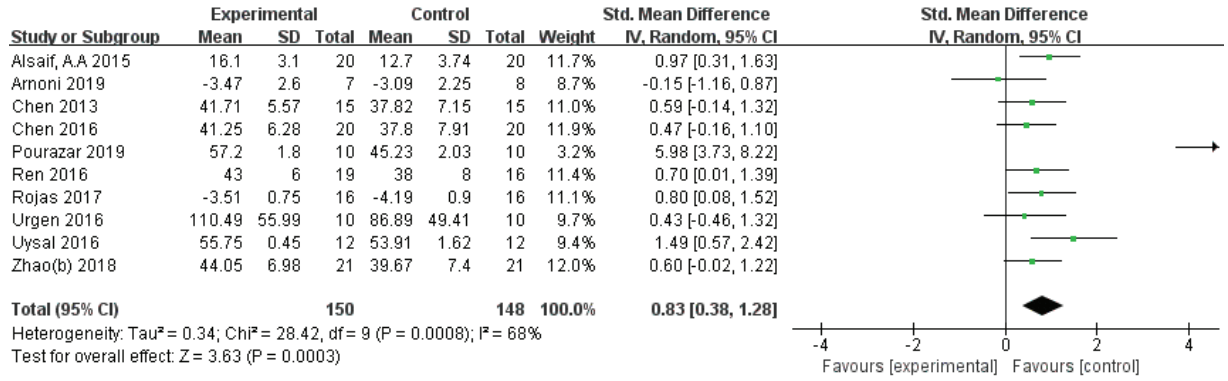

Fig. 4. Effects of VGT on NLS of Children with CP.

Table 4
Subgroup analyses of the intervention effects of VGT on NLS of Children with CP.

Moderator variable	Subgroup	Included literature	Heterogeneity test			Effect size	95% CI	Two-tailed test	
			χ2	P	I2			Z	P
Gaming platform	Nintendo Wii™	4	2.79	0.43	0%	0.91	(0.52,1.30)	4.60	<0.00001**
	Xbox™ 360	3	24	<0.00001	92%	1.81	(-0.41,4.03)	1.60	0.11
	Q4 Scene Interactive Training System	3	0.23	0.89	0%	0.58	(0.19,0.97)	2.90	0.004**
Intervention setting	Home	1	0	0	0	0.97	(0.31,1.63)	2.89	0.004**
	Medical institutions	7	24.66	0.0004	76%	1.04	(0.43,1.65)	3.36	0.0008**
Intervention cycle	≤8 weeks	4	24.06	<0.0001	88%	1.34	(0.01,2.68)	1.98	0.04*
	9-12 weeks	6	4.36	0.50	0%	0.74	(0.44,1.04)	4.85	<0.00001**
Duration of single intervention	≤30 min	4	2.38	0.50	0%	0.91	(0.54,1.28)	4.81	<0.00001*
	≥40 min	6	24.49	0.0002	80%	0.86	(0.09,1.62)	2.19	0.03*
Intervention frequency	<3 times/week	4	26.39	<0.00001	89%	1.63	(-0.03,3.29)	1.92	0.06
	3-5 times/week	6	1.39	0.93	0%	0.68	(0.41,0.96)	4.88	<0.00001*

*: $p<0.05$; **: $p<0.01$.

which need to constantly transfer the weight between the lower limbs. All of these stimulated the player's muscle strength, especially the lower limbs, and improved the individual's functional muscle strength. The integrated development of strength, balance, and coordination, coupled with the continuous involvement of neural networks and cognitive components, as well as visual or auditory feedback, triggered positive neuroplasticity changes in participants [13]. These are important reasons to improve the speed and agility of participants.

Analyses of the intervention effect of VGt on OCS of CP

There is a general lack of research on how AVGs interfere with OCS of CP, and recent studies have shown varied results [43]. There are only three studies on OCS included in this study, and the intervention effect is limited, the conclusion does not support a significant improvement of OCS. The reason for this may be that the OCS are relatively complex. When applying force to an object or intercepting an object, it includes not only the gross motor, such as balance and upper limb coordination, but also the hand-eye coordination and even the flexible ability of fingers, which is the combination of fine motor and gross motor [44]. Simple upper limb or arm movement training has limited impact on tasks requiring hand-eye upper limb coordination.

Another reason may be that OCS require upper or lower limbs to contact objects for object control and perform actions such as throwing, slapping and kicking. In this process, the touch between the body and the object plays an important role, which is difficult to replicate in virtual reality technology. Neither the game handle in hand nor the controller worn on the body can provide timely haptic feedback, such as the weight and size of the control object. Therefore, some scholars began to try to use haptic feedback gloves when using video games to simulate ball operations in real life. By wearing gloves, participants can timely feedback more haptic information, so as to improve the intervention effect of VGT on OCS [45].

Although the overall effect of VGT on improving OCS in this study is not significant, the research of Chiu *et al.* [27] shows that the range and frequency of use of children's upper limbs have a significant increase, compared with the past, after video game intervention, which greatly improves their independence level in daily activities [46], This undoubtedly has an important impact on the development and improvement of upper limb function in CP. Because there is few literature on the impact of VGT on OCS, the conclusions may have some uncertainty.

Analyses of the intervention effect of VGT on NLS of CP

Balance ability is the ability to maintain the human body's posture and is a very important physiological function [47]. Gait instability or difficulty in maintaining balance is an important behavior of many special children, so the intervention of balance ability is an important measure to promote their gross motor. Posture control ability and muscle tension deficiency are considered to be important factors affecting poor gait and balance ability, and AVGs are considered to improve the posture control ability in CP [48]. Among the 13 research literature included in this study, the research on NLS is the most concentrated (10 studies), and the intervention effect was also obvious (SMD=0.83). A reason for the impact of VGT intervention on NLS may be that the AVGs platform is a whole-body interactive video game, which uses sensory motor experiences, such as vision and sound to simulate environment and activities, and its design method can more fully replicate the balance skills of the real world [45]. Using virtual games to perform balance training on the screen provides users with the ability to mirror in real time and adjust their action amplitude, speed and accuracy [27,49]. Lee *et al.* found that virtual reality tools can provide more realistic visual

feedback, which is the key to balance and control skills [50].

Video game training requires players to perform fast and accurate local or whole body movements in the standing position, which is very important to promote trunk stability and posture adjustment required for balance during movement [51]. It can significantly improve the symmetry of both sides of the body, make the body center of gravity evenly distributed in the lower limbs, increase the stability of standing, and improve the posture control ability [52]. In a systematic review of groups of CP by Page and colleagues [43], 10 of the 15 studies, that included balance measures, found significant improvement, with the most compelling evidence being for improvement in balance, those data are consistent with the results of our meta-analysis.

Research Limitations

This study had three main limitations. First, only 13 RCTs were included in our meta-analysis. Second, the sample size was relatively small. Third, although the subjects included in the studies all CP, there may be differences in etiology and pathogenesis, and the severity of the disease is inconsistent. The final intervention effect may have been different because of different disease mechanisms.

CONCLUSIONS

VGT provide a safe and interesting environment, produces less fatigue and greater load intensity and total amount by the body, which increases the physical activity level of game participants and improves the practice effect. The results of this study show that VGT is an effective rehabilitation treatment tool in the intervention of GMS of CP. Especially in stability skills and locomotor skills, the research conclusions are relatively consistent and the intervention effects results in a large effect. The intervention effect of VGT on OCS is uncertain because there are few studies published. Future research should increase the inclusion of high quality literature and a larger sample size, and it is expected that more scientific conclusions can be drawn on the intervention of VGT in the development of GMS in CP.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Authors' Contributions

All authors contributed to the conception and design of this meta-analysis. YongHe Pan drafted the manuscript. GuangFeng Zhao and Qiang Liu searched the literature and determined which studies should be included and excluded. Sen Li proffered suggestions for modification of the manuscript. All authors approved the final version of the manuscript.

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